CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 022023/S-004

Trade Name: **EMEND**

Generic Name: **Fosaprepitant dimeglumine**

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

Approval Date: 11/12/2010

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

(1): 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;
(2): prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022023/S-004

SUPPLEMENT APPROVAL

Merck Sharp & Dohme Corp.
Attention: Nicholas Andrew
Associate Director, Regulatory Affairs
126 East Lincoln Avenue
P.O. Box 2000, RY 33-200
Rahway, NJ 07065-0900

Dear Mr. Andrew:

Please refer to your Supplemental New Drug Application (sNDA) dated October 12, 2009, received October 13, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EMEND (fosaprepitant dimeglumine) for Injection, 150 mg.

We acknowledge receipt of your amendments dated December 17, 2009; December 18, 2009; January 8, 2010; January 27, 2010; April 8, 2010; June 11, 2010; July 27, 1010; August 30, 2010; September 7, 2010; September 28, 2010; October 27, 2010; November 2, 2010; November 3, 2010; November 9, 2010; and November 11, 2010.

This "Prior Approval" supplemental new drug application proposes a new dosing regimen for the use of a single intravenous dose of fosaprepitant 150 mg, dosed concomitantly with a 5HT3 receptor antagonist and corticosteroid, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert and text for the patient package insert) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. 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 for this NDA, including pending "Changes Being Effected" (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.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and 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 titled "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 "**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 022023/S-004**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric studies because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

1663-1 A PK/PD study to characterize aprepitant PK parameters following administration of a single dose of intravenous fosaprepitant, in combination with a 5HT3 antagonist and dexamethasone, in pediatric cancer patients ages 0 to 17 years undergoing treatment with highly emetogenic chemotherapy. You must conduct this study with an age appropriate formulation.

Final Protocol Submission: February 2011
Study/Trial Completion: February 2014

Final Report Submission: May 2014

1663-2 An adequate, placebo-controlled, double-blind, randomized, add-on design, superiority study to evaluate the safety and efficacy of a single dose of intravenous fosaprepitant, in combination with a 5HT3 antagonist, as compared to standard therapy (a 5HT3 antagonist) in pediatric cancer patients ages 0 to 17 years undergoing treatment with highly emetogenic chemotherapy. You must conduct this study with an age appropriate formulation.

Final Protocol Submission: August 2014
Study/Trial Completion: August 2017
Final Report Submission: December 2017

Submit final study reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated "**Required Pediatric Assessment(s)**".

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

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 Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures: Content of Labeling
Carton and Container Labeling

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

/s/

DONNA J GRIEBEL
11/12/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022023/S-004

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

EMEND (fosaprepitant dimeglumine) for Injection, for intravenous use

Initial U.S. Approval: 2008

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

Dosage and Administration, HEC (2.1)	11/2010
Dosage and Administration, MEC (2.2)	11/2010
Dosage and Administration, Preparation (2.3)	11/2010
Dosage and Administration, Administration with Food (2)	removal 11/2010

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

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

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

Limitations of Use (1)

- Chronic continuous administration is not recommended.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Revised: 11/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EMEND for Injection is a substance P/neurokinin-1 (NK_1) receptor antagonist indicated in adults for use in combination with other antiemetic agents for the:

- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin *[see Dosage and Administration (2.1)]*
- prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) *[see Dosage and Administration (2.2)]*.

Limitations of Use

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

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

2 DOSAGE AND ADMINISTRATION

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

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

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

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

	Day 1	Day 2	Day 3	Day 4
EMEND	150 mg intravenous	none	none	none
Dexamethasone**	12 mg orally	8 mg orally	**8 mg orally twice daily**	**8 mg orally twice daily**
Ondansetron†	32 mg intravenous	none	none	none

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

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

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

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

Table 2 Recommended dosing (3-Day Dosing Regimen of EMEND) for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy				
	Day 1	Day 2	Day 3	Day 4
EMEND	115 mg intravenous	80 mg orally	80 mg orally	none
Dexamethasone**	12 mg orally	8 mg orally	**8 mg orally once daily**	**8 mg orally once daily**
Ondansetron†	32 mg intravenous	none	none	none

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

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

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

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

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

Table 3 Recommended dosing (3-Day Dosing Regimen of EMEND) for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy			
	Day 1	Day 2	Day 3
EMEND	115 mg intravenous	80 mg orally	80 mg orally
Dexamethasone**	12 mg orally	none	none
Ondansetron†	8 mg orally twice daily	none	none

**Dexamethasone should be administered 30 minutes prior to chemotherapy treatment on Day 1. The dose of dexamethasone accounts for drug interactions.
†Ondansetron 8-mg capsule should be administered 30 to 60 minutes prior to chemotherapy treatment and one 8-mg capsule should be administered 8 hours after the first dose on Day 1.

2.3 Preparation of EMEND for Injection

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

Step 4	Gently invert the bag 2-3 times.	Gently invert the bag 2-3 times.
	Note: *The differences in preparation for each dose are displayed as bolded text.*	

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

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

4 CONTRAINDICATIONS

4.1 Hypersensitivity

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

4.2 Concomitant Use with Pimozide or Cisapride

Aprepitant, when administered orally, is a moderate cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitor following the 3-day antiemetic dosing regimen for CINV. Since fosaprepitant is rapidly converted to aprepitant, do not use fosaprepitant concurrently with pimozide or cisapride. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 CYP3A4 Interactions

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

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

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

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

5.2 Hypersensitivity Reactions

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

5.3 Coadministration with Warfarin (a CYP2C9 substrate)

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

5.4 Coadministration with Hormonal Contraceptives

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

5.5 Chronic Continuous Use

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

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

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

Oral Aprepitant

Highly Emetogenic Chemotherapy (HEC)

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

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

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

Table 5 Adverse Reactions (incidence ≥1%) in patients receiving HEC with a greater incidence in the Aprepitant Regimen relative to Standard Therapy		
	Aprepitant Regimen (N=544)	**Standard Therapy (N=550)**
Respiratory System		
hiccups	4.6	2.9
Body as a Whole/Site Unspecified		
asthenia/fatigue	2.9	1.6
Investigations		
ALT increased	2.8	1.5
AST increased	1.1	0.9
Digestive System		
constipation	2.2	2.0
dyspepsia	1.5	0.7
diarrhea	1.1	0.9
Nervous System		
headache	2.2	1.8
Metabolism and Nutrition		
anorexia	2.0	0.5

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

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

Moderately Emetogenic Chemotherapy (MEC)

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

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

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

Table 6 Adverse Reactions (incidence ≥1%) in patients receiving MEC with a greater incidence in the Aprepitant Regimen relative to Standard Therapy		
	Aprepitant Regimen (N=868)	**Standard Therapy (N=846)**
Gastrointestinal disorders		
eructation	1.0	0.1
General disorders and administration site conditions		
fatigue	1.4	0.9

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

Less Common Adverse Reactions

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

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

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

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

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

Fosaprepitant

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

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

Table 8 Adverse Reactions (incidence >0.1%) in patients receiving Fosaprepitant 150 mg and not reported above for the Oral Aprepitant Regimen	
General disorders and administration site conditions	infusion site erythema, infusion site pruritus, infusion site induration, infusion site pain
Investigations	blood pressure increased
Skin and subcutaneous tissue disorders	erythema
Vascular disorders	thrombophlebitis (predominantly, infusion-site thrombophlebitis)

Other Studies with Postoperative Nausea and Vomiting

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

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

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

Table 9 Adverse Reactions (incidence <1%) in patients receiving Aprepitant 40 mg with a greater incidence in the Aprepitant group relative to ondansetron	
Psychiatric disorders	insomnia
Nervous system disorders	dysarthria, hypoesthesia, sensory disturbance
Eye disorders	miosis, visual acuity reduced
Cardiac disorders	bradycardia
Respiratory, thoracic and mediastinal disorders	dyspnea, wheezing
Gastrointestinal disorders	abdominal pain upper, bowel sounds abnormal, dry mouth, nausea, stomach discomfort

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

Other Studies

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

6.2 Postmarketing Experience

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

Skin and subcutaneous tissue disorders: pruritus, rash, urticaria.

Immune system disorders: hypersensitivity reactions including anaphylactic reactions.

7 DRUG INTERACTIONS

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

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

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

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

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

CYP3A4 Substrates:

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

5-HT_3 antagonists:

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

Corticosteroids:

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

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

Methylprednisolone: An oral aprepitant regimen of 125 mg on Day 1 and 80 mg/day on Days 2 and 3, increased the AUC of methylprednisolone, by 1.34-fold on Day 1 and by 2.5-fold on Day 3, when methylprednisolone was coadministered intravenously as 125 mg on Day 1 and orally as 40 mg on Days 2 and 3. The intravenous methylprednisolone dose should be reduced by approximately 25%, and the oral methylprednisolone dose should be reduced by approximately 50% when coadministered with a regimen of fosaprepitant 115 mg followed by aprepitant.

Chemotherapeutic agents:

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

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

Oral contraceptives:

When oral aprepitant, ondansetron, and dexamethasone were coadministered with an oral contraceptive containing ethinyl estradiol and norethindrone, the trough concentrations of both ethinyl estradiol and norethindrone were reduced by as much as 64% for 3 weeks post-treatment.

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

Midazolam:

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

Table 10 Pharmacokinetic Interaction Data for Aprepitant/Fosaprepitant and Coadministered Midazolam		
Dose of fosaprepitant/ aprepitant	**Dose of Midazolam**	**Observed Drug Interactions**
fosaprepitant 150 mg on Day 1	oral 2 mg on Days 1 and 4	AUC ↑ 1.8-fold on Day 1 and AUC ↔ on Day 4
fosaprepitant 100 mg on Day 1	oral 2 mg	oral midazolam AUC ↑ 1.6-fold
oral aprepitant 125 mg on Day 1 and 80 mg on Days 2 to 5	oral 2 mg SD on Days 1 and 5	oral midazolam AUC ↑ 2.3-fold on Day 1 and ↑ 3.3-fold on Day 5
oral aprepitant 125 mg on Day 1 and 80 mg on Days 2 and 3	intravenous 2 mg prior to 3-day regimen of aprepitant and on Days 4, 8 and 15	intravenous midazolam AUC ↑ 25 % on Day 4, AUC ↓ 19 % on Day 8 and AUC ↓ 4 % on Day 15
oral aprepitant 125 mg	intravenous 2 mg given 1 hour after aprepitant	intravenous midazolam AUC ↑ 1.5-fold

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

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

CYP2C9 Substrates (Warfarin, Tolbutamide):

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

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

7.2 Effect of Other Agents on the Pharmacokinetics of Aprepitant

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

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

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

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

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

7.3 Additional Interactions

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

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

In 2 well-controlled chemotherapy-induced nausea and vomiting clinical studies, of the total number of patients (N=544) treated with oral aprepitant, 31% were 65 and over, while 5% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger

subjects. Greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment in the elderly is not necessary *[see Clinical Pharmacology (12.3)]*.

8.6 Patients with Severe Hepatic Impairment

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

10 OVERDOSAGE

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

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

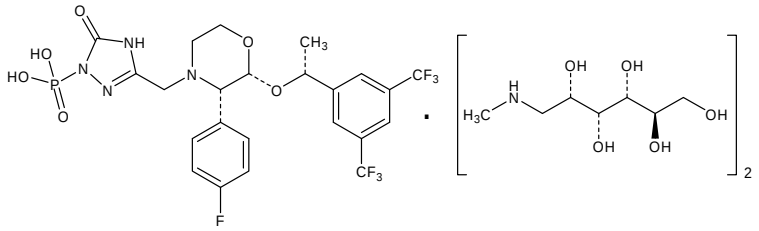
Aprepitant cannot be removed by hemodialysis.

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

11 DESCRIPTION

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

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



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

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

Each vial of EMEND for Injection 115 mg for intravenous administration contains 188 mg of fosaprepitant dimeglumine equivalent to 115 mg of fosaprepitant free acid and the following inactive ingredients: edetate disodium (14.4 mg), polysorbate 80 (57.5 mg), lactose anhydrous (287.5 mg), sodium hydroxide and/or hydrochloric acid (for pH adjustment). Each vial of EMEND for Injection 150 mg for intravenous administration contains 245.3 mg of fosaprepitant dimeglumine equivalent to 150 mg of fosaprepitant free acid and the following inactive ingredients: edetate disodium (18.8 mg), polysorbate 80 (75 mg), lactose anhydrous (375 mg), sodium hydroxide and/or hydrochloric acid (for pH adjustment). Fosaprepitant dimeglumine hereafter will be referred to as fosaprepitant.

12 CLINICAL PHARMACOLOGY

Fosaprepitant, a prodrug of aprepitant, when administered intravenously is rapidly converted to aprepitant, a substance P/neurokinin 1 (NK_1) receptor antagonist. Plasma concentrations of fosaprepitant are below the limits of quantification (10 ng/mL) within 30 minutes of the completion of infusion *[see*

Clinical Pharmacology (12.3)]. Upon conversion of 188 mg of fosaprepitant dimeglumine (equivalent to 115 mg fosaprepitant free acid) to aprepitant, 18.3 mg of phosphoric acid and 73 mg of meglumine are liberated. Upon conversion of 245.3 mg of fosaprepitant dimeglumine (equivalent to 150 mg fosaprepitant free acid) to aprepitant, 23.9 mg of phosphoric acid and 95.3 mg of meglumine are liberated.

12.1 Mechanism of Action

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

Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK_1) receptors. Aprepitant has little or no affinity for serotonin ($5\text{-}HT_3$), 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

NK_1 Receptor Occupancy

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

Cardiac Electrophysiology

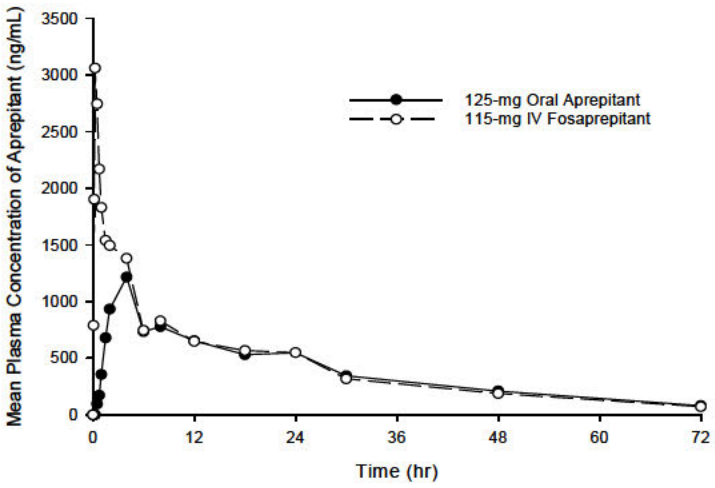
In a randomized, double-blind, positive-controlled, thorough QTc study, a single 200-mg dose of fosaprepitant had no effect on the QTc interval.

12.3 Pharmacokinetics

Aprepitant after Fosaprepitant Administration

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

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



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

Distribution

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

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

Metabolism

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

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

Excretion

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

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

Special Populations

Gender

Following oral administration of a single 125-mg dose of aprepitant, no difference in AUC_{0-24hr} was observed between males and females. The C_{max} for aprepitant is 16% higher in females as compared

with males. The half-life of aprepitant is 25% lower in females as compared with males and T_{max} occurs at approximately the same time. These differences are not considered clinically meaningful. No dosage adjustment is necessary based on gender.

Geriatric

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

Pediatric

Fosaprepitant has not been evaluated in patients below 18 years of age.

Race

Following oral administration of a single 125-mg dose of aprepitant, the $AUC_{0\text{-}24hr}$ is approximately 25% and 29% higher in Hispanics as compared with Whites and Blacks, respectively. The C_{max} is 22% and 31% higher in Hispanics as compared with Whites and Blacks, respectively. These differences are not considered clinically meaningful. There was no difference in $AUC_{0\text{-}24hr}$ or C_{max} between Whites and Blacks. No dosage adjustment is necessary based on race.

Hepatic Insufficiency

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

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

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

Renal Insufficiency

A single 240-mg dose of oral aprepitant was administered to patients with severe renal impairment (CrCl<30 mL/min) 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. In patients with ESRD undergoing hemodialysis, the $AUC_{0\text{-}\infty}$ of total aprepitant decreased by 42% and C_{max} decreased by 32%. Due to modest decreases in protein binding of aprepitant in patients with renal disease, the AUC of pharmacologically active unbound drug was not significantly affected in patients with renal impairment compared with healthy subjects. Hemodialysis conducted 4 or 48 hours after dosing had no significant effect on the pharmacokinetics of aprepitant; less than 0.2% of the dose was recovered in the dialysate.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

follicular cell adenomas and carcinomas in male rats. In female rats, it produced hepatocellular adenomas at 5 to 1000 mg/kg twice daily and hepatocellular carcinomas and thyroid follicular cell adenomas at 125 to 1000 mg/kg twice daily. In the mouse carcinogenicity studies, the animals were treated with oral doses ranging from 2.5 to 2000 mg/kg/day. The highest dose produced a systemic exposure of about 2.8 to 3.6 times the human exposure at the recommended dose. Treatment with aprepitant produced skin fibrosarcomas at 125 and 500 mg/kg/day doses in male mice. Carcinogenicity studies were not conducted with fosaprepitant.

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

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

14 CLINICAL STUDIES

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

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

14.1 Highly Emetogenic Chemotherapy (HEC)

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

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

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

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

Table 11
Treatment Regimens
Highly Emetogenic Chemotherapy Trials*

	Day 1	Day 2	Day 3	Day 4
CINV Aprepitant Regimen				
Aprepitant	125 mg orally	80 mg orally	80 mg orally	none
Dexamethasone	12 mg orally	8 mg orally	8 mg orally	8 mg orally
Ondansetron	32 mg intravenously	none	none	none
CINV Standard Therapy				
Dexamethasone	20 mg orally	8 mg orally twice daily	8 mg orally twice daily	8 mg orally twice daily
Ondansetron	32 mg intravenously	none	none	none

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

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

The antiemetic activity of oral aprepitant was evaluated during the acute phase (0 to 24 hours post-cisplatin treatment), the delayed phase (25 to 120 hours post-cisplatin treatment) and overall (0 to 120 hours post-cisplatin treatment) in Cycle 1. Efficacy was based on evaluation of the following endpoints in which emetic episodes included vomiting, retching, or dry heaves:

Primary endpoint:

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

Other prespecified endpoints:

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

A summary of the key study results from each individual study analysis is shown in Table 12 and in Table 13.

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

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

†N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.
‡Overall: 0 to 120 hours post-cisplatin treatment.
§Acute phase: 0 to 24 hours post-cisplatin treatment.
‖Delayed phase: 25 to 120 hours post-cisplatin treatment.
*Not statistically significant when adjusted for multiple comparisons.
**Not statistically significant.
Visual analogue scale (VAS) score range: 0 mm = no nausea; 100 mm = nausea as bad as it could be.

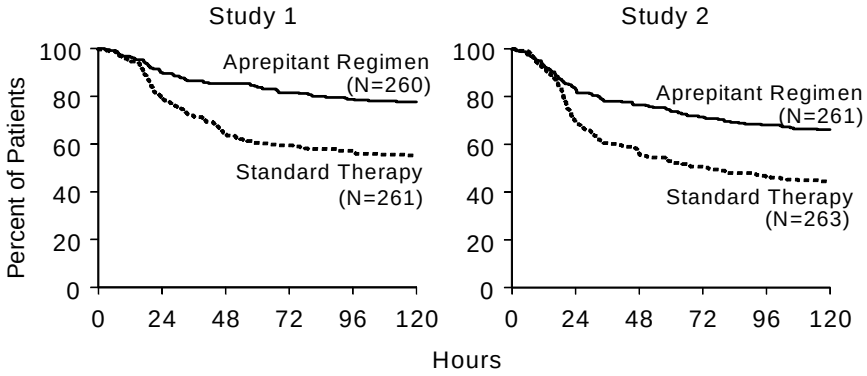
Table 13 Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 2 — Cycle 1			
ENDPOINTS	**Aprepitant Regimen (N = 261)† %**	**Standard Therapy (N = 263)† %**	**p-Value**
PRIMARY ENDPOINT			
Complete Response			
Overall‡	63	43	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase§	83	68	<0.001
Delayed phase‖	68	47	<0.001
Complete Protection			
Overall	56	41	<0.001
Acute phase	80	65	<0.001
Delayed phase	61	44	<0.001
No Emesis			
Overall	66	44	<0.001
Acute phase	84	69	<0.001
Delayed phase	72	48	<0.001
No Nausea			
Overall	49	39	NS*
Delayed phase	53	40	NS*
No Significant Nausea			
Overall	71	64	NS**
Delayed phase	73	65	NS**

†N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.
‡Overall: 0 to 120 hours post-cisplatin treatment.
§Acute phase: 0 to 24 hours post-cisplatin treatment.
‖Delayed phase: 25 to 120 hours post-cisplatin treatment.
*Not statistically significant when adjusted for multiple comparisons.
**Not statistically significant.
Visual analogue scale (VAS) score range: 0 mm = no nausea; 100 mm = nausea as bad as it could be.

In both studies, a statistically significantly higher proportion of patients (both p<0.001) receiving the aprepitant regimen in Cycle 1 had a complete response in the overall phase (primary endpoint), compared with patients receiving standard therapy. A statistically significant difference in complete response in favor of the aprepitant regimen was also observed when the acute phase and the delayed phase were analyzed separately.

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

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

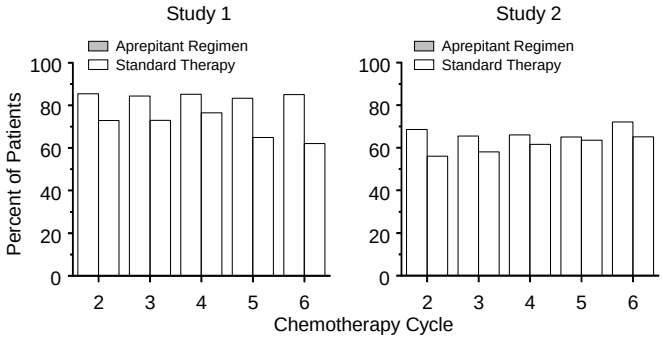


p-Value <0.001 based on a log rank test for Study 1 and Study 2; nominal p-values not adjusted for multiplicity.

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

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

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



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

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

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

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

with a mean age of 56 years. Other concomitant chemotherapy agents were administered similar to those in prior HEC studies described above.

Table 14
Treatment Regimens
Highly Emetogenic Chemotherapy Trial*

	Day 1	Day 2	Day 3	Day 4
CINV Fosaprepitant Regimen				
Fosaprepitant	150 mg intravenously	none	none	none
Dexamethasone	12 mg orally	8 mg orally	8 mg orally twice daily	8 mg orally twice daily
Ondansetron	32 mg intravenously	none	none	none
CINV Aprepitant Regimen				
Aprepitant	125 mg orally	80 mg orally	80 mg orally	none
Dexamethasone	12 mg orally	8 mg orally	8 mg orally	8 mg orally
Ondansetron	32 mg intravenously	none	none	none

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

The efficacy of fosaprepitant 150 mg was evaluated based on the primary and secondary endpoints listed in Table 15 below and was shown to be non-inferior to that of the 3-day oral aprepitant regimen with regard to complete response in each of the evaluated phases. The pre-specified non-inferiority margin for complete response in the overall phase was 7%. The pre-specified non-inferiority margin for complete response in the delayed phase was 7.3%. The pre-specified non-inferiority margin for no vomiting in the overall phase was 8.2%.

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

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

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

14.2 Moderately Emetogenic Chemotherapy (MEC)

In a multicenter, randomized, double-blind, parallel-group, clinical study in breast cancer patients, the aprepitant regimen (see Table 16) was compared with a standard of care therapy in patients receiving a

moderately emetogenic chemotherapy regimen that included cyclophosphamide 750-1500 mg/m^2; or cyclophosphamide 500-1500 mg/m^2 and doxorubicin (≤60 mg/m^2) or epirubicin (≤100 mg/m^2).

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

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

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

Table 16
Treatment Regimens
Moderately Emetogenic Chemotherapy Trial*

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

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

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

Primary endpoint:

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

Other prespecified endpoints:

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

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

Table 17 Percent of Patients Receiving Moderately Emetogenic Chemotherapy Responding by Treatment Group and Phase — Cycle 1			
ENDPOINTS	Aprepitant Regimen (N = 433)[†] %	Standard Therapy (N = 424)[†] %	p-Value
PRIMARY ENDPOINT[‡]			
Complete Response	51	42	0.015
OTHER PRESPECIFIED ENDPOINTS[‡]			
No Emesis	76	59	NS*
No Nausea	33	33	NS
No Significant Nausea	61	56	NS
No Rescue Therapy	59	56	NS
Complete Protection	43	37	NS

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

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

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

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

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

Of the 430 patients who were randomized to receive the aprepitant regimen, 76% were women and 24% were men. The distribution by race was 67% White, 6% Black or African American, 11% Asian, and 12% multiracial. Classified by ethnicity, 36% were Hispanic and 64% were non-Hispanic. The aprepitant-treated patients in this clinical study ranged from 22 to 85 years of age, with a mean age of 57 years; approximately 59% of the patients were 55 years or older with 32 patients being over 74 years. Patients receiving the aprepitant regimen were receiving chemotherapy for a variety of tumor types including 50% with breast cancer, 21% with gastrointestinal cancers including colorectal cancer, 13% with lung cancer and 6% with gynecological cancers.

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

A summary of the key results from this study is shown in Table 18.

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

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

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

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

In a subgroup analysis by tumor type, a numerically higher proportion of patients receiving aprepitant were observed to have no vomiting and complete response compared to patients receiving standard therapy. For gender, the difference in complete response rates between the aprepitant and standard regimen groups was 14% in females (64.5% and 50.3%, respectively) and 4% in males (82.2% and 78.2%, respectively) during the overall phase. A similar difference for gender was observed for the no vomiting endpoint.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

NDC 0006-3884-32 1 vial per carton.

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

NDC 0006-3941-32 1 vial per carton.

Storage

Vials: Store at 2-8°C (36-46°F).

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

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling]

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

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

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

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

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

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

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

FDA-Approved Patient Labeling

Manufactured for:
Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ 08889, USA

Manufactured by:
DSM Pharmaceuticals, Inc., 5900 Martin Luther King Jr. Highway, Greenville, NC 27834, USA

9995306

U.S. Patent Nos.: 5,512,570; 5,691,336

Patient Information
EMEND® (EE mend)
(fosaprepitant dimeglumine)
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 to your doctor about your medical condition or your treatment.

What is EMEND for Injection?

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

EMEND for Injection is not used to treat nausea and vomiting that you already have.

EMEND for Injection should not be used continuously for a long time (chronic use).

It is not known if EMEND for Injection is safe and effective in children.

Who should not take EMEND for Injection?

Do not take EMEND for Injection if you:

- are taking any of the following medicines:
  - pimozide (ORAP®)
  - cisapride (PROPULSID®)

Taking EMEND for Injection with any of these medicines could cause serious or life-threatening problems.

- are allergic to any of the ingredients in EMEND for Injection. See the end of this leaflet for a list of all the ingredients in EMEND for Injection.

What should I tell my doctor before receiving EMEND for Injection?

Before you receive EMEND for Injection, tell your doctor 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 during treatment with EMEND for Injection and for up to 1 month after using EMEND for Injection to prevent pregnancy.

- are breastfeeding or plan to breastfeed. It is not known if EMEND for Injection passes into your milk and if it can harm your baby. You and your doctor should decide if you will take EMEND for Injection or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

EMEND for Injection may cause serious life-threatening reactions if used with certain medicines. See the section "Who should not take EMEND for Injection?".

EMEND for Injection may affect how other medicines work, and other medicines may affect how EMEND for Injection works. Ask your doctor or pharmacist before you take any new medicine. They can tell you if it is safe to take the medicine with EMEND for Injection.

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

How will I receive EMEND for Injection?

You will receive EMEND for Injection in one of two ways:

1. EMEND for Injection 150 mg given on Day 1 only.

- Day 1 (Day of chemotherapy): EMEND for Injection 150 mg will be given to you by infusion in your vein (intravenous) about 30 minutes before you start your chemotherapy treatment.

Or

2. EMEND for Injection 115 mg given along with capsules of EMEND.

- Day 1 (Day of chemotherapy): EMEND for Injection 115 mg will be given to you by infusion in your vein (intravenous) about 30 minutes before you start your chemotherapy treatment.
- You will get a prescription for two capsules of EMEND.
- Day 2 and Day 3 (the two days after chemotherapy): Take one 80-mg capsule of EMEND (white) by mouth, each morning for the 2 days after your chemotherapy treatment.

- If you take the blood thinner medicine warfarin sodium (COUMADIN®, JANTOVEN®), your doctor may do blood tests after you take EMEND 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 suddenly with EMEND for Injection and may be serious. Tell your doctor or nurse right away if you have flushing or redness of your face or skin, or trouble breathing during or soon after you receive EMEND for Injection.

  EMEND capsules can also cause allergic reactions. If you receive EMEND for Injection on Day 1, and then take EMEND capsules on Days 2 and 3, stop taking the EMEND capsules and call your doctor right away if you have any of these signs or symptoms of an allergic reaction:
  - hives
  - rash
  - itching
  - redness of the face or skin
  - trouble breathing or swallowing.

The most common side effects of EMEND for Injection include:

- hiccups
- weakness or tiredness
- changes in liver function blood test results. Your doctor will check you for this.
- headache

- constipation
- loss of appetite
- indigestion
- diarrhea
- belching

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 doctor if you get any infusion-site side effects.

Tell your doctor 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 doctor 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 EMEND for Injection

This Patient Information leaflet summarizes the most important information about EMEND for Injection. If you would like to know more information, talk with your doctor. You can ask your doctor 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 dimeglumine

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:
DSM Pharmaceuticals, Inc., 5900 Martin Luther King Jr. Highway, Greenville, NC 27834, USA

Issued November 2010

U.S. Patent Nos.: 5,512,570; 5,691,336

The brands listed in the above sections “Who should not take EMEND for Injection?” and “What should I tell my doctor before receiving 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.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022023/S-004

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA#	022023/S-004 (HEC) (b) (4)
Applicant Name	Merck & Co.
Date of Submission	Dated October 12, 2009 Received October 13, 2009
PDUFA Goal Date	August 13, 2010 (original) November 13, 2010 (due to PDUFA extension)
Proprietary Name / Established (USAN) Name	Emend/Fosaprepitant
Dosage Forms / Strength	Intravenous solution, 150 mg
Proposed Indication(s)	1) Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin (cisplatin $\geq$70 mg/m^2) (CINV-HEC) (b) (4)
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Tamara Johnson, MD/ Nancy Snow, MD
Biostatistical Review	Wen Jen Chen, PhD/Mike Welch, PhD
Pharmacology Toxicology Review	Sushanta Chakder, PhD
CMC Review	David Lewis/Hasmukh Patel, PhD
Microbiology	Steven E. Fong, Ph.D./Bryan Riley, Ph.D.
Clinical Pharmacology Review	Kristina Estes, PharmD/Sue-Chih Lee, PhD
DDMAC	Kathleen Klemm/Sheetal Patel/Lisa Hubbard/Robert Dean
CDTL Review	Nancy Snow, MD
OSE/DMEPA	Jibril Abdus-Samad, PharmD/Todd Bridges, RPh/ Kellie Taylor, PharmD, MPH
SEALD	Jeanne M. Delasko, RN, MS//Laurie Burke, RPh., MPH
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OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
CDTL=Cross-Discipline Team Leader
DRISK= Division of Risk Management

Division Director Review

1. Introduction

In this NDA supplement, the applicant proposes a new dosing regimen for fosaprepitant, a single dose regimen that does not require Day 2 and 3 oral doses, for the following indications:

- Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin (cisplatin ≥70 mg/m^2) (CINV-HEC)

[redacted] (b) (4)

A single noninferiority trial was submitted to support the efficacy and safety of the new dose regimen for [redacted] (b) (4) HEC. The active control arm was the aprepitant oral 3-day regimen approved for HEC. The trial only enrolled patients who were being treated with HEC. The primary endpoint was Complete Response in the overall phase. The secondary endpoints were Complete Response in the delayed phase and No Vomiting in the overall phase.

[redacted] (b) (4)

The HEC wording specifies "acute and delayed". (b) (4)

I concur with the CDTL's recommendation for an Approval action for the HEC indication for the new single dose fosaprepitant regimen. [redacted] (b) (4)

2. Background

Aprepitant is an oral antiemetic in the NK-1 inhibitor class. It was the first product approved in this class and was incorporated as part of standard-of-care guidelines by professional associations such as the Multinational Association of Supportive Cancer Care (MASCC), the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN). The labeled Dosage and Administration instructions for use in prevention of acute and delayed nausea and vomiting associated with MEC and HEC for the oral product (aprepitant) state that it should be administered daily for 3 days. The dose on the first day of the oral regimen (125 mg) is higher than on Day 2 and Day 3 (80 mg), and doses are the same for MEC and HEC. There is also an approved IV regimen, in which fosaprepitant 115 mgsubstitutes for the Day 1 oral aprepitant dose. The Days 2 and 3 oral doses continue unchanged in that regimen. The approved HEC and MEC regimens differ in that dexamethasone is administered only on Day 1 in MEC, and the 5HT3 antagonist ondansetron is administered orally (also on day 1 only) and at a lower dose in MEC. In HEC dexamethasone is administered on Days 1-4, and the Day 1 dose of ondansetron, which is higher than the dose used in MEC, is administered IV.

The 2003 approval of aprepitant was based on three trials. The subsequent approval of its intravenous pro-drug fosaprepitant in 2008 for the same two indications (HEC and MEC) was based on a phase 2 trial in CINV-HEC, and pharmacokinetic and bioequivalence studies. The approved fosaprepitant dose was 115 mg, and the product label stated that it was intended for use as a substitute for the Day 1 dose of aprepitant in the 3-Day regimen. The Days 2 and 3 oral aprepitant doses were still required, and the intravenous dose was not to be used as a substitute on those subsequent days.

The original HEC approval was based on a primary endpoint of Complete Response (no emetic episodes and no use of rescue medication) in the overall phase (0-120 hours) in two trials (each enrolled approximately 520 patients). Other prespecified endpoints were Complete response in the acute phase (0-24 hours) and delayed phase (24-120 hours). All evaluated periods were statistically significantly superior to the standard therapy control arm ($p < 0.001$ for each phase in each trial), and the indication is "Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin."

The original MEC approval was based on a single trial that enrolled patients (n = 857 total across arms) receiving chemotherapy for breast cancer (anthracyline chemotherapy). The primary endpoint was Complete response (no emetic episodes and no use of rescue medication) in the overall phase (0-120 hours). Complete Response in the acute and delayed phases were also prespecified endpoints. The aprepitant regimen was superior in the overall phase to standard therapy, although the incremental increase in Complete Response in the aprepitant arm (9%) of this larger trial was not as large as observed in the HEC trials (20% and 21%). Although the proportion of patients who had a Complete Response in each of the acute (0-24 hours) and delayed (24-120 hours) phases was higher in the aprepitant arm than the control arm of the MEC trial, after multiplicity adjustment the difference relative to standard therapy in each of the acute and delayed phases was not statistically significant. The labeled indication for MEC is: "Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy."

A supplement was submitted in 2009 in response to a PMC to provide additional data to support efficacy in men who were treated with MEC. (The previous MEC trial had enrolled women receiving chemotherapy for breast cancer.) The applicant submitted data from a MEC trial that enrolled 848 patients, of whom 24% were men. The analyses of efficacy by time period in that second trial found a statistically significant improvement of efficacy with the addition of Emend to the standard regimen in overall, acute (0-24 hours) and delayed (24-120 hours) phases. The incremental increase in Complete Response observed in the full analysis population in the aprepitant arm of this trial relative to placebo (14%) was numerically higher than that observed in the previous MEC trial (9%). The incremental increase in CR in the delayed phase relative to placebo in this second trial was 11%, and 8% for the acute phase.

(b) (4)

Although the Applicant pre-specified No Vomiting in the Overall phase as the primary endpoint, the endpoint of major interest to FDA was Complete Response in the overall phase. The Applicant specified Complete Response as the key secondary endpoint and prespecified in the statistical analysis plan a method for multiplicity adjustment to evaluate other secondary endpoints that were grouped in families. The Statistical Review of NDA 21-549/SE1-008 states that "a sequential procedure was proposed by the applicant to adjust the multiplicity issues induced by the multiple efficacy comparisons (assessed by the primary, key secondary endpoints, four groups of other secondary endpoints, and exploratory endpoint) such that the overall type I error rate of 5% was controlled in the strong sense. The sequential multiplicity adjustment method suggest that subsequent groups of efficacy endpoints were not tested unless the prior groups' testing revealed at least one statistically significant finding. For family with more than one endpoint, Hochberg procedure was used to control the Type I error at the 0.05 level. ……Since for each of the five families (primary, key secondary, and the three families of other secondary endpoints – Group 1 to Group 3), all endpoints tested were shown significant results, it is valid to carry the full alpha level of 0.05 to the next family." The Statistical reviewer concluded that statistical significance was not shown in the Group 4 family of secondary endpoints and the Exploratory endpoint. The summary data are presented in the table below, which is reproduced here from the Statistical Review of NDA 21-540/SE1-008 (Table 3.1.5.1 in that review, and reproduced there from sponsor table). A statistically significant difference, favoring the Emend regimen, was observed for Complete Response in the overall, acute and delayed phases.

Table 3.1.5.1 (Applicant's) Summary of Statistical Significance by Hypothesis

Hypothesis Level and Endpoint	Actual P-Value†	Hochberg P-Value‡	Statistical Significance§
Primary			
No Vomiting – overall phase	<0.0001	--	S**
Key Secondary			
Complete Response – overall phase	0.0003	--	S**
Other Secondary – Group 1			
No Vomiting – delayed phase	0.0005	<0.05	S
No Vomiting – acute phase	0.0002		S
Other Secondary – Group 2			
No Impact on Daily Life (FLIE total score >108) – overall phase	0.035	<0.05	S
Time to First Vomiting Episode – overall phase	<0.0001		S
Other Secondary – Group 3			
Complete Response – delayed phase	0.0042	<0.05	S
Complete Response – acute phase	0.0005		S
Other Secondary – Group 4			
No Use of Rescue Therapy – delayed phase	0.0922	<0.05	NS
No Use of Rescue Therapy – overall phase	0.0427	<0.025	NS
No Use of Rescue Therapy – acute phase	0.0179	<0.017	NS
No Vomiting and No Significant Nausea (VAS <25 mm) – overall phase	0.0011	<0.013	S
Exploratory			
No Significant Nausea (VAS <25 mm) – overall phase	0.0383	<0.05	S

** p<0.01 when compared with Standard Regimen.

† Aprepitant Regimen versus Standard Regimen based on a logistic regression model with terms for treatment group, region, and gender. Time to first vomiting episode based on the log rank statistic.

‡ Hochberg procedure p-value required for significance based on 0.05/i, where 'i' is the rank of the ith p-value in that group.

§ For the primary and key secondary endpoints, significance test was based on the logistic regression analysis. Significance (S, NS) for the other secondary and exploratory endpoint tests was determined by Hochberg's multiple comparison procedure, using the p-values from the logistic regression model.

S = significant, NS = non-significant.

Acute Phase: 0 to 24 hours following initiation of chemotherapy.

Delayed Phase: 25 to 120 hours following initiation of chemotherapy.

Overall Phase: 0 to 120 hours following initiation of chemotherapy.

Source: Applicant's Table 11-2 "Summary of Statistical Significance by Hypothesis" presented in Study P130.

In the current sNDA, the applicant proposes a new higher single dose of fosaprepitant, 150 mg, which is intended to eliminate the need for the subsequent aprepitant doses (Days 2 and 3). As stated above, the previously approved Emend regimens are administered in combination with other antiemetics, ondansetron and dexamethasone. The doses of dexamethasone and ondansetron differ by clinical setting - HEC vs. MEC. Dexamethasone and ondansetron are also part of the newly proposed single dose fosaprepitant 150 mg regimen. The dexamethasone and ondansetron doses are the same as the corresponding doses in the respective MEC and HEC "all oral" aprepitant regimens, with the exception of the dexamethasone in the HEC regimen. In the new single dose regimen the Days 3 and 4 doses are doubled, to 8 mg twice daily. The evidence to support that the Days 3 and 4 dexamethasone dose doubling in the new single dose regimen produces the same Days 3 and 4 dexamethasone exposures as the currently approved HEC regimen (secondary to aprepitant/dexamethasone drug interactions) is discussed later in this review, in Section 5 Clinical Pharmacology. Establishing the comparability of the dexamethasone exposure between the two HEC regimens is important for interpreting the results of the noninferiority study submitted in support of this application, since more than one thing changed in the new regimen (a new dose of fosaprepitant and a new Day 3 and 4 dexamethasone dose).

The following table summarizes the dexamethasone and ondansetron doses and administration schedules in the currently approved regimens for HEC and MEC, in addition to the doses proposed for the new single dose fosaprepitant regimen.

Table 2: Summary Comparison of Dexamethasone and Ondansetron Doses and Schedule in the Approved Emend HEC and MEC Regimens and the New Fosaprepitant Single Dose Regimen

Currently Approved Regimens		
	Dexamethasone	**Ondansetron**
HEC Aprepitant All Oral Regimen	Day 1 = 12 mg Day 2-4 = **8 mg**	Day 1 = 32 mg IV
MEC Aprepitant All Oral Regimen	Day 1 = 12 mg only	Day 1 = 2 x 8 mg orally
HEC and MEC Fosaprep Day 1 + Aprepitant Day 2 and 3	Same as All Oral Regimen	Same as All Oral Regimen
Proposed New Single Dose Regimen		
	Dexamethasone	**Ondansetron**
HEC Fosaprep 150 mg single Dose Regimen	Day 1 = 12 mg Day 2 = 8 mg Day 3-4 = **8 mg twice daily**	Same as All Oral Regimen

(b) (4)

(b) (4)

In a January 11, 2007 Type C meeting, the applicant asked the division the following general question, "Does the Agency concur with the concept and that one single dose IV study is adequate to support the registration of an IV formulation as an alternative to EMEND 3-day regimen, with the supporting data from the MK-0517 Phase II studies and data from pivotal studies with approved EMEND? Does the Agency concur with the concept and that one single dose IV study is adequate to support the registration of an IV formulation as an alternative to EMEND 3-day regimen and the proposed study design, dose and non-inferiority margin?"

(b) (4)

" Typically applicants need to conduct two adequate and well controlled phase 3 trials to demonstrate confirmation of positive trial results, in the sense that one study shows a significant efficacy result and the other study confirms the significant result. Accordingly, in order to provide substantial evidence to support the study drug for use in this indication, two well-controlled trials are recommended. Please consider the following: You stated that receptor occupancy of 80-90% is needed to demonstrate the antiemetic effect. However, the

approved dosing regimen for oral aprepitant has trough concentrations much higher than (≈ 7 times) the concentration needed for 90% receptor occupancy. Compared to the approved oral regimen, the proposed single IV administration of fosaprepitant 150 mg over 15 minutes is associated with lower concentrations from approximately 30 hours onwards. It is unclear how this may affect the efficacy at your proposed dose."

(b) (4)

In this meeting the division referred to the January 11, 2007 meeting minutes and recommended that the applicant "conduct two, well-controlled phase 3 trials in order to provide substantial evidence to support the study drug fosaprepitant IV regimen for use in the proposed indication." In addition, the Division expressed concerns that "Increasing the fosaprepitant dose level from 115 to 150 mg may not improve the efficacy against CINV. This is because previous phase 2 studies showed a plateau of efficacy of 125 mg aprepitant in the treatment of CINV. The dose level of 125 mg aprepitant is equivalent to 115 mg fosaprepitant."

The noninferiority trial submitted in support of this application was subject to a SPA. In response to the SPA, the DGP issued a letter on November 29, 2007. (b) (4)

Again, the Division responded that it did not concur that the single trial would stand alone. See below, which is reproduced from the letter:

Sponsor Question 1
MRL believes that a single, large, randomized, non-inferiority clinical study with a margin of 7 percentage points (half the lower bound of the 95% CI for the treatment effect that was observed in previous studies with aprepitant) as recommended by the Agency is sufficient to demonstrate that the safety and efficacy of a single IV dose (150 mg) of fosaprepitant given on Day 1 is equivalent to the safety and efficacy of the approved EMEND™ regimen (a three day oral regimen with a single 125-mg dose given on Day 1 followed by 80-mg dose each on Days 2 and 3). MRL believes that data from this study, in conjunction with the safety and efficacy data derived from Phase II clinical trials of MK-0517 (incorporated in the original NDA for EMEND™ for Injection [22,023]), and the efficacy and safety data from the pivotal studies in CINV patients using the approved EMEND™ oral capsule, will be adequate evidence for the efficacy and safety of MK-0517 to support registration of a 150 mg IV dose of MK-0517 as an alternative to the EMEND™ 3-day regimen in CINV patients. Does the Agency concur?

FDA Response
We do not concur at this time. Please refer to our clinical and statistical comments regarding this issue from our Type C meeting held on April 19, 2007. The extent to which the NDA 22023 submission will provide any supportive efficacy data for the fosaprepitant I.V. regimen planned in this IND submission will be determined during the review process. The level of evidence necessary to support the efficacy of the proposed fosaprepitant I.V. regimen will mainly be judged from the results of your single phase 3 study. This study should be of high quality with substantial demonstration of efficacy; we expect the study to show results that are internally consistent among different endpoints and subgroups; and show clear clinical benefit

as recommended in the Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998.

3. CMC

The applicant proposes a new 150 mg strength, (b) (4) The microbiology reviewer identified no issues related to sterility assurance. The endotoxin specification for the new 150 mg dose (b) (4) I concur with the CMC reviewer that the NDA has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product. The manufacturing facilities were approved in the original NDA 22-023 and did not need to be re-inspected.

4. Nonclinical Pharmacology/Toxicology

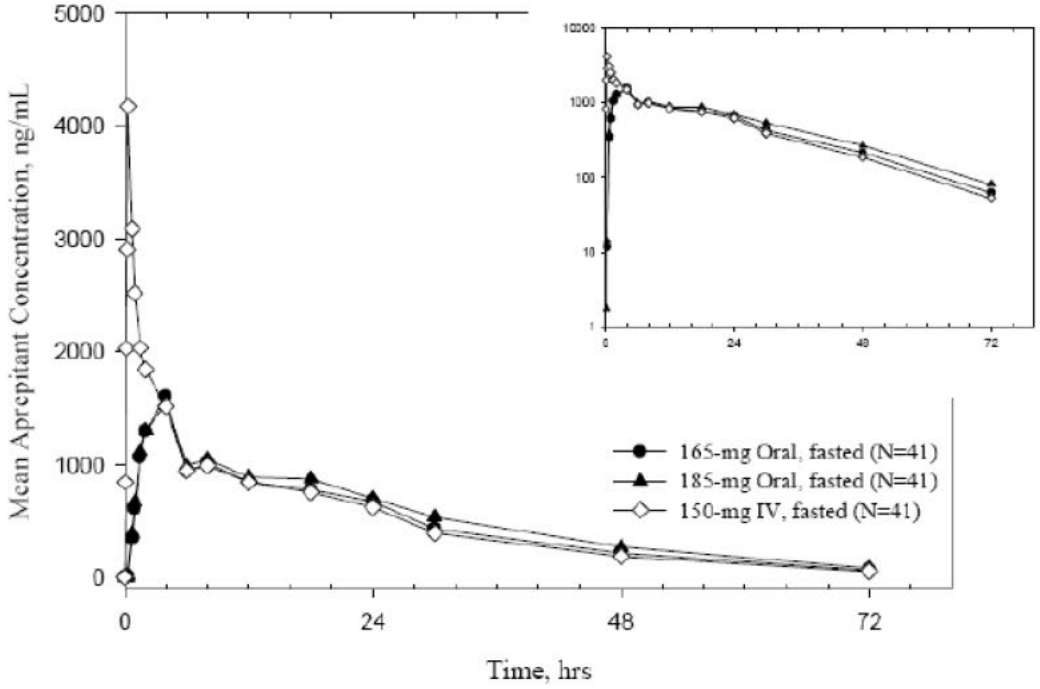
There was one new nonclinical study report in this submission. The applicant evaluated local tolerability of fosaprepitant for injection (1 mg/ml) following single intravenous, intramuscular, paravenous and subcutaneous administration in rabbits. Histomorphologic changes included slight to moderate acute inflammation and slight to moderate hemorrhage in the subcutis. Intramuscular injection sites had changes of focal skeletal muscle necrosis (slight to moderate) with mineralization bordered by subacute inflammation. The Pharmacology reviewer recommended approval of this NDA. His labeling recommendations were incorporated in label negotiations.

5. Clinical Pharmacology

Fosaprepitant is rapidly converted to aprepitant upon infusion. The applicant studied the PK of the new fosaprepitant 150 mg intravenous dose in a bioequivalence study in 41 healthy volunteers. Fosaprepitant 150 mg was compared to two dose levels of oral aprepitant. The infusion rate in the bioequivalence study was 20 minutes. The infusion rate in the clinical efficacy trial was 20-30 minutes. The infusion rate in a drug interaction study conducted in support of this application was 30 minutes. The Clinical Pharmacology review found the PK data and the instructions to infuse fosaprepitant 150 mg over 20-30 minutes acceptable.

The mean aprepitant plasma concentrations over time are described graphically in the figure below, which is reproduced from the Clinical Pharmacology Review (Section 2.2.3). The curve for the 150 mg IV product is marked with open diamonds.

Figure 1



Pharmacokinetic data were critical in considering whether the noninferiority study design appropriately isolated the effect of the change of the fosaprepitant/aprepitant regimen, in light of known pharmacokinetic interactions between aprepitant and dexamethasone. (b) (4) [redacted] Each of those issues is discussed below.

Dexamethasone Drug Interaction: Aprepitant is a CYP3A4 inhibitor known to increase exposure of dexamethasone 1.6-fold in the approved 3-day regimen. The new single day regimen necessitated re-evaluation of the appropriate dose of the dexamethasone in the combination. In the currently approved HEC regimen, dexamethasone is administered for 4 days at doses of 12 mg on Day 1 and 8 mg on Days 2-4. Elimination of the oral aprepitant doses on Days 2 and 3 of the new regimen has the potential of modifying dexamethasone exposure in the new regimen.

The Clinical Pharmacology reviewer concluded that there were adequate drug-drug interaction data with the new single day IV fosaprepitant dose (with no subsequent Day 2 and 3 aprepitant) to support unchanged dexamethasone doses from the currently labeled regimen's Days 1 and 2, and doubling of the Days 3 and 4 dexamethasone doses. With the new single dose regimen, the Days 3 and 4 aprepitant exposure had declined to a level that made it unnecessary to continue the halved dose of dexamethasone in the currently approved regimen.

She concluded that the doubled dexamethasone dose on Days 3 and 4 of the new single dose regimen resulted in comparable dexamethasone exposure to the previously approved regimen.

The drug interaction study examining the impact of a single 150 mg IV dose of fosaprepitant on the PK of dexamethasone was a randomized, open-label, 2-part, 2-period, crossover study. In Part 1, subjects (n= 23) received two different dexamethasone treatments (A = single 8 mg dose on Day 1, 2 and 3; B = single 8 mg dose on Day 1, 2 and 3, co-administered with a single fosaprepitant 150 mg dose on Day 1) in two periods. In Part 2 midazolam interactions were studied. Eleven subjects completed Part 1. The dexamethasone PK data are summarized in the table below, which is reproduced from the Clinical Pharmacology review:

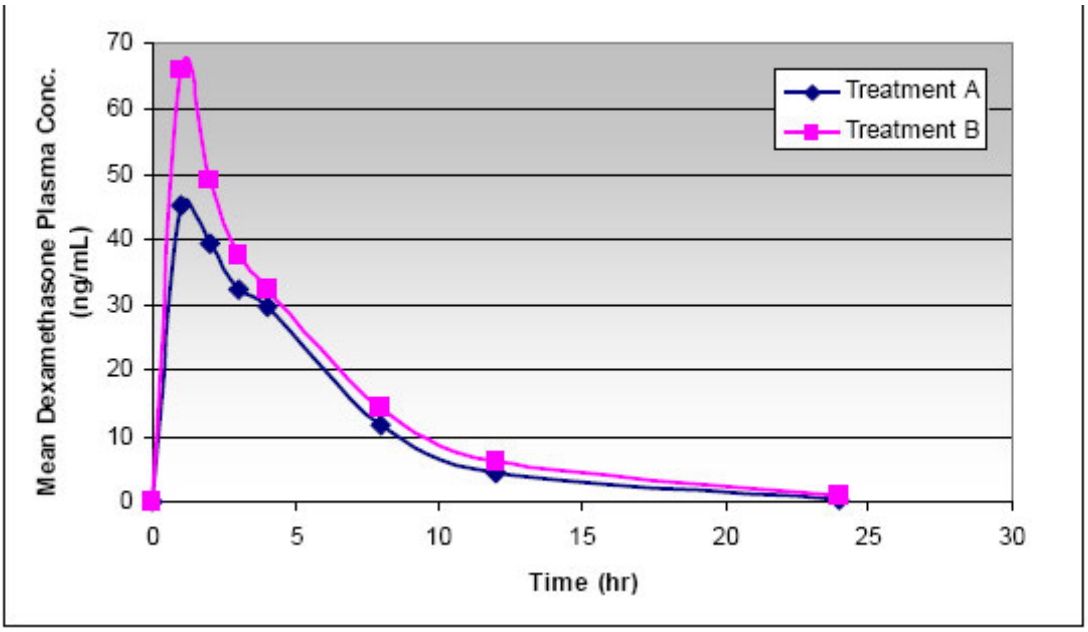
Table 3: Dexamethasone/Fosaprepitant Drug Interaction Pharmacokinetic Summary Data

DEX PK Parameter	Day	DEX + FOS		DEX alone		DEX + FOS / DEX	
		Geo. Mean	90% CI	Geo. Mean	90% CI	GM Ratio	90% CI for GMR
AUC0-24 (ng*h/mL)	1	732.6	(620, 866)	363.8	(308, 430)	2.01	(1.84, 2.20)
	2	528.2	(447, 624)	283.3	(240, 335)	1.86	(1.71, 2.03)
	3	298.0	(252, 352)	252.5	(214, 298)	1.18	(1.08, 1.29)
Cmax (ng/mL)	1	87.53	(75, 101)	70.36	(61, 81)	1.24	(1.09, 1.42)
	2	82.28	(71, 95)	62.99	(55, 73)	1.31	(1.14, 1.49)
	3	67.11	(58, 77)	57.01	(49, 66)	1.18	(1.03, 1.34)
T½ (hr)	1	5.7	1.3	3.6	0.7	-	-
	2	4.0	0.9	3.0	0.5	-	-
	3	3.3	0.7	3.1	0.6	-	-

The Days 1 and 2 dexamethasone AUC doubled when fosaprepitant was administered on Day 1. On Day 3, the AUC was numerically higher, but the 90% confidence intervals overlapped. The Days 1 and 2 dexamethasone Cmax increased by 24-31% when fosaprepitant was administered. The Day 3 Cmax was numerically higher, however, the 90% confidence intervals overlapped. The Clinical Pharmacology reviewer concluded that the increase in dexamethasone exposure after a single 150 mg dose of fosaprepitant did not exceed the increase in dexamethasone exposure associated with the 3-day oral aprepitant regimen. She also determined that these data support doubling the dexamethasone dose on Days 3 and 4 in the new regimen.

Treatment A in the figure below, which is reproduced from the Clinical Pharmacology review, is the dexamethasone concentration curve for dexamethasone 8 mg administered alone. Treatment B is dexamethasone 8 mg administered on Day 3 after fosaprepitant administration 2 days prior. On Day 3, the dexamethasone concentrations post fosaprepitant two days prior are slightly elevated relative to no prior fosaprepitant, but the difference diminishes over the course of Day 3. The graphic display of the Day 3 PK data suggest that Cmax is approximately 40% greater in Treatment B, after prior exposure to fosaprepitant on Day 1;

however, the figure reflects data for mean concentrations at each time point, and patients display variability in time to Cmax. For this reason, the summary table above is the best representation of the relative mean Cmax.



The reviewers also considered whether the doubled dexamethasone dose on Day 4 of the new regimen could be supported, since no aprepitant is administered concomitantly with dexamethasone on Day 4 of the currently approved regimen. The question was, "Is and how are dexamethasone pharmacokinetics on Day 4 impacted by the Day 3 aprepitant dose administered in the currently approved 3-day regimen for HEC?" The following figure from the Clinical Pharmacology review of the original NDA submission shows the pharmacokinetics of oral aprepitant over time after administration of 125 mg on Day 1, followed on Days 2 and 3 by 80 mg daily. There are detectable aprepitant concentrations on Day 4 in the range of 750 ng/mL at 24 hours post the Day 3 oral aprepitant dose and 400 ng/mL at 36 hours post the Day 3 oral aprepitant dose.

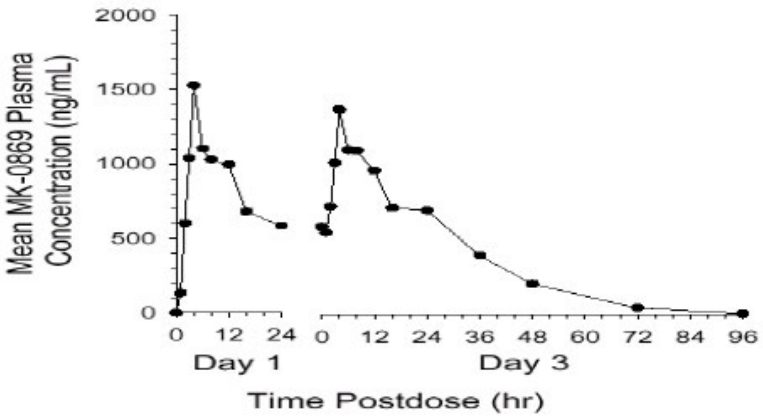


Figure 2. Mean Plasma Concentration (ng/mL) versus Time Profiles of MK-0869 (aprepitant) Following the Days 1 and 3 Doses of a 125-mg/80-mg/80-mg 3-Day Aprepitant Dosing Regimen.

The Clinical Pharmacology reviewer noted in her addendum review that although there are no data on plasma dexamethasone exposures on Day 4 of the 3 day aprepitant regimen, that in light of the aprepitant concentrations on Day 4, one would expect the dexamethasone exposure on Day 4 to "remain approximately 2-fold higher than baseline without dosage adjustment." She notes that at 24 hours post the Day 3 dose of oral aprepitant, that PK studies have documented aprepitant concentrations of 702-1007 ng/ml, which are similar to levels documented 24 hours after a single IV 150 mg fosaprepitant dose (range =621-713 ng/ml).

(b) (4)

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6. Clinical Microbiology

Not applicable.

7. Clinical-Efficacy

The major phase 3 efficacy trial submitted to support this application (P017L1) was conducted in the setting of HEC. This multicenter, randomized, double-blind noninferiority trial enrolled 2322 patients who were to be treated with cisplatin-based (≥70 mg/m^2) HEC. The majority were male (n=1470, 63%). The trial arms appeared balanced for demographic features and risk factors for chemotherapy induced nausea and vomiting. The primary endpoint was proportion of patients with Complete Response over 120 hours (overall phase). Complete Response was defined as no vomiting and no use of rescue medications. There were two secondary endpoints: 1) proportion of patients with complete response in the delayed phase, and 2) proportion of patients with no vomiting in the overall phase. The two regimens were:

	Fosaprepitant/Aprepitant	Ondansetron	Dexamethasone
Active Control (approved and labeled)	**Day 1 = Aprepitant 125 mg** **Day 2 = Aprepitant 80 mg** **Day 3 = Aprepitant 80 mg**	Day 1 = 32 mg IV	Day 1 = 12 mg Day 2 = 8 mg **Day 3 = 8 mg** **Day 4 = 8 mg**
New Single Dose Regimen	**Day 1 = Fosaprepitant 150 mg**	Day 1 = 32 mg IV	Day 1 = 12 mg Day 2 = 8 mg **Day 3 = 16 mg** **Day 4 = 16 mg**

The new single dose regimen of fosaprepitant 150 mg included not only an altered fosaprepitant/aprepitant dose and administration schedule, but a different dexamethasone dose regimen. Please see the Section 5 Clinical Pharmacology above for the justification for these differences in dexamethasone dose between arms. The Clinical Pharmacology reviewer concluded that pharmacokinetic data submitted in this application and prior applications indicate that the dexamethasone exposures in the two regimens are comparable. The Clinical Pharmacology reviewer acknowledged that there is an 18% higher Cmax and AUC on Day 3 with the new proposed regimen relative to the previously approved regimen, but she did not believe that that incremental difference in exposure would be clinically significant.

The applicant did not include a multiplicity adjustment for the primary efficacy analysis (Complete Response Overall Phase, 0-120 hours), since there was only one primary efficacy endpoint. The two secondary efficacy analyses (Complete Response in the delayed phase and No Vomiting in the overall phase) were to be conducted only after the primary efficacy analysis was found to be significant. Hochberg's Procedure was used to preserve the overall Type I error rate at 0.05 for the secondary efficacy analyses, with the delayed phase Complete Response tested first. The applicant presented efficacy results for both the full analysis set (FAS) population and the per protocol population.

The prespecified noninferiority margin for the primary efficacy analysis was a lower bound of the 95% CI for the difference (fosaprepitant-aprepitant) of ≥ 7%. The Applicant's efficacy analysis results for the FAS population are summarized in the table below, which is accepted by the FDA Statistical review. For the primary efficacy analysis, the lower bound of the 95% CI for the difference fell within (was higher than) the -7% margin, and the applicant concluded that the single dose fosaprepitant 150 mg regimen was noninferior to the 3 day oral aprepitant regimen in the setting of HEC. Complete response (CR) in the delayed phase, a major prespecified secondary endpoint, also fell within the prespecified noninferiority margin for that endpoint, -7.3%. The Statistical reviewer reanalyzed the data utilizing a different methodology and was able to replicate the results reported by the applicant.

Hypothesis Level and Endpoint	Lower Bound Needed For Non-inferiority	Actual Lower Bound	Actual P-Value†	Conclusion
Primary				
Complete Response – overall phase	>-7 percentage points	-4.1 percentage points	--	Non-inferior
Secondary				
No Vomiting – overall phase	>-8.2 percentage points	-5.3 percentage points	0.0002	Non-inferior
Complete Response – delayed phase	>-7.3 percentage points	-3.5 percentage points	0.00003	Non-inferior
† P-value associated with the 95% confidence interval for the difference (fosaprepitant – aprepitant) in response rates.				

The proportions of patients in each arm that achieved CR in the overall, acute, and delayed phases (FAS population) are summarized in the table below, which is reproduced from the Statistical review:

Phase	Fosaprepitant Regimen (A)		Aprepitant Regimen (B)		Difference(A-B)
	n/m	% (95% CI)	n/m	% (95% CI)	% (95% CI)†
Overall Phase	795/1106	71.9 (69.1, 74.5)	820/1134	72.3 (69.6, 74.9)	-0.4 (-4.1, 3.3)
Acute Phase	963/1082	89.0 (87.0, 90.8)	974/1107	88.0 (85.9, 89.8)	1.1 (-1.6, 3.8)
Delayed Phase	822/1106	74.3 (71.6, 76.9)	841/1133	74.2 (71.6, 76.8)	0.1 (-3.5, 3.7)

† The difference and the confidence interval (CI) for the difference 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 phase = 0 to 120 hours post-initiation of cisplatin chemotherapy.

Acute phase = 0 to 24 hours post-initiation of cisplatin chemotherapy.

Delayed phase = 25 to 120 hours post-initiation of cisplatin chemotherapy.

n/m = Number of patients with Complete response/number of patients included in the analysis.

After conducting exploratory analyses, the Statistical reviewer expressed concern that the observed efficacy did not appear consistent across countries. He was particularly concerned that the efficacy associated with the oral aprepitant regimen in the US was numerically higher than with the single dose IV regimen. The US patients only accounted for a small percentage of the total study population (2.6%), and the numerically higher results in the oral aprepitant arm in the US did not substantially influence the overall outcome of the trial. These analyses are reproduced from his review below:

US (2.6% of total study population=58/2240)

ENDPOINT	TREATMENT GROUPS	
	Fosaprepitant Regimen N= **27**	Aprepitant Regimen N = **31**
Complete Response, n (% = n/N) Therapeutic Gain (TG), %‡ 95.0% two-sided CI for TG†	15 (56.0%)	22 (71.0%) -15.0% (-0.4, 0.09)

Non-US (97.4% of total study population=2182/2240)

ENDPOINT	TREATMENT GROUPS	
	Fosaprepitant Regimen N= **1079**	Aprepitant Regimen N = **1103**
Complete Response, n (% = n/N) Therapeutic Gain (TG), %‡ 95.0% two-sided CI for TG†	780 (72.3%)	798 (72.4%) -0.1% (-0.038, 0.037)

†: 95.0% two-sided confidence interval for the Therapeutic Gain without using stratum factor;
‡: Therapeutic Gain defined as the Complete response rate of Aprepitant minus that of Standard;

Based on these analyses, the Statistical reviewer expressed concern that the US population may not experience the same efficacy demonstrated in the overall study population; however, the very small sample size in this exploratory analysis (n=58), precludes drawing any conclusions. There is no clear physiological explanation for the US subgroup having a different outcome than other populations. The Statistical and Clinical reviewers conducted a number of analyses examining the observed efficacy by country, plotting the efficacy by number of patients studied in each country. The largest apparent discrepancies between arms occurred in the countries that enrolled the smallest number of patients, and the discrepancies were distributed evenly between favoring the aprepitant regimen and favoring the fosaprepitant regimen. They also explored data from previously submitted noninferiority trials of antiemetics and found a similar pattern, with the largest discrepancies between arms occurring in countries that enrolled the smallest number of patients.

In subgroup analyses of age, race and gender, the Statistical reviewer found that the efficacy comparison of fosaprepitant relative to aprepitant observed in patients ages > 65 years (N=455/2322), non-White (981/2322), and females (824/2322) fell outside the noninferiority margin of -7% (lower bound of the 95% CI for the difference), and he could not conclude that fosaprepitant was noninferior in those subgroups. However, the total number in each subgroup was relatively small compared to the total population. The summary tables for those analyses are reproduced below.

Age > 65 years

ENDPOINT	TREATMENT GROUPS	
	Fosaprepitant Regimen (F) N= 214	Aprepitant Regimen (A) N = 241
Complete Response, n (%) Two-sided 95% CI of F - A	162 (76%)	192 (80%) (-0.12, 0.040)

Non- White

ENDPOINT	TREATMENT GROUPS	
	Fosaprepitant Regimen (F) N= 484	Aprepitant Regimen (A) N = 497
Complete Response, n (%) Two-sided 95% CI of F - A	325 (67%)	347 (70%) (-0.08, 0.030)

Female

ENDPOINT	TREATMENT GROUPS	
	Fosaprepitant Regimen (F) N= 408	Aprepitant Regimen (A) N = 416
Complete Response, n (%) Two-sided 95% CI of F – A	258 (63%)	265 (64%) (-0.0704, 0.0611)

The Clinical reviewer explored the US subgroup for clinical characteristics that might explain the discrepant outcomes from the ex-US subgroup and found no definitive explanation.

	Fosaprepitant Regimen		Aprepitant Regimen		Total	
	n	(%)	n	(%)	n	(%)
Patients in population EX-US	**1,105**		**1,130**		**2,235**	
Patients in population US	**32**		**35**		**67**	
		Gender EX-US				
Male	701	(63.4)	721	(63.8)	1,422	(63.6)
Female	404	(36.6)	409	(36.2)	813	(36.4)
		Gender US				
Male	16	(50.0)	22	(62.9)	38	(56.7)
Female	16	(50.0)	13	(37.1)	29	(43.3)

The table above shows that the distribution of females to males in the aprepitant (oral regimen) arms was similar in the US and ex-US, but that in the fosaprepitant arm there was a higher proportion of females relative to males in the US (50% female vs. 37% in ex-US).
The proportion of patients enrolled in the trial who were 65 years and older was higher in the US than in the ex-US. The distribution between arms in this age group was similar in the ex-US subgroup. The proportion over the age of 74 years was somewhat higher in the aprepitant arm than in the fosaprepitant arm in the US subgroup (17.1% vs. 12.5%).

Examination of types of malignancies revealed that there was a higher proportion of patients with gastrointestinal cancer in the ex-US subgroup (22%) than in the US (9%), and in this subgroup of patients, the distribution between treatment arms was equal in the ex-US (22% vs. 21%), but uneven in the US (6% fosaprepitant vs. 11% aprepitant). There was a higher proportion of patients with respiratory and mediastinal cancer in the US subgroup (61%) than in the ex-US (47%), but the distribution between treatment arms was relatively even in each of those subgroups. There was a somewhat higher proportion of patients with "miscellaneous or

site unspecified" in the US subgroup 8% vs. 5%. An even distribution of these patients between treatment arms was reported in the ex-US subgroup, but the distribution between treatment arms was imbalanced in the US subgroup – 13% fosaprepitant vs. 3% aprepitant.

The total number of US patients in this trial was so small relative to non-US, it is impossible to draw any definitive conclusions from these exploratory analyses. The observed differences in distribution of demographic factors between the US and non-US subgroups likely reflects the very small sample size of the US subgroup relative to the non-US subgroup. I cannot conclude that the results of the exploratory efficacy analysis in the US is meaningful and reflects a true difference in efficacy in the US population. It is limited by total number of subjects in the analysis.

The Statistical reviewer concluded that the data support the use of a single intravenous dose of fosaprepitant 150 mg (dosed concomitantly with a 5HT3 receptor antagonist and a corticosteroid) for the prevention of acute and delayed nausea and vomiting with HEC, (b) (4) [redacted] The Statistical reviewer also expressed reservations regarding the robustness of the data from this single trial, in light of his observation that the trial "does not show convincing evidence that clinical benefit is consistent across different countries." He did acknowledge that the small number of patients enrolled in US sites made it difficult to interpret the apparent discrepant efficacy results between the US and non-US sites.

The Clinical reviewers also recommended approval of the new single dose regimen in HEC (b) (4) [redacted]

The indications proposed for the single dose 150 mg fosaprepitant product include prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin (cisplatin ≥70 mg/m^2), (b) (4) [redacted]

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8. Safety

The safety database included 1128 patients treated with fosaprepitant 150 mg in the noninferiority trial. In addition, there were 22 subjects who were administered fosaprepitant 150 mg in a small clinical trial, P018L1. All patients received only a single dose of fosaprepitant. Fosaprepitant 115 mg IV is currently approved and marketed as part of a regimen that includes Day 2 and 3 oral aprepitant dosing. In addition, a daily x 3 aprepitant regimen is approved and marketed. The Clinical Reviewers evaluated the postmarketing study safety data available from March 2003 through June 2009 for aprepitant, and from August 2007 to June 2009 for fosaprepitant. The reported marketing distribution of aprepitant is much greater than fosaprepitant (b) (4) Based upon her review of this information, the Clinical reviewer recommended inclusion of information on hypersensitivity in the fosaprepitant label. There were 42 "hypersensitivity reaction" postmarketing reports, including 12 that occurred within minutes of administration. Six of those 12 were called anaphylaxis.

The two regimens studied in the noninferiority trial that supports this application included an intravenous administration arm and an "all oral" administration arm. There was a higher incidence of thrombophlebitis in patients treated with fosaprepitant compared to patients treated with aprepitant, but the overall incidence in the fosaprepitant arm was low (0.8%), and all were mild to moderate in intensity. (Infusion site reactions have also been reported in the post-marketing experience with the approved intravenous fosaprepitant 115 mg product.) Infusion site pain occurred at a higher incidence in patients receiving the fosaprepitant regimen (1.4%) relative to the aprepitant regimen (0.1%).

The Clinical reviewer carefully evaluated the hypersensitivity reports in the safety database. There was a similar number of patients in the aprepitant arm reported to have hypersensitivity reactions considered related to study drug than in the fosaprepitant arm, 8 vs. 7. The one severe hypersensitivity adverse event occurred on the aprepitant arm. Although no event in the study was called an anaphylaxis event, there was a single patient with bronchospasm in each treatment arm, a single "allergic respiratory symptom" in the fosaprepitant arm, a single "throat tightness" in the fosaprepitant arm, one pharyngeal edema in the fosaprepitant arm, and two patients with wheezing in the fosaprepitant arm. The remainder were pruritis, itching, urticaria, swelling and rash. The Clinical reviewer carefully evaluated these reports and concurred with the applicant that none were manifestations of anaphylaxis.

Information on hypersensitivity has been included in the product label in the Contraindications section (4.1), Warnings & Precautions section (5.2), and Postmarketing sections (6.2). These sections address hypersensitivity symptoms, including anaphylaxis. Hypersensitivity was addressed in a prior labeling supplement, so changes during the current review were not substantive. Changes made during this review cycle include addition of a description of hypersensitivity reactions in the Contraindications section, and the addition of "anaphylaxis" to the list of reported immediate hypersensitivity reactions in Warnings and Precautions.

Urinary tract infections occurred at a higher rate in patients in the fosaprepitant group (1%) compared to aprepitant (0.3%), but there was no difference in the incidence of overall infections and infestations between regimens.

There was a slightly higher incidence of hypertension in patients treated with fosaprepitant (1.5%) compared to aprepitant (0.6%). The Statistical reviewer noted that the overall incidence of hypertension adverse events in the fosaprepitant arm in this noninferiority trial was similar to that previously reported in the phase 3 trials that supported the original aprepitant indication for HEC (1.6%). The CDTL noted that there was a higher prevalence of essential hypertension in the fosaprepitant arm (1.4%) than in the aprepitant arm (0.9%) and stated that the observation of increased incidence of hypertension in the fosaprepitant arm might have been secondary to this baseline imbalance. There were two patients treated with fosaprepitant who had SAEs of hypertensive crisis, and both occurred days after exposure to fosaprepitant, one 5 days later and one 14 days later.

There was a higher incidence of elevation of serum alanine aminotransferase >5X ULN in patients treated with fosaprepitant (1.8%) compared to aprepitant (0.5%). The Statistical reviewer noted that many patients had baseline elevations in their ALT and that underlying malignancy could have caused significant increases in transaminases. The increases in ALT >3 ULN were not associated with increases in total serum bilirubin >2 X ULN. There was no significant imbalance in proportion of patients with AST elevation between arms. The majority of the increases were transient and resolved by the last study visit. There were, however, two patients who were reported to have "hepatic failure" in the fosaprepitant arm and none on the aprepitant arm. Those two patients had underlying cytopenias and infection. One had bacteremia and febrile neutropenia. The second patient, who died, had peritonitis, thrombocytopenia and acute renal failure. Underlying sepsis was more likely to have caused the hepatic failure than fosaprepitant. The CDTL review contains a typographical error in the last sentence of the safety review about the liver function tests. I discussed this with the CDTL to confirm that there were no cases of concomitant transaminase and bilirubin elevations in the safety dataset. She confirmed that there were no cases and clarified that the sentence was intended to read, "There were no clear cut cases of drug-induced liver injury, or increased ALT >5x ULN or >3x ULN associated with increased total bilirubin >2x ULN."

The applicant submitted additional safety analyses to allow investigation for evidence of adverse events related to the EDTA levels present in the fosaprepitant 150mg intravenous product. These included analyses of serum calcium, magnesium, dizziness, loss of consciousness, presyncope, and syncope. The Clinical reviewers found no clinically relevant adverse events that could be attributed to EDTA.

Overall there were 49 deaths in the major clinical trial that supports this application, and all were considered unrelated to study drug. The number of deaths in each arm was similar: 23 (2%) on the fosaprepitant arm and 26 (2%) on the aprepitant arm. The proportion of patients with SAEs was also similar between study arms, 12.9% and 13.4%, respectively. This rate of SAEs was not unexpected in light of the fact that patients had underlying malignancy and were being treated with chemotherapy.

9. Advisory Committee Meeting

There was no Advisory Committee for this application. The product is not a new molecular entity and there were no scientific issues that required discussion in an Advisory Committee.

10. Pediatrics

The CDTL noted in her review that we are currently unable to extrapolate adult efficacy data to the pediatric population for this class of product (NK1 inhibitor). The applicant will be required under the Pediatric Research and Equity Act to conduct PK/PD, safety and efficacy studies of single dose fosaprepitant IV in combination with a 5HT3 antagonist and dexamethasone in children with cancer, ages 0 to 17 years, who are undergoing treatment with highly emetogenic chemotherapy.

The level of EDTA in the fosaprepitant formulation, 15.1 mg per 10 mL vial (in the currently approved 115 mg intravenous dose) and 19.7 mg/vial (in the proposed new 150 mg intravenous dose) caused concerns about the safety of the current intravenous formulation in children. For this reason, the applicant must develop an age appropriate formulation for the younger pediatric age group, in order to conduct these studies. (b) (4)

[redacted]

The plans for pediatric studies were discussed with the Pediatrics Review Committee (PeRC) and the PeRC found them acceptable.

The following deferred pediatric studies will be required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act.

1663-1 A PK/PD study to characterize aprepitant PK parameters following administration of a single dose of intravenous fosaprepitant, in combination with a 5HT3 antagonist and dexamethasone, in pediatric cancer patients ages 0 to 17 years undergoing treatment with highly emetogenic chemotherapy. You must conduct this study with an age appropriate formulation.

Final Protocol Submission:	February 2011
Study/Trial Completion:	February 2014
Final Report Submission:	May 2014

1663-2 An adequate, placebo-controlled, double-blind, randomized, add-on design, superiority study to evaluate the safety and efficacy of a single dose of intravenous fosaprepitant, in combination with a 5HT3 antagonist, as compared to standard therapy (a 5HT3 antagonist) in pediatric cancer patients ages 0 to 17 years undergoing treatment with highly emetogenic chemotherapy. You must conduct this study with an age appropriate formulation.

Final Protocol Submission:	August 2014
Study/Trial Completion:	August 2017
Final Report Submission:	December 2017

11. Other Relevant Regulatory Issues

Financial Disclosures: The Applicant submitted an FDA form 3454 certifying that it had not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study. The Applicant certified that no investigator disclosed a proprietary interest in the product or significant equity in Merck.

DSI: There were no DSI inspections due to the prior FDA approval of fosaprepitant for the same proposed indications.

12. Labeling

I concur with the reviewers' recommendations for labeling. (b) (4)

The CDTL summarized the major issues addressed in the labeling review. The major safety issue raised was whether there would be confusion with the new single IV dose regimen, which is intended to be the only dose of fosaprepitant/aprepitant administered each chemotherapy cycle. It is a higher dose than the currently approved fosaprepitant dose, 115 mg, which is currently administered as part of a regimen in which the IV dose is administered on Day 1 only, followed on Days 2 and 3 by oral aprepitant. The DMEPA, Clinical, DRISK and SEALD reviewers worked very hard to make it a clear distinction between these two IV dose regimens in the label, in an effort to avoid medication errors.

SEALD: Reviewers from the SEALD team participated in labeling negotiations. They reviewed the label and their recommendations were incorporated.

DMEPA: Reviewers from DMEPA were actively involved in the labeling review and label negotiations. They identified important areas where the labels could be clarified and improved to minimize potential for medication errors. Their recommendations were incorporated.

DDMAC and DRISK; Reviewers from DDMAC and DRISK were actively involved in the labeling review. Their recommendations were considered and included in label negotiations.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action –Approval of the indication for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin (cisplatin $\geq$ 70 mg/m^2) (CINV-HEC)

(b) (4)

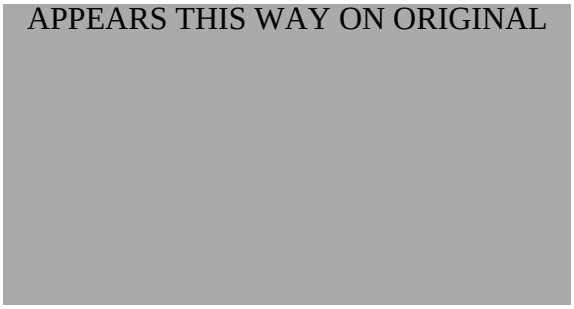
- Risk Benefit Assessment – I concur with the CDTL that the risk and benefit characteristics of fosaprepitant 150 mg IV as a single dose are favorable, for the indication for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin (cisplatin $\geq$70 mg/m^2). The product has been marketed for years for the same indication in both an oral formulation (administered daily x 3) and in a lower intravenous dose, which is administered on Day 1, followed on Day 2 and 3 with subsequent doses of the oral product. The noninferiority trial submitted in support of this indication demonstrated noninferiority to the approved regimen and no new safety concerns were identified with the somewhat higher intravenous dose in this new regimen, which is administered as a single dose to cover the entire Overall Phase (0-120 hours post chemotherapy).

(b) (4)

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies - None

- Recommendation for other Postmarketing Requirements and Commitments

The two deferred pediatric studies that are required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are listed in the approval letter and in Section 10 Pediatrics of this review.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/s/

DONNA J GRIEBEL
11/12/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022023/S-004

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: NDA 022023/S-004 EMEND (fosaprepitant dimeglumine) for Injection

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified:

Bridges, Todd
Burke, Laurie
Chakder, Sushanta K.
Delasko, Jeanne
Estes, Kristina
Fong, Steven
Grewal, Jagjit
Griebel, Donna
Klemm, Kathleen
Korvick, Kathleen
Lee, Sue Chih
Lewis, David
Patel, Hasmukh B.
Riley, Bryan S.
Strongin, Brian K.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022023/S-004

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	15-OCT-2010
From	Nancy Snow, Acting Team Leader DGP
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 22-023 SE004
Applicant	Merck
Date of Submission	12-October-2009
PDUFA Goal Date	13-November-2010
Proprietary Name / **Established (USAN) names**	Emend for Injection/ fosaprepitant
Dosage forms / Strength	intravenous/150 mg
Proposed Indication(s)	1. acute and delayed CINV-HEC (b) (4)
Recommended:	Approval CINV-HEC, (b) (4)

1. Introduction

The sponsor, Merck, Sharpe and Dohme Corp., has submitted an efficacy supplement for a new dosage and dosing regimen (one single 150 mg I.V. dose) for fosaprepitant dimeglumine (EMEND®). Emend is currently available in both oral (aprepitant) and intravenous (fosaprepitant) formulations. Fosaprepitant is a pro-drug phosphoramide derivative of aprepitant, and is rapidly converted to the parent compound after intravenous administration.

Emend is an antinauseant and antiemetic of the neurokinin 1 receptor (NK-1) antagonist class. No other drugs in this class are currently approved in the United States. In 2009 Emend for Injection (fosaprepitant) was reclassified as a new chemical entity, based on the fact that it is a non-ester covalent derivative of aprepitant.

The currently approved aprepitant regimen for CINV is a 125 mg oral tablet (or 115 mg I.V.) given on day one of chemotherapy, followed by 80 mg aprepitant (oral) on day 2 and 3. Patients also receive a 5-HT3 receptor antagonist and dexamethasone. For patients receiving highly emetogenic chemotherapy (HEC) a 5-HT3 antagonist is administered on day 1 only, and dexamethasone is administered on days 1 through 4. For chemotherapeutic regimens of moderate emetogenic potential (MEC) the Emend dosing is the same as for HEC, but the 5-HT3 dose is less, and dexamethasone is given on day one only . Emend was originally approved as a three day oral regimen; in 2008 Fosaprepitant was approved as an alternative dosage form on day one of the 3 day regimen by showing bioequivalence to the 125 mg oral formulation. Hence the current label allows for the first Emend dose of the 3 day regimen to be given intravenously as Fosaprepitant, or orally as Aprepitant.

In the current application the sponsor is seeking (b) (4) acute and delayed CINV- HEC, (b) (4)

(b) (4)

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One phase 3 trial in HEC was submitted as part of this application. The trial was performed using the single dose 150 mg Fosaprepitant formulation, predominately in sites outside the United States. Most (97.4%) patients were non-US. The trial was a non-inferiority, active control design, with the primary endpoint of complete response (CR-no vomiting, no retching, no use of rescue medication) measured from 0 to 120 hours. The key secondary endpoints were CR during the delayed phase (25-120 hours), and no nausea overall (0-120 hours). The active control was the three day oral aprepitant regimen. Consistent with standard of care, a 5-HT3 (ondansetron), and dexamethasone were used as part of a three drug regimen to prevent CINV. As will be discussed further, the dose of dexamethasone was reduced when administered with the 3 day regimen, but not for the single day regimen, based on a CYP3A4 mediated drug-drug interaction between dexamethasone and Emend.

(b) (4)

The original goal date for the application was extended by three months after receipt of a major amendment (11 June 2010) in order to allow time for a review of the submission. Therefore the user fee goal data was extended to November 13, 2010.

In general the phase 2 and 3 trials in support of the single day dosing did not identify any major new safety issues of concern with the I.V. formulation except for infusion site reactions.

Among the key issues associated with the application are:

- reliance on a single HEC trial to support HEC (b) (4)
- poor efficacy of fosaprepitant compared to aprepitant in the US population
- lower therapeutic gain at US sites compared to non-US sites
- generalizability of data obtained from foreign site to US patients
- need for dose adjustment of dexamethasone due to the effects of fosaprepitant on the CYP3A4 enzyme system
- different pharmacokinetics with the 3 day regimen and the single dose regimen
- potential safety concerns posed by the amount of EDTA in the I.V. formulation
- NK-1 receptor occupancy as a predictor of efficacy

2. Background

The risk of developing nausea and vomiting after cancer chemotherapy is influenced by gender, age, alcohol use, previous CINV, and the emetogenicity and dose of the chemotherapy agents.

The classification of the emetogenic potential of drugs for cancer chemotherapy is as follows: high emetic risk (>90%), moderate risk (30% to 90%), low risk (10% to 30%), and minimal (<10%). The dose and schedule of antiemetic drugs to prevent CINV is based on the emetic risk into which the chemotherapy regimen falls. An additional consideration is the time frame in which the nausea and vomiting occur. Emesis may be experienced during the first 24 hours, and again 48 to 72 hours after receiving chemotherapy. Cisplatin is the prototype for this phenomenon. Without effective antiemetic prophylaxis, patients receiving cisplatin will have nausea and vomiting 1 to 2 hours after chemotherapy, and again at 48 to 72 hours.[1] Other chemotherapies are also known to produce delayed nausea and vomiting.

As a result, antiemetic regimens are utilized which aim to prevent both acute and delayed CINV through the use of 5-HT3 receptor antagonists, NK-1 receptor antagonists, and dexamethasone. 5-HT3 antagonists are most effective for the prevention of acute CINV, and NK-1 antagonists work to prevent delayed CINV (although there is overall for both). Corticosteroids prevent both acute and delayed CINV. The following table, taken from a 2008 NEJM article (Hesketh) shows a typical antiemetic regimen, based on emetic risk.

Table 4. Recommended Antiemetic Treatment for Single-Day, Intravenously Administered Chemotherapy.

Emetogenic Level	Risk of Emesis	Antiemetic Regimen	
		Before Chemotherapy (day 1)	After Chemotherapy
	%		
1	<10 (minimal)	None	None
2	10–30 (low)	Dexamethasone or prochlorperazine	None
3	31–90 (moderate)		
For anthracycline plus cyclophosphamide		5-HT_3–receptor antagonist, dexamethasone, and aprepitant*	Aprepitant on days 2 and 3 or dexamethasone on days 2 and 3*
For other regimens		5-HT_3–receptor antagonist and dexamethasone†	5-HT_3–receptor antagonist or dexamethasone on days 2 and 3
4	>90 (high)	5-HT_3–receptor antagonist, dexamethasone, and aprepitant*	Dexamethasone on days 2–4 and aprepitant on days 2 and 3*

* The recommendations for aprepitant are supported by level 1 evidence (data from at least one high-quality randomized trial).[91]

† The recommendation for 5-HT_3–receptor antagonist and dexamethasone administered on day 1 with emetogenic level 3 chemotherapy is supported by level 1 evidence.

When drugs used to prevent chemotherapy induced nausea and vomiting are submitted to the FDA to review for marketing approval these various classifications of highly vs. moderately emetogenic, and acute vs. delayed CINV become key components of the approved indication and label.

[1] Hesketh, Paul. Chemotherapy-Induced Nausea and Vomiting. New England Journal of Medicine. 358:2482-2494.

There are currently four drugs of the 5-HT3 antagonist class approved in the United States (palonosetron, ondansetron, dolasetron, granisetron). Emend, the trade name shared by aprepitant and fosaprepitant, is the only drug of the NK-1 antagonist class that is currently approved, and is given once daily for 3 days.

According to the sponsor, a 150 mg dose of fosaprepitant was chosen for the proposed single day intravenous regimen based on NK-1 receptor occupancy, and tolerability. The 150 mg dosage achieves >90% receptor occupancy through day 3, and ≥80% through day 4. However, a clear correlation between receptor occupancy and efficacy has not yet been established.

The current application is for a single intravenous dosage of Fosaprepitant (150 mg) to be given in place of the 3 day oral regimen (the sponsor plans to stop marketing the 3 day IV-PO-PO regimen). The aim of this change in dosing regimen and dosage is convenience and enhanced compliance. Patients will still need to take a 5-HT3 antagonist (day 1) and dexamethasone on days 2-4 when receiving HEC. (b) (4)

3. CMC/Device

As noted, this application provides for a new dosing regimen and a new dosage strength for an already approved product. The 150 mg product is dose-proportional to the approved 115 mg product, (b) (4) As such there are no new or unresolved CMC issues.

Because the 150 mg injection will be manufactured, (b) (4) located at sites for the approved product, no inspections were conducted. Further, the characterization, manufacture, and controls for the drug substance are supported by reference to the approved NDA for fosaprepitant.

4. Nonclinical Pharmacology/Toxicology

The nonclinical safety of fosaprepitant has been established in toxicology studies submitted in the original NDA application. In the current supplement the sponsor submitted a nonclinical study report assessing the local tolerability of the commercial formulation of fosaprepitant for injection.

When administered as a single intravenous, paravenous, subcutaneous and intramuscular dose in rabbits, the incidence of physical signs (purple red discoloration) at the I.V. and paravenous injection sites was comparable between study drug and placebo, but the severity was slightly greater in the rabbits receiving fosaprepitant. In previous repeat dose toxicity studies in rats and dogs, the injection site was also a target organ of toxicity.

The nonclinical reviewer recommends approval of this supplement with correction to the 'Pregnancy' section of the proposed label.

5. Clinical Pharmacology/Biopharmaceutics

(b) (4)

, there are no new biopharmaceutical issues. A drug-drug interaction single dose pharmacokinetic study was conducted (P018L1) in support of this application.

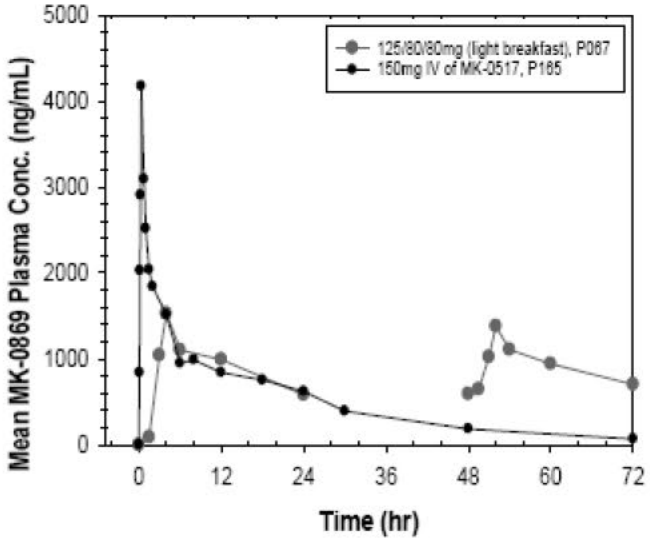
Dose Selection

The sponsor justifies the use of a 150 mg I.V. dose level based on NK_1 receptor occupancy, and infusion site tolerability. NK_1 receptor occupancy is predicted to remain >90% through Day 3, and ≥80% through Day 4 following an infusion of 150 mg fosaprepitant over 20 to 30 minutes. In addition, dose ranging studies of oral aprepitant conducted in patients showed a dose-response relationship up to 125 mg. A clear relationship between NK_1 receptor occupancy and clinical efficacy has not yet been established, however.

A comparison of the 150 mg single dose Fosaprepitant plasma concentration versus time with the 3 day oral Aprepitant regimen shows a difference in concentration on Days 2 and 3, as seen in sponsor's Figure 2.5:2. The graphic shows that the plasma concentration at 24 hours after administration of fosaprepitant 150 mg IV or oral aprepitant is the same (~600ng/ml). However beyond 24 hours the IV plasma concentration of fosaprepitant is less than that expected after repeated dosing of oral aprepitant.

Figure 2.5: 2

Mean Aprepitant (MK-0869) Plasma Concentrations (ng/mL) Versus Time From Single-Dose Intravenous (IV) 150-mg Fosaprepitant (MK-0517) as a 20-Minute Infusion (1 mg/mL) in Healthy Young Adult Subjects in P165 and From Oral Aprepitant 125/80/80-mg Regimen in Healthy Young Adult Control Subjects in P067



Note: The above plot for the 125/80/80-mg regimen does not show Day 2 (24 to 48 hrs) because aprepitant exposure was not measured at that time.
[Ref. 5.3.1.2: 2028] [Ref. 5.3.2.2: 713]

At 48 hours, the plasma single dose fosaprepitant concentration is ~200ng/mL, one-third the trough level for the 3-day oral aprepitant dosing.

Drug Interactions

Aprepitant, the active metabolite of fosaprepitant, is a CYP3A4 substrate, inhibitor and inducer. When administered as a single dose, aprepitant does not induce CYP3A4. However when fosaprepitant or aprepitant is administered with the CYP3A4 substrates midazolam and dexamethasone at doses used in the 3 day regimen, exposure of the two substrates was

increased by 2.3 fold, and 1.6 fold, respectively. Hence a further study was done to explore this interaction.

To address the potential for drug interactions with the higher dose of fosaprepitant, the sponsor conducted a randomized, open-label, 2-part, 2-period, crossover drug interaction study with dexamethasone and midazolam. In each part of the study, 150 mg fosaprepitant was administered only on Day 1 while the study drugs were administered on multiple days. In Part 1 subjects were randomized to one of two dexamethasone treatments. Results of the study showed that the dexamethasone AUC was increased approximately 2-fold on Days 1 and 2, but not on Day 3 following fosaprepitant coadministration. Therefore a reduction in dexamethasone dose by half is necessary for the first two days with the single 150 mg fosaprepitant dose, but no adjustment is needed on day 3. This is in contrast to the 3-day aprepitant regimen where a reduction is necessary for four days. Notably, the total increase in dexamethasone exposure following a single 150 mg I.V. dose of fosaprepitant does not exceed the increase in dexamethasone exposure observed following administration of the 3-day oral aprepitant regimen.

Likewise the effects of a single 150 mg administration of I.V. fosaprepitant on the 3A4 probe midazolam were explored. Both the mean midazolam AUC and C_{max} were increased when administered with fosaprepitant on Day 1 relative to administration of midazolam alone. The AUC was increased in all subjects; however, C_{max} was increased in only 6 (60%) subjects following fosaprepitant coadministration. Although there are no recommended dosage adjustments for midazolam, there may be a prolonged sedative effect when midazolam and fosaprepitant are coadministered.

QT prolongation potential

A thorough QT study has been previously conducted that showed no QT signal for fosaprepitant 200 mg infused over 15 minutes. Therefore the proposed dosing regimen of fosaprepitant 150 mg infused over 30 minutes is not expected to prolong the QT interval.

Besides the dosage adjustment of dexamethasone required with administration of the 150 mg I.V. regimen, there are no other pharmacology issues with the current application. The Clinical Pharmacology reviewer recommends approval, pursuant to agreement on the label.

6. Clinical Microbiology

From a Microbiology perspective there are no issues limiting approval of fosaprepitant 150 mg I.V. The 150 mg lyophilized powder is provided in a 10 mL glass vial. The powder is reconstituted with 5mL sterile saline and diluted with 145 mL sterile saline. The proposed (b) (4) manufacturing procedure for the 150 mg dose format for Fosaprepitant Dimeglumine for Injection is acceptable (b) (4)

The 24 month refrigerated shelf life for the 150 mg format (b) (4) is acceptable.

The post-dilution hold period of 24 hours at room temperature is the same as that approved for the 115 mg dose. The Microbiology reviewer sent an IR to the sponsor requesting data to support the proposed reconstitution hold period of 24 hours at room temperature. The reviewer concluded that the microbial challenge data for the 115 mg dose is applicable to fosaprepitant 150 mg, and provides adequate justification for the proposed post-dilution hold period.

7. Clinical/Statistical- Efficacy

As noted previously, the sponsor is (b) (4) this new dosing regimen and dosage as are currently approved for the 3-day Emend regimen; acute and delayed CINV- HEC, (b) (4)

(b) (4)

(b) (4)

The primary endpoint was the complete response (no vomiting and no use of rescue therapy) in the overall phase (120 hours following initiation of cisplatin).The primary hypothesis test (Complete Response in the overall phase) was based on the comparison of the lower bound of the 95% CI for the difference between treatment groups (fosaprepitant – aprepitant) to the pre-defined non-inferiority margin of >-7 percentage points. The secondary endpoints were the proportion of patients with Complete Response in the delayed phase (25 to 120 hours following initiation of cisplatin chemotherapy), and the proportion of patients with No Vomiting in the overall phase. For Complete Response in the delayed phase, the criterion used to establish non-inferiority of fosaprepitant to aprepitant was that the lower bound of the 95% CI for the difference was >-7.3 percentage points. The criterion used to establish non-inferiority of fosaprepitant with aprepitant for No Vomiting in the overall phase was that the lower bound of the 95% CI for the difference was >-8.2 percentage points.

Sponsor's table 3.1.5.1 provides a summary of efficacy based on primary and secondary hypotheses.

Summary of efficacy by primary and secondary hypotheses using FAS Population

Hypothesis Level and Endpoint	Lower Bound Needed For Non-inferiority	Actual Lower Bound	Actual P-Value†	Conclusion
Primary				
Complete Response – overall phase	>-7 percentage points	-4.1 percentage points	--	Non-inferior
Secondary				
No Vomiting – overall phase	>-8.2 percentage points	-5.3 percentage points	0.0002	Non-inferior
Complete Response – delayed phase	>-7.3 percentage points	-3.5 percentage points	0.00003	Non-inferior
† P-value associated with the 95% confidence interval for the difference (fosaprepitant – aprepitant) in response rates.				

The Statistical Reviewer validated the analysis conducted by the sponsor for the NDA submission, and these data are presented in Table 3.1.6.1. The results are numerically identical to those of the applicant, and support the finding of non-inferiority of fosaprepitant regimen versus standard regimen.

Table 3.1.6.1 (Reviewer's) Efficacy comparisons assessed by the complete response in the overall phase using FAS population

ENDPOINT	TREATMENT GROUPS	
	Fosaprepitnat Regimen N= 1106	Aprepitant Regimen N = 1134
Complete Response, n (% = n/N)	795 (71.9%)	820 (72.3%)
Therapeutic Gain (TG), %‡		-0.4%
95.0% two-sided CI for TG†		(-4.1%, 3.3%)

Proportion Difference by Country

The therapeutic gains in the overall phase for seven out of twenty seven countries [Brazil (TG -12%), Canada (TG -29%), Guatemala (TG -25%) , Hong Kong (TG -32%), Mexico (TG -13%), Sweden (TG -20%) , and United States (TG -15%)], were less for the fosaprepitant regimen than the aprepitant regimen by more than 7% (non-inferiority margin). However for six other countries [Chile (TG 10%), Denmark (TG 50%), Lithuania (TG 20%), New Zealand (TG 20%), Panama (TG 13%), and Spain (TG 26%)] the opposite was seen; the therapeutic gain was higher for the fosaprepitant regimen than aprepitant regimen by more than 7%. The statistical reviewer notes that "the treatment effects of the fosaprepitant regimen versus those of the aprepitant regimen may not be internally consistent across countries".

Efficacy comparison by country/US vs. Non-US

An analysis of efficacy results in the small US population (2.8% of patients enrolled in the trial) shows a complete response rate of 56% for fosaprepitant over the period 0 to 120 hours compared to 71% seen with aprepitant. The same pattern existed with the secondary endpoint of no vomiting, in which the fosaprepitant arm performed worse than active control (63% vs. 90.3%).

A second issue is poor performance of US sites compared to non US sites with respect to complete response rates. For example an analysis by subgroup and treatment group shows that

when US and non-US sites are compared by treatment arm, fosaprepitant performed worse in the US compared to non US (56% vs. 72%) compared to 71% vs. 72% for the aprepitant arm.

Efficacy comparisons by US Vs. Non-US region assessed by the complete response in the overall phase using FAS population

	US (2.60%=58/2240)	
	Fosaprepitant Regimen N= 27	Aprepitant Regimen N = 31
Complete Response, n (% = n/N) Therapeutic Gain (TG), %‡ 95.0% two-sided CI for TG†	15 (56.0%)	22 (71.0%) -15.0% (-40.0%,9.0%)
	Non-US (97.4%=2182/2240)	
	Fosaprepitant Regimen N= 1069	Aprepitant Regimen N = 1093
Complete Response, n (% = n/N) Therapeutic Gain (TG), %‡ 95.0% two-sided CI for TG†	772 (72%)	790 (72%) -0.1% (-3.8%, 3.7%)

† 95.0% two-sided confidence interval for the Therapeutic Gain without using stratum factor

In addition, fosaprepitant did not perform as well within the US as did aprepitant, as seen by a CR of 56% and 71% respectively. The difference between fosaprepitant and aprepitant seen in the US sites, in which aprepitant seemed to perform better than fosaprepitant, does not persist in foreign sites.

8. Safety

The safety of fosaprepitant 150 mg was evaluated in two clinical studies; Phase 3 CINV-HEC study P017L1, and Phase 1 drug interaction study P018L1. A total of 1153 patients and subjects were exposed to a single dose of fosaprepitant 150 mg I.V. In Phase 3 trials 1128 patients were given fosaprepitant. Patients were not studied beyond cycle one.

A tiered approach was prespecified for the analysis of adverse events. Tier 1 AEs were severe infusion site pain, severe infusion site erythema and/or severe infusion site induration, and infusion site thrombophlebitis. Tier 2 AEs were clinical or laboratory AEs occurring in ≥1% patients. AEs occurring in <1% patients were classified as Tier 3.

The incidence of AEs, drug-related AEs, serious AEs, and deaths were similar for both fosaprepitant and aprepitant treatment groups. The incidence of adverse events leading to discontinuation was slightly higher in the fosaprepitant treatment group (n=11 (1.0%)) than in the aprepitant treatment group (n=7 (0.6%)). However these numbers are very small, and no incidence pattern was demonstrated by system organ class or treatment group.

The common adverse events (>5% incidence) in the fosaprepitant treatment group are similar to those known for the approved oral aprepitant capsules and include constipation (10.6%), asthenia (8.6%), diarrhea (7.8%), anorexia (6.6%), vomiting (6.6%), nausea (5.9%), and hiccups (5.6%). More infusion site pain reactions were seen with the fosaprepitant group (n=16) than the aprepitant group (n=1).

Infusion Site Reactions

Since early clinical development, infusion site reactions have been a known risk with administration of fosaprepitant intravenously, and incidence thresholds for these AEs were

built into P017L1 as study stopping criteria. The AEs of severe infusion site erythema, severe infusion site induration, severe infusion site pain, and infusion site thrombophlebitis were considered events of clinical interest (ECI). The incidence of injection site AEs was higher in the fosaprepitant group (n=11,1.0%) compared to the aprepitant group (n=1,0.1%).

Because of a risk of hypersensitivity reactions with fosaprepitant and aprepitant use seen in postmarketing reports, hypersensitivity AEs were evaluated for Study P017L1. The incidence of hypersensitivity AEs was similar between treatment groups for severity; however, more events occurred in the fosaprepitant treatment group compared to the aprepitant treatment group for days 1 (30% vs. 18%) and 2 (17% vs. 8%) of study drug administration.

The Sponsor also evaluated potential differences in the reporting of adverse events within Study P017L1 by US and Ex-US sites. Total US patients reported a ~14% higher incidence of reported adverse events (74.2% [n=49]) compared to the total Ex-US patients (60% [n=1336]). The incidence of drug-related AE was 2-3x greater in the US patients than the Ex US patients.

In Study P017L1, 49 deaths occurred: 23 (2.0%) in the fosaprepitant treatment group, 26 (2.2%) in the aprepitant treatment group. All the deaths were considered unrelated to the study drug and due to natural history of cancer in these patients. Nonfatal serious adverse events (SAE) were reported in 305 patients in Study P017L1. SAE incidence was similar between the fosaprepitant treatment group and the aprepitant treatment group. Each event was reported in <1% of patients in both treatment arms with the exception of febrile neutropenia, neutropenia, vomiting, and dehydration. The adverse events demonstrated no incidence pattern by system organ class or treatment group.

Hypertension was reported as an adverse event more often in patients treated with the fosaprepitant regimen (17/1143, 1.5%) compared to patients in the aprepitant regimen (7/1169, 0.6%). The increased incidence of hypertension in the fosaprepitant treatment group may stem from an imbalance of hypertension as baseline medical history between the treatment groups. There was a higher prevalence of essential hypertension in the fosaprepitant group (n=16 (1.4%)) compared to the aprepitant group (n= 11 (0.9%)).

The Sponsor conducted a post-hoc analysis of adverse events related to the presence of EDTA in the fosaprepitant formulation in Study P017L1 which showed that there were no apparent imbalances in adverse events related to hypocalcaemia (fosaprepitant 0.5%; aprepitant 0.4%), hypomagnesaemia (fosaprepitant 0.1%; aprepitant 0.3%), dizziness (fosaprepitant 3.3%; aprepitant 3.0%), dizziness postural (fosaprepitant 0%; aprepitant0.1%), loss of consciousness (fosaprepitant 0.1%; aprepitant 0%), presyncope (fosaprepitant 0.1%; aprepitant 0%), syncope (fosaprepitant 0.6%; aprepitant 0.5%), or hypotension (fosaprepitant 1.0%; aprepitant 1.2%). The above findings did not discern any clinically relevant consequences due to the presence of EDTA in the fosaprepitant formulation.

Although there was no imbalance in treatment arms with regard to medical history of hepatobiliary disorders or baseline levels of liver enzymes greater than the upper limit of normal, there was a higher incidence of serum ALT >5X ULN in patients treated with the fosaprepitant single day regimen (1.8%) compared to patients treated with the aprepitant 3-day

regimen (0.5%). As the medical reviewer notes, although there were elevations in ALT, the elevation of liver enzymes could be attributed to fosaprepitant, chemotherapy agents or patient history. There were no clear cut cases of drug-induced liver injury, or increased ALT>5x ULN or >3x ULN associated with total bilirubin >2x ULN.

9. Advisory Committee Meeting

No advisory committee was required for this non-NME new dosing regimen for fosaprepitant.

10. Pediatrics

Because we are unable to extrapolate adult efficacy data to the pediatric population, under the Pediatric Research and Equity Act the sponsor will be required to conduct a PK/PD, safety and efficacy study of a single dose of fosaprepitant I.V. in combination with a 5HT3 antagonist and dexamethasone in pediatric cancer patients ages 0 to 17 years undergoing treatment with highly emetogenic chemotherapy (b) (4)
Because of concern about the amount of EDTA in the single dose I.V. formulation the sponsor must develop an age appropriate formulation. The plan was presented to PeRC, and found acceptable.

11. Other Relevant Regulatory Issues

No DSI inspections were obtained for this application because Emend is an approved drug, and because a hypothetical invalidation of study sites that were considered for inspection had no impact on efficacy results.

12. Labeling

Among the labeling issues addressed with this application are:

- (b) (4)
- the need to clearly distinguish between the various regimens of fosaprepitant to avoid dosing and administration errors
- creation of a table to show the difference in preparation between the 115mg and 150 mg I.V. dosages
- include only drug related adverse reactions in the clinical trails section
- change adverse experiences to adverse reactions
- tables should only include ARs which have an incidence rate greater with aprepitant than standard therapy

13. Recommendations/Risk Benefit Assessment

After a consideration of all aspects of this application, and pursuant to recommendations of the review team, the CDTL recommends an approval action be taken for the HEC indication, (b) (4)

With respect to the HEC indication, the single day regimen offers an alternative to the approved three day I.V.-oral-oral, or oral-oral-oral regimen. The single dose regimen provides

an administration option to patients who cannot easily tolerate orally administered medication prior to initiating chemotherapy.

Although ample data exist concerning the safety and efficacy of aprepitant and fosaprepitant from other trials, only one Phase 3 clinical trial was conducted using the single day high dose of Emend. [redacted] (b) (4) the Clinical and Statistical reviewers have noted the difference in results between US and non-US sites.

The data show that the 150mg I.V. regimen works as well as the 3 day regimen in preventing CINV-HEC in the overall and delayed phases. Because fosaprepitant for injection works for chemotherapeutic agents of the highest emetogenic potential, and is already approved as part of the three day regimen, it is expected to work to prevent nausea and vomiting from chemotherapeutic agents of less emetogenic potential. However without clinical data, these conclusions are speculative.

During the review cycle the question of EDTA arose, particularly pertaining to studies in children. As noted in this review, the sponsor did a post-hoc analysis looking for AE that could be seen with EDTA, such as hypomagnesemia and hypocalcemia, but did not find any. (b) (4) [redacted] In addition the sponsor is required to develop an age appropriate formulation of fosaprepitant with reduced EDTA content.

For the HEC population the simplicity of a single dose regimen (although subsequent days of other drugs are still required) may afford some benefit, tempered, however by the possibility of infusion site reactions. (b) (4) [redacted]

(b) (4) [redacted]

[redacted]

[redacted] . Because of concerns about generalizability of results from non-US sites to the US the sponsor is strongly encouraged to increase the number of sites in the United States.

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/s/

NANCY C SNOW
11/10/2010
corrected typo from previous version

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022023/S-004

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22023/S-004
Priority or Standard	Standard
Submit Date(s)	October 12, 2009
Received Date(s)	October 13, 2009
PDUFA Goal Date	August 13, 2010
Extended PDUFA Date	November 13, 2010
Division / Office	Division of Gastroenterology Products
Reviewer Name(s)	Tamara Johnson, MD, MS
Review Completion Date	October 13, 2010
Established Name	fosaprepitant
(Proposed) Trade Name	EMEND for Injection
Therapeutic Class	NK_1 receptor antagonist
Applicant	Merck & Co.
Formulation(s)	Intravenous
Dosing Regimen	150mg, single dose
Indication(s)	HEC, (b) (4)
Intended Population(s)	Adults

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This efficacy supplement presents EMEND™ for Injection (fosaprepitant dimeglumine) 150mg as a new dosage level and single day regimen for this previously approved intravenous drug. The following indications are proposed:

- Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin (cisplatin ≥70 mg/m2) (CINV-HEC)
- (b) (4) [redacted]

The pivotal clinical trial P017L1 demonstrates that fosaprepitant 150mg single day regimen was non-inferior to the aprepitant oral 3-day regimen for the prevention of CINV-HEC and lacks any significant safety signals for this new dosing regimen of fosaprepitant. This reviewer, therefore, recommends approval of fosaprepitant 150mg for the proposed indication of prevention of CINV-HEC in the adult patient population. Trial P017L1, (b) (4) [redacted]

1.2 Risk Benefit Assessment

The fosaprepitant 150mg IV single day regimen offers convenient dosing to improve compliance over the aprepitant 3-day oral regimen. Results of the CINV-HEC clinical study (P017L1) finds comparable rates of complete response between the fosaprepitant single day regimen and aprepitant 3-day regimen for the total study population and the subpopulations by age, race, gender, and concomitant chemotherapy on Day 1. The lack of comparable efficacy demonstrated in the small US study population (n=56) prohibits a definitive conclusion that the single day fosaprepitant 150mg regimen would not be comparable to the aprepitant 3-day regimen in a larger US chemotherapy patient population. The major safety concern with fosaprepitant 150mg single day regimen was local tolerability due to an increase in infusion site related reactions. The incidence of this risk was at most 3.0%, however, in this reviewer's opinion, does not preclude approval of the single day regimen. While the risk of hypersensitivity, elevated liver enzymes, and hypertension occurred at a higher incidence in the fosaprepitant

treatment group compared to the aprepitant treatment group, only the additional risk of infusion site related adverse reactions needs to be described in the proposed labeling.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for Risk Evaluation and Mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

The recommended postmarketing requirements include only the Pediatric Research Equity Act (PREA) obligations. As the fosaprepitant single day regimen offers an advantage for the administration of CINV antiemetic therapy in pediatrics, the suggested studies outlined below address ages 0 to 17 years for the CINV indication:

Study 1: PK/PD study to characterize aprepitant PK parameters following administration of a single dose of fosaprepitant I.V. in combination with a 5HT3 antagonist and dexamethasone in pediatric cancer patients ages 0 to 17 years undergoing treatment with highly emetogenic chemotherapy.

Study 2: An adequate, double-blind, placebo controlled, randomized, parallel-group, add-on design, superiority study to evaluate the safety and efficacy of a single dose of fosaprepitant I.V. in combination with a 5HT3 antagonist as compared to standard therapy (a 5HT3 antagonist) in pediatric cancer patients ages 0 to 17 years undergoing treatment with highly emetogenic chemotherapy.

(b) (4)

, this pediatric plan has been modified from that approved by Pediatrics Review Committee (PeRC) to restrict study of a single dose of fosaprepitant IV to the pediatric patient population receiving highly emetogenic chemotherapy.

2 Introduction and Regulatory Background

Chemotherapy-induced nausea and vomiting (CINV) are the complications of cancer chemotherapy that most significantly affect the quality of life of cancer patients, and influence their compliance with future chemotherapy treatments.[1] The severity of CINV is determined by various factors that include the specific chemotherapy drug's ability to induce emesis, the dose of the drug, the duration of drug infusion, as well as the individual patient characteristics such as age, gender, alcohol use, and predisposition to

[1] National Comprehensive Cancer Network I. Practice guidelines in oncology: Antiemesis (Version 3.2009). http://www.nccn.org.

nausea and vomiting.[2] Chemotherapy drugs have been classified according to their emetogenic potential: high, moderate, low, and minimal. Those drugs considered highly emetogenic are associated with vomiting in the majority of patients (>90%) which initially peaks within a couple hours following drug administration.[3,4] The risk of CINV from HEC classified drugs typically lasts for 4 days. Those drugs considered moderately emetogenic are associated with vomiting in many patients (30-90%). The risk of CINV from MEC classified drugs typically lasts for 3 days. The standard CINV prevention regimen covers these total risk periods. Proper emetic control reduces the risk of anticipatory emesis in cancer chemotherapy patients.

Since approval, aprepitant has been adopted by the medical oncologic community as an essential part of the standard emetic control regimen. This new standard-of-care is included in guidelines by professional associations such as the Multinational Association of Supportive Cancer Care (MASCC), the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN). The Sponsor maintains that despite the demonstrated benefits of oral aprepitant, there is a medical need for treatment options (such as intravenous administration) to prevent CINV in patients who cannot easily tolerate orally administered medication prior to initiating chemotherapy. Also, a single-day fosaprepitant regimen is expected to improve patient compliance, compared to the multiple-day regimens.

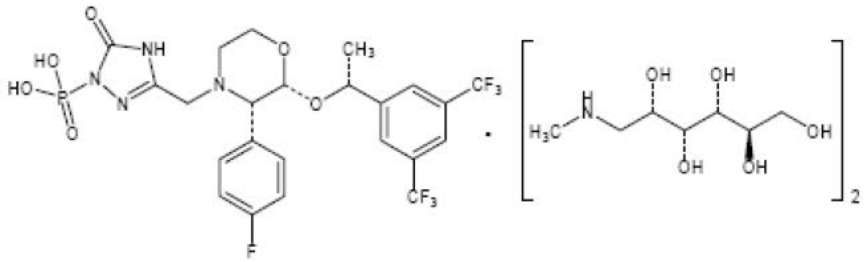
The approval of aprepitant in 2003 was based on three pivotal trials of the 3-day aprepitant regimen: two trials performed for CINV-HEC (Study 052 and Study 054) and 1 study for CINV-MEC (Study 071). The approval of fosaprepitant in 2008 was based upon a Phase 2 clinical trial for CINV-HEC (Study 007L1), and pharmacokinetic and bioequivalence studies. Since approval, there have been labeling supplements for aprepitant and fosaprepitant. The majority of the labeling changes were minor editorial changes, negative pharmacological study data additions, postmarketing adverse events (i.e.. hypersensitivity) additions, and labeling conversion to PLR format. There have been no withdrawals or restriction of indications for aprepitant or fosaprepitant.

2.1 Product Information

Trade name: EMEND™ for Injection
Established name: Fosaprepitant dimeglumine
Pharmacological Class: Neurokinin type 1 receptor antagonist

2 Grunberg SM and Hesketh PJ. Control of Chemotherapy-Induced Emesis. NEJM 1993: 1790-1796.
3 MASCC. Prevention of Chemotherapy and Radiotherapy Induced Emesis: Results of the 2004 Perugia International Antiemetic Consensus Conference. Ann Oncology 2006 (17):20-28.
4 Hesketh PJ et al. Differential Time Course of Action of 5-HT3 and NK1 Receptor Antagonists when Used with Highly and Moderately Emetogenic Chemotherapy (HEC and MEC). Support Care Cancer. Published online 11 July 2010.

Figure 1: Chemical Structure of Fosaprepitant Dimeglumine



Chemical formula: 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).

Empirical formula: $C_{23}H_{22}F_7N_4O_6P \cdot 2(C_7H_{17}NO_5)$

Molecular weight: 1004.83

Fosaprepitant dimeglumine is a white to off-white amorphous powder that is freely soluble in water. Fosaprepitant dimeglumine is supplied in a 10ml vial as a sterile lyophilized formulation for reconstitution and dilution prior to intravenous infusion. The content of each 10 mL vial is listed in the table below.

Table 1: Chemical Composition of Fosaprepitant Dimeglumine for Injection*

Component	Reference	Function	mg/vial†	mg/dose
Fosaprepitant Dimeglumine (Fosaprepitant free acid)		Active	(b) (4)	245.3‡ (150.0)§
Edetate Disodium				18.8
Polysorbate-80				75.0
Lactose Anhydrous				375.0
Sodium Hydroxide‖	NF/Ph. Eur.	pH adjustment		(b) (4)
Hydrochloric Acid‖	NF/Ph. Eur.	pH adjustment		
				(b) (4)

*Sponsor's Table 3.2.P.1-0517-injectable150mg: 1, Fosaprepitant Dimeglumine for Injection —Market Composition, Description and Composition, Module 3, page 3.

Fosaprepitant dimeglumine is the water-soluble, phosphorylated prodrug of aprepitant. Fosaprepitant 115mg was approved in 2008 as an alternative administration route for Day 1 of the aprepitant oral 3-day regimen.[5] Fosaprepitant was, therefore, approved for the same indications as aprepitant (CINV-HEC and CINV-MEC); (b) (4) In this efficacy supplement, the Sponsor proposes use of fosaprepitant 150mg in a single-day dosing regimen for the approved indications of CINV-HEC (b) (4) for adult chemotherapy patients. See the table below for details of single-day fosaprepitant regimen. Note that the dexamethasone dose is reduced 50% (Days 1 and 2 for HEC, (b) (4) due to drug interaction.

Table 2: Fosaprepitant 150mg Single Day Dosing Regimens

		Day 1	*Day 2*	*Day 3*	*Day 4*
CINV-HEC	**Fosaprepitant**	150 mg IV	none	none	none
	Dexamethasone	12 mg oral	8 mg oral	16 mg oral	16 mg oral
	Ondansetron	32 mg IV	none	none	none

(b) (4)

5 The currently approved aprepitant oral 3-day regimen is 125 mg on Day 1 followed by 80 mg on Days 2 and 3.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently approved drug products indicated for CINV-HEC and CINV-MEC include serotonin type 3 receptor antagonists (5-HT3 RA), H1 receptor antagonists, and NK1 receptor antagonists. These drug products are routinely used in combination with corticosteroids and anti-anxiety drugs to prevent CINV for a period of 3 to 4 days.

Table 3: Currently Available Prescription Products for the Proposed Indications

DRUG NAME Formulation (Sponsor)	Approval Date	Indications and Dosages*
NK1 Receptor Antagonists		
EMEND (aprepitant) Oral capsule (Merck)	2003	• **Adults** **CINV-HEC** – 125mg PO on Day 1; 80mg PO on Days 2 & 3 **CINV-MEC –** 125mg PO on Day 1; 80mg PO on Days 2 & 3 **PONV –** 40mg PO x 1 • ***No Approved Pediatric Indications***
EMEND for Injection (fosaprepitant dimeglumine) Intravenous (Merck)	2008	• **Adults** **CINV-HEC** – 115mg IV on Day 1; 80mg ***PO*** on Days 2 & 3 **CINV-MEC –** 115mg IV on Day 1; 80mg ***PO*** on Days 2 & 3 • ***No Approved Pediatric Indications***
H1 Receptor Antagonists		
Hydroxyzine hydrochloride oral capsule oral suspension intramuscular injection (Generic) *Note: other available formulations are approved for different indications.*	1957	• **Adults** **NV --** 25–100 mg IM **Pre- and Postoperative adjunctive medication --** 25–100 mg IM • **Pediatrics** **NV--** 0.5 mg/lb body weight IM **Pre- and Postoperative adjunctive medication --** 0.5 mg/lb body weight IM

DRUG NAME Formulation (Sponsor)	Approval Date	Indications and Dosages*
5-HT3 Receptor Antagonists‡		
ZOFRAN® (ondansetron) Oral tablets Orally disintegrating tablets Oral solution Intravenous injection (GlaxoSmithKline)	1991	• **Adults** **CINV –**32mg IV x 1 or 0.15mg/kg IV q4 hrs. x 3 **CINV-HEC** -- 24mg oral x 1 day **CINV-MEC –** 8mg oral BID x 2-3 days **PONV—** 4mg IV; 16mg oral 1 hr prior to induction **RINV –** 8mg oral TID x 1-3 days • **Pediatrics** **CINV –** for ≥6 mo., 0.15-mg/kg IV q4 hrs. x 3 **CINV-MEC –** for 6mo. to 18yrs, 0.15mg/kg IV q4 hrs x 3; for ≥12 y.o., same oral as adult; 4-11y.o., 4mg oral TID x 2-3 days **PONV—**IV only, 1 month to 12 y.o. – a single 0.1-mg/kg dose for patients weighing ≤ 40 kg, or a single 4-mg dose for patients weighing > 40 kg
ANZEMET (dolasetron mesylate) Oral tablet Oral solution Intravenous injection (Aventis Pharmaceuticals)	1997	• **Adults** **CINV--**1.8 mg/kg IV x1 or 100mg mg IV x1; 100mg oral x 1 **PONV –** 12.5mg IV x 1; 100mg oral x 1 • **Pediatrics** **CINV** – for 2y.o. and older, 1.8mg/kg IV x 1; for 2 y.o. and older, 1.8mg/kg oral x 1 **PONV–** for 2 y.o. and older, 0.35mg/kg IV x 1; 1.2mg/kg oral x1

DRUG NAME Formulation (Sponsor)	Approval Date	Indications and Dosages*
5-HT3 Receptor Antagonists‡ (continued)		
KYTRIL (granisetron) Oral tablet Oral solution Intravenous injection (Roche Pharmaceuticals)	1993	• **Adults** **CINV-** 10mcg/kg IV on the days chemotherapy is given; 2mg oral on the days chemotherapy is given **PONV –** 1mg IV x 1 **RINV–** 2mg oral x 1 • **Pediatrics** **CINV –** IV same as adults for 2 y.o. and older
SANCUSO (granisetron) Transdermal patch (ProStrakan Inc)	2008	• **Adults** **CINV-HEC & CINV-MEC –** 34.3 mg patch applied for 24 to 48 hours before chemotherapy, removed 1 to 7 days after chemotherapy
ALOXI (palonosetron HCl) Oral capsule Intravenous injection (MGI Pharma)	2003	• **Adults** **CINV-HEC** – 0.25mg IV x 1 **CINV-MEC –** 0.25mg IV x 1; 0.5mg oral x 1 capsule **PONV** – 0.075mg IV x 1 • ***No Approved Pediatric Indications***

‡ 5-HT3 = serotonin type 3

2.3 Availability of Proposed Active Ingredient in the United States

Fosaprepitant dimeglumine has been available in the US as a 115mg dose since 2008. Its active metabolite, aprepitant, to which its efficacy is attributed, has been available since 2003. Fosaprepitant 115mg was approved for use on Day1 of the aprepitant 3-day regimen for both CINV-HEC and CINV-MEC based upon its bioequivalence to aprepitant 125mg.

2.4 Important Safety Issues with Consideration to Related Drugs

Only two drugs in the NK1 receptor antagonist class have been approved by the FDA; fosaprepitant and aprepitant. The majority of postmarketing adverse event reports is consistent with the known safety profiles of both fosaprepitant and aprepitant. Special focus on hypersensitivity reactions is provided in section 8 below.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

- January 11, 2007 -- Type C meeting between FDA and Merck Research Laboratories (MRL) to discuss study design, dose selection, non-inferiority (NI) margin, and adequacy of a single study in support of a single dose of fosaprepitant as an alternative to the approved oral 3-day aprepitant regimen. MRL to submit justification for NI margin, single study, and dexamethasone dosing.
- April 19, 2007 -- follow-up Type C Meeting between FDA and MRL. At this meeting, FDA requested that MRL perform a study to verify appropriate dexamethasone dosing, evaluate the safety of the 150mg fosaprepitant dose before Phase 3, use the Agency method to calculate NI margin, and submit a complete protocol with SAP for review.
- October 12, 2007 – Special protocol assessment on clinical study, and FDA's November 29, 2007 responses that a single study may not be adequate to support approval. Efficacy analyses must use the ITT and PP populations
- June 17, 2009 – teleconference between FDA and MRL to discuss FDA's letter (May 28, 2009) providing comments regarding the statistical methods proposed in the Statistical Analysis Plan. MRL preferred to use Miettinen and Nurminen statistical method as primary analysis and will use FDA-recommended method as secondary analysis. As such, FDA states results must be positive for both methods.

2.6 Other Relevant Background Information

Fosaprepitant and aprepitant are used worldwide. As of June 2009, aprepitant is approved in 69 countries for the prevention of chemotherapy induced nausea and vomiting (CINV) and in 33 countries for PONV. Fosaprepitant is approved in 37

countries for the prevention of CINV. The marketing approval of aprepitant and fosaprepitant has not been suspended, revoked, or withdrawn by any Agency in any country. Since approval, the labeling for both aprepitant and fosaprepitant was changed to include the following postmarketing adverse events (2008):

Skin and subcutaneous tissue disorders: pruritus, rash, urticaria
Immune system disorders: hypersensitivity reactions including anaphylactic reactions

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Although the overall quality of the submission was good, the sponsor failed to place appropriate links to allow easy navigation from clinical study reports to documents listed in the appendices. An amendment was submitted in response to the filing letter. Additional information was requested for study site identifying data to link to other datasets and a data table summarizing all infusion site reactions regardless of severity.

(b) (4)

3.2 Compliance with Good Clinical Practices

The Sponsor reports that the clinical study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. Investigators were trained and signed a Protocol Investigator Signature Page indicating their commitment to comply with applicable Good Clinical Practice regulations and guidance and to conduct the study in accordance with the protocol.

Each investigator was responsible for obtaining Review Board Approval of the protocol and subsequent changes, in compliance with local laws. The sponsor further attests that all review boards met the definition as outlined in the Food and Drug Administration Code of Federal Regulations (CFR) Title 21, Part 312.3, and were adequately constituted in accordance with local regulations to provide assurance of human subject protection.

Prior to initiation of the study, a written informed consent agreement explaining the procedures of the study, together with the potential risk, was read by and explained to

all patients, or their legally authorized representatives. Before any study procedures were performed, each patient (or representative) signed and received a dated copy of such an informed consent form and was assured of his/her freedom to withdraw from participation in the study, without prejudice, at any time.

Although DSI inspections of three clinical study sites were initially considered, a decision was made to dispense with inspections due to prior FDA-approval of fosaprepitant, non-impact of invalidation of these study sites on efficacy results, and limited resources.

3.3 Financial Disclosures

Many study sites used incentives to enroll patients, such as tote bag, mp3 player, pen, fleece blanket, transportation, breakfast, Emend for additional cycles, and/or $34 USD per visit. These study sites were located in Brazil, Canada, Chile, Columbia, Denmark, Germany, Guatemala, Hong Kong, Hungary, India, Korea, Lithuania, Mexico, New Zealand, Panama, Peru, Russia, Sweden, Venezuela.

Reviewer's Comment:
A majority of the study sites used incentives for patient enrollment into the clinical trial. All sites within a given country were involved in the incentive program, although the type of incentive may vary by study site. Nineteen of the twenty-seven countries used incentives. It is not clear to this reviewer why so much incentive was needed for a drug that has gained worldwide acceptance as standard of care for prevention of CINV. These incentives may have thwarted the forthright reporting of adverse events from patients and contributed to a lower incidence of drug-related adverse events in these populations.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The fosaprepitant 150mg dose contains an increase in edetate disodium (EDTA) over the fosaprepitant 115mg dose, relative to the increase in fosaprepitant dimeglumine. The fosaprepitant 150mg dose contains 245.3mg fosaprepitant dimeglumine and 18.8mg EDTA, while the fosaprepitant 115mg dose contains 188.1 mg fosaprepitant dimeglumine and 14.4mg EDTA. (b) (4) For further details on the CMC evaluation of fosaprepitant 150mg, please see the full review by Dr. David Lewis.

4.2 Clinical Microbiology

The Microbiology review of fosaprepitant 150mg found no significant issues. The Microbiology reviewer noted a post-dilution hold time of 24 hours, however, results of growth studies, where 40ml of fosaprepitant was inoculated with bacteria, yielded less than 0.3 logs increase in growth after 24 hours at room temperature. These data satisfied the acceptance criterion which requires that challenge microorganism growth does not exceed 0.5 logs and that the drug product demonstrates bacteriostatic or bacteriocidal activity. For further details on the Microbiology evaluation of fosaprepitant 150mg, please see the full review by Dr. Steven Fong.

4.3 Preclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review of fosaprepitant 150mg found no significant issues for this supplement. Toxicology studies submitted to the original NDA application described histomorphologic changes at the fosaprepitant injection site with single dose administration to rabbits and repeat dose administration to rats and dogs. These changes include very slight to moderate acute inflammation, and very slight to moderate hemorrhage in the subcutis in rabbits; cellular proliferation of venous intima, venous necrosis or thrombosis, skin necrosis, subcutaneous edema, cellular infiltration and degeneration of muscle fibers in rats; and venous thrombosis, fibroplasia and necrosis in dogs. For further details on the Pharmacology/Toxicology evaluation of fosaprepitant 150mg, please see the full review by Dr. Sushanta Chakder.

4.4 Clinical Pharmacology

The Clinical Pharmacology review of fosaprepitant 150mg focused on clinical study protocol P018L1, a drug interaction study of fosaprepitant in combination with dexamethasone (Part 1) or midazolam (Part 2).

- Part 1: A known interaction exists between dexamethasone, a 3A4 substrate, and aprepitant when administered as a part of the 3-day dosing regimen. Study P018L1 showed that the dexamethasone AUC was increased approximately 2-fold on Days 1 and 2 but not on Day 3 following fosaprepitant coadministration. The increase in dexamethasone AUC is similar to that observed following administration of the 115 mg fosaprepitant dose. This leads to a 50% reduced dexamethasone dose for Days 1 and 2, and requires a return to dexamethasone full dosing on Days 3 and 4, when single dose fosaprepitant 150mg is administered. This is different from the 3-day regimen, where a 50% reduced dexamethasone dose is required for all four days of therapy.
- Part 2: Midazolam is a common 3A4 probe for enzyme inhibition or induction. The results of this study indicate that mean midazolam AUC is elevated by 77% and the mean C_{max} is increased by 17% on Day 1 when 150 mg fosaprepitant is coadministered. There is no difference in midazolam exposure on Day 4.

Fosaprepitant 150 mg I.V. is, therefore, a weak CYP3A4 inhibitor as a single dose on Day 1 with no evidence of induction of CYP3A4 observed on Day 4.

For further details on the Clinical Pharmacology evaluation of fosaprepitant 150mg, please see the full review by Dr. Kris Estes.

4.4.1 Mechanism of Action

Fosaprepitant dimeglumine is the water-soluble, phosphorylated prodrug of aprepitant. Aprepitant is a high affinity antagonist of the substance P/neurokinin type 1 (NK-1) receptors, which are located in the emetic centers of the brainstem and gastrointestinal tract.[6] Inhibition of these receptors prevents the vomiting that may be induced by chemotherapeutic agents.

4.4.2 Pharmacodynamics

Phase 1 studies were conducted to explore the relationship between plasma aprepitant concentrations on Days 2-4 after a single infusion of fosaprepitant 150mg and NK1 receptor occupancy. NK1 receptor occupancy after a single 150mg I.V. dose of fosaprepitant was found to be >90% through Day 3 and >80% through Day 4. The sponsor hypothesized that efficacy of fosaprepitant 150mg would be similar to that of the aprepitant 3-day regimen; although, no relationship between NK1 receptor occupancy and efficacy has been established.

No pharmacodynamic evaluation was conducted for fosaprepitant; however, PD studies conducted with aprepitant focus on 50-90% NK1 receptor occupancy in relation to oral doses of 10, 30, 100, and 300mg. The sponsor reports that >90% receptor occupancy has been considered generally efficacious based on the percentage of patients achieving complete response.

No QT prolongation is expected with fosaprepitant 150mg based on the results of a prior thorough QT study, where no QT prolongation was evidenced for fosaprepitant 200 mg infused over 15 minutes.

4.4.3 Pharmacokinetics

Within 30 minutes of the end of infusion, fosaprepitant is rapidly converted to aprepitant. This conversion is not CYP dependent and may occur in many extrahepatic tissues. Aprepitant is metabolized primarily by CYP3A, with minor metabolism by CYP1A2 and CYP2C19. PK characteristics of aprepitant after a 20 minute infusion of 150mg fosaprepitant in 41 healthy volunteers are as follows:

6 K Jordan, C Sippel, and H-J Schmoll. The Oncologist 2007;12:1143–1150.

- AUC = 35467 ng*h/mL
- Cmax = 4035 ng/mL
- T1/2 = 11.1 hours
- Vdss = 70 mL (aprepitant is >95% bound to plasma proteins)

With a 30% increase in fosaprepitant between the 150mg and 115mg doses, AUC increases by 20-50% and Cmax increases by 30-47%. No dosage adjustment is required for gender, race, age (>18 years-old), mild to moderate hepatic impairment, renal impairment, or ESRD patients undergoing hemodialysis. Aprepitant has not been studied in patients with severe hepatic impairment.

5 Sources of Clinical Data

Clinical data to support this single dose fosaprepitant 150mg regimen is provided from two trials: clinical efficacy and safety trial (P017L1) and pharmacokinetic study (P018L1). The table below summarizes the details of these trials.

5.1 Tables of Studies/Clinical Trials

Table 4: Clinical Trials in Support of Fosaprepitant 150mg*

Study Number	Methodology	Study Population			Diagnosis/Inclusion Criteria	Dosage/ Duration	Evaluation Criteria
		M	F	Age Range			
P017L1	A worldwide, multicenter, randomized, double-blind, parallel-group trial to assess the safety, tolerability, and efficacy of a single dose of intravenous fosaprepitant for the prevention of CINV in patients receiving cisplatin chemotherapy	1470	852	19-83 20-86	Male and female patients ≥ 18 years of age, scheduled to receive their first course of cisplatin chemo-therapy for a documented solid malignancy at a dose of 70 mg/m2 administered over a maximum of 3 hours.	Fosaprepitant Regimen: • Day 1 = fosaprepitant 150 mg IV with ondansetron 32 mg IV and dexamethasone 12 mg • Day 2 =dexamethasone 8 mg • Days 3 and 4 = dexamethasone 16 mg Aprepitant regimen: • Day 1 = aprepitant 125 mg PO with ondansetron 32 mg IV and dexamethasone 12 mg • Days 2 and 3 = aprepitant 80 mg with dexamethasone 8mg • Day 4 = dexamethasone 8mg	Efficacy: • 1º endpoint = proportion of patients with Complete Response (no vomiting and no use of rescue therapy) overall (120 hours). • 2º endpoints = proportion of patients with Complete Response in the delayed phase (25 to 120 hours) and proportion of patients with no vomiting overall (120 hours). Safety: • Events related to the primary endpoint (vomiting, retching, nausea) were not defined as adverse experiences during Day 1 until the morning of Day 6, unless they met the definition of a serious adverse experience. • Severe infusion site pain, severe infusion site erythema and/or severe infusion site induration, as well as any episode of infusion site thrombophlebitis were designated Events of Clinical Interest (ECI).

		Study Population					
P018L1	An open-label, 2-part, randomized, 2-period, crossover, single- center study to evaluate the effect of a single 150-mg I.V. dose of fosaprepitant dimeglumine on pharmacokinetics of oral dexamethasone in Part 1, and on pharmacokinetics of oral midazolam in Part 2, in healthy young adult subjects.	M: 16	F: 7	Age Range: 18 to 45 yrs.	Healthy, nonsmoking adult males and females between 18 and 45 years of age who were within 30% of ideal weight. Female subjects could not be pregnant or breast- feeding. Female subjects of childbearing potential were required to use specified birth control measures.	Study drug was administered in the fasted state. Minimum 14-day washout period. The duration of the study for each subject was ~7 weeks. • Part 1: Trt A: a single 8-mg oral daily dose of dexamethasone on Days 1, 2, and 3; Trt B: a single 8-mg oral daily dose of dexamethasone on Days 1, 2, and 3 with a single 150-mg fosaprepitant I.V. dose infused over 30 mins on Day 1 • Part 2: Trt C: a single 2-mg oral daily dose of midazolam syrup on Days 1 and 4; Trt D: a single 2-mg oral daily dose of midazolam syrup on Days 1 and 4 with a single 150-mg fosaprepitant I.V. dose infused over 30 mins on Day 1.	Pharmacokinetics: • Plasma pharmacokinetics (AUC, Cmax, Tmax, and t½) with fosaprepitant/ without fosaprepitant were determined for dexamethasone (AUC0-24hr) in Part 1 and for midazolam (AUC0-∞) in Part 2. Plasma samples collected for possible fosaprepitant and aprepitant concentration assay were archived. • Safety: The safety and tolerability of the study drugs administered were assessed through clinical and laboratory safety evaluations including physical examination, vital sign measurements, 12-lead ECGs, laboratory safety tests, and monitoring for adverse experiences. In periods when fosaprepitant was administered (Trts B and D), an injection site evaluation was obtained at various time points to evaluate tolerability.

*Adapted from Sponsor's Table 5.2: Table of All Clinical Studies.

5.2 Review Strategy

This clinical review discusses both efficacy and safety results for the single dose fosaprepitant 150mg regimen. One pivotal trial (P017L1) was performed to support the efficacy of this new single dose regimen, while the safety population is taken from both the pivotal efficacy trial and the pharmacokinetic study (P018L1).

5.3 Discussion of Individual Studies/Clinical Trials

The clinical trial P017L1 was a multicenter, randomized, double-blind, parallel-group trial to assess the safety, tolerability, and efficacy of a single dose of intravenous fosaprepitant for the prevention of CINV in patients receiving cisplatin chemotherapy.

5.3.1 Study Design

- **Study Title:** A Phase III, Randomized, Double-Blind, Active Controlled, Parallel-Group Study, Conducted Under In-House Blinding Conditions, to Examine the Safety, Tolerability, and Efficacy of a Single Dose of Intravenous MK-0517 for the Prevention of Chemotherapy-Induced Nausea And Vomiting (CINV) Associated with Cisplatin Chemotherapy

- **Study Objectives**:
    - **Primary:** (1) To compare the single-dose fosaprepitant dimeglumine regimen and the aprepitant regimen with respect to efficacy in the first cycle of cisplatin-based HEC. (2) To evaluate the safety and tolerability of the single-dose fosaprepitant dimeglumine regimen for CINV.
    - **Secondary:** (1) To compare the single-dose fosaprepitant dimeglumine regimen and the aprepitant regimen in terms of the proportion of patients with a complete response (no vomiting and no use of rescue therapy) in the delayed phase (25 to 120 hours following initiation of cisplatin). (2) To compare the single-dose fosaprepitant dimeglumine regimen and the aprepitant regimen in terms of the proportion of patients with no vomiting overall (in the 120 hours following initiation of cisplatin).

- **Study dates:** February 13, 2008 to June 29,2009

- **Study sites**: 149 sites worldwide, representing 27 countries**:**
    - 22 study sites in North America (United States, Mexico, Panama, Canada, Guatemala);
    - 33 study sites in South America (Columbia, Venezuela, Peru, Brazil, Chile);
    - 64 study sites in Europe (Lithuania, Italy, Portugal, Germany, Netherlands, Denmark, Spain, Hungary, Romania, Sweden, Poland, Russia);
    - 30 study sites in the Asia Pacific (Hong Kong, India, New Zealand, Korea);

- 5 sites in South Africa.

- **Major inclusion/exclusion criteria**:
  - Male and female patients ≥ 18 years of age
  - Scheduled to receive their first course of cisplatin chemotherapy for a documented solid malignancy at a dose of 70 mg/m2 administered over a maximum of 3 hours.
  - Patient has not vomited in the 24 hours prior to Treatment Day 1.
  - Patient has not received or will not receive radiation therapy to the abdomen or pelvis in the week prior to Treatment Day 1 through Day 6.
  - Patient does not have a history of hypersensitivity to aprepitant, ondansetron, or dexamethasone
  - Patient will not receive multiple-day chemotherapy with cisplatin in a single cycle.
  - Patient will not receive chemotherapy of moderate or high emetogenicity during the 6 days prior to the cisplatin infusion and/or during the 6 days following cisplatin infusion.

- **Treatments**:
  - Fosaprepitant regimen: Fosaprepitant dimeglumine 150 mg IV, ondansetron 32 mg IV, and dexamethasone 12 mg PO on Day 1, dexamethasone 8 mg PO on Day 2, and dexamethasone 16 mg PO on Days 3 and 4.
  - Aprepitant regimen: Aprepitant 125 mg PO, ondansetron 32 mg IV, and dexamethasone 12 mg PO on Day 1, aprepitant 80 mg PO and dexamethasone 8 mg PO on Days 2 and 3, dexamethasone 8 mg PO on Day 4.

Reviewer's Comments
The choice of active control is appropriate for this study because the current standard of care for prevention of CINV-HEC includes aprepitant.

5.3.2. Patient Disposition

Of the 2322 patients randomized, >93% completed the study in either treatment group. Approximately 3% discontinued due to a clinical adverse event, 1.2% lost to follow-up and 1.7% due to voluntary withdrawal.

Table 5: Patient Disposition for Study P017L1 by Treatment Group

	Fosaprepitant Regimen		Aprepitant Regimen		Total	
	n	(%)	n	(%)	n	(%)
SCREENING FAILURES:					163	
RANDOMIZED:	1147		1175		2322	
COMPLETED:	1080	94.2	1094	93.1	2174	93.6
DISCONTINUED:	67	5.8	81	6.9	148	6.4
Clinical adverse experience	32	2.8	36	3.1	68	2.9
Laboratory adverse experience	0	0.0	0	0.0	0	0.0
Other	35	3.1	45	3.8	80	3.4

- **Study populations:**
  - Full Analysis Set (FAS) population (n = 2247) are patients who have received cisplatin, taken at least one dose of study drug and completed at least one post-treatment efficacy assessment. The FAS population was used to evaluate all efficacy endpoints.
  - Per Protocol (PP) population (n = 2203) are patients without major protocol deviations. The PP population was used to evaluate primary and secondary endpoints.
  - Safety population are patients who have received at least one dose of the study drug

5.3.3 Patient Demographics

The study population consisted of mostly males (63.3%), patients aged over 55 years (58.4%), of Caucasian race (56.1%), of non-Hispanic or Latino ethnicity (67.1%), and located outside of the US (96.7%). These demographic characteristics were similarly balanced between the two treatment groups.

Table 6: Baseline Patient Demographic by Treatment Group

	Fosaprepitant Regimen n (%)	Aprepitant Regimen n (%)	Total n (%)
Patients in population	1,147	1,175	2,322
Gender			
Male	722 (62.9)	748 (63.7)	1,470 (63.3)
Female	425 (37.1)	427 (36.3)	852 (36.7)
Age (YEARS)			
< 55	491 (42.8)	475 (40.4)	966 (41.6)
≥ 55	656 (57.2)	700 (59.6)	1,356 (58.4)
17 and under	0 (0.0)	0 (0.0)	0 (0.0)
18 to 34	67 (5.8)	68 (5.8)	135 (5.8)
35 to 54	424 (37.0)	407 (34.6)	831 (35.8)
55 to 64	402 (35.0)	418 (35.6)	820 (35.3)
65 to 74	226 (19.7)	246 (20.9)	472 (20.3)
Over 74	28 (2.4)	36 (3.1)	64 (2.8)
Mean	55.2	55.9	55.6
SD	11.9	12.0	12.0
Median	56.0	57.0	57.0
Range	19 to 86	19 to 82	19 to 86
Race			
AMERICAN INDIAN OR ALASKA NATIVE	32 (2.8)	33 (2.8)	65 (2.8)
ASIAN	296 (25.8)	306 (26.0)	602 (25.9)
BLACK OR AFRICAN AMERICAN	21 (1.8)	22 (1.9)	43 (1.9)
MULTI-RACIAL	149 (13.0)	157 (13.4)	306 (13.2)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (0.1)	2 (0.2)	3 (0.1)
WHITE	648 (56.5)	655 (55.7)	1,303 (56.1)
Ethnicity			
HISPANIC OR LATINO	370 (32.3)	393 (33.4)	763 (32.9)
NOT HISPANIC OR LATINO	777 (67.7)	782 (66.6)	1,559 (67.1)
Region			
US	31 (2.7)	35 (3.0)	66 (2.8)
EX-US	1,112 (96.9)	1,134 (96.5)	2,246 (96.7)

Sponsor's Table 10-7, Study Report p017L1, p. 71-72.

The most common primary tumor types in the study population were respiratory and mediastinal cancer (46.9%), gastrointestinal cancer (21.4%) reproductive and genitourinary (15.1%). The treatment groups were similarly balanced for tumor types, history of motion sickness, vomiting with pregnancy, and receiving concomitant highly or moderately emetogenic chemotherapy on Day 1.

Table 7: Baseline Patient Characteristics by Treatment Group

	Fosaprepitant Regimen n (%)	Aprepitant Regimen n (%)	Total n (%)
Type of malignancy			
Breast Cancer	33 (2.9)	26 (2.2)	59 (2.5)
Endocrine Cancer	1 (0.1)	10 (0.9)	11 (0.5)
Gastrointestinal Cancer	251 (21.9)	247 (21.0)	498 (21.4)
Hepatic and Biliary Cancer	8 (0.7)	16 (1.4)	24 (1.0)
Lymphoma	10 (0.9)	13 (1.1)	23 (1.0)
Miscellaneous or Site Unspecified	60 (5.2)	57 (4.9)	117 (5.0)
Nervous System Cancer	1 (0.1)	1 (0.1)	2 (0.1)
Renal and Urinary Tract Cancer	49 (4.3)	41 (3.5)	90 (3.9)
Reproductive and Genitourinary Cancer	172 (15.0)	178 (15.1)	350 (15.1)
Respiratory and Mediastinal Cancer	530 (46.2)	558 (47.5)	1,088 (46.9)
Skeletal Cancer	8 (0.7)	7 (0.6)	15 (0.6)
Skin Cancer	21 (1.8)	15 (1.3)	36 (1.6)
History of motion sickness			
Yes	0 (0.0)	3 (0.3)	3 (0.1)
No	1,143 (99.7)	1,166 (99.2)	2,309 (99.4)
History of vomiting associated with Pregnancy			
Yes	3 (0.3)	3 (0.3)	6 (0.3)
No	420 (36.6)	421 (35.8)	841 (36.2)
Concomitant HEC or MEC on Day 1			
Yes	78 (6.8)	84 (7.1)	162 (7.0)
No	1,065 (92.9)	1,085 (92.3)	2,150 (92.6)

Patients are counted a single time for Type of Malignancy, Motion Sickness and Vomiting Associated with Pregnancy. Treated patients are considered for the categories: Type of Malignancy, History of motion sickness and History of vomiting associated with pregnancy Only female patients are considered for History of vomiting associated with pregnancy. HEC= highly emetogenic chemotherapy MEC=moderately emetogenic chemotherapy

Sponsor's Table 10-7, Study Report p017L1, p. 72

5.3.4 Study Procedure

Study participants were administered the fosaprepitant single dose IV or aprepitant 3-day oral regimen, and the placebo equivalent for blinding, based upon their randomization allocation. Dosing began 1 hour prior to cisplatin infusion and ended on the evening of Day 4 with dexamethasone 8mg or the matching placebo.

Patients used a diary to monitor efficacy for 120 hours following the cisplatin infusion. The dairy was used to record vomiting or retching episodes, use of rescue therapy, and daily nausea ratings (by VAS, visual analog scale) each morning. Nurse coordinators trained the patients on the definition of vomiting and how to use the VAS. Patients were monitored for adverse events and tolerability at all visits plus 14 days post therapy.

- **Study endpoints**:
    - **Efficacy:** The primary endpoint assessed was the proportion of patients with Complete Response (no vomiting and no use of rescue therapy) overall (in the 120 hours following initiation of cisplatin). The secondary endpoints were 1) the proportion of patients with Complete Response (no vomiting and no use of rescue therapy) in the delayed phase (25 to 120 hours following initiation of cisplatin), and 2) the proportion of patients with no vomiting overall (in the 120 hours following initiation of cisplatin).

Reviewer's Comments

The choice of primary endpoint and secondary endpoint #1 was based on historical clinical studies where Complete Response was used to support approval of antiemetic drugs for CINV prevention. The endpoint has also been used in pivotal trials of both aprepitant and fosaprepitant. The secondary endpoint of No Vomiting Overall is directed towards a feared side effect of chemotherapy and supportive of the proposed indication. The decision to not include Complete Response acute phase as a primary or secondary endpoint seems logical to this reviewer, as the NK1 receptor antagonists are valued for their treatment effect during the delayed phase, while other antiemetic drugs perform better in the acute phase (e.g.. ondansetron). The Sponsor may also have chosen not to use Complete Response acute phase because of failure to succeed with this endpoint in a prior Phase 2 study of the combination fosaprepitant mannitol 100mg/ oral aprepitant multi-day regimen (Study P007L1). Complete Response in the acute phase is included as an exploratory endpoint.

    - **Safety:** Pre-study and post-study measurements were collected: medical history, physical exam, 12- lead ECG (pre-study only), laboratory tests including hematology, chemistry, urinalysis and pregnancy tests for females of child-bearing potential. Events related to the primary endpoint (vomiting, retching, nausea) were not defined as adverse experiences during the period of data collection with the diary, Day 1 until the morning of Day 6, unless they

met the definition of a serious adverse experience. Severe infusion site pain, severe infusion site erythema and/or severe infusion site induration, as well as any episode of infusion site thrombophlebitis were designated Events of Clinical Interest (ECI). All adverse events were analyzed using the NCI Common Toxicity Criteria for Adverse Events v3.0.

Efficacy and safety outcomes are reviewed below in sections 6 and 7, respectively.

6 Review of Efficacy

Efficacy Summary

A multicenter, randomized, double-blind, parallel-group trial (P017L1) was performed to assess the efficacy, safety, and tolerability of a single dose of intravenous fosaprepitant for the prevention of CINV in patients receiving highly emetogenic cisplatin chemotherapy. Patients were randomized to receive either the single day fosaprepitant 150mg regimen or the approved 3-day oral aprepitant regimen. The primary endpoint assessed was the proportion of patients with Complete Response (no vomiting and no use of rescue therapy) overall (in the 120 hours following initiation of cisplatin). The secondary endpoints were 1) the proportion of patients with Complete Response (no vomiting and no use of rescue therapy) in the delayed phase (25 to 120 hours following initiation of cisplatin), and 2) the proportion of patients with no vomiting overall (in the 120 hours following initiation of cisplatin). The difference in treatment response between the fosaprepitant and aprepitant groups was evaluated and the fosaprepitant single day regimen demonstrated non-inferiority compared to the 3-day oral aprepitant regimen. See Table 8.

Table 8: Summary of Efficacy Endpoints with Non-Inferiority Margins

Hypothesis Level and Endpoint	Lower Bound Needed For Non-inferiority	Actual Lower Bound	Actual P-Value†	Conclusion
Primary				
Complete Response – overall phase	>-7 percentage points	-4.1 percentage points	--	Non-inferior
Secondary				
No Vomiting – overall phase	>-8.2 percentage points	-5.3 percentage points	0.0002	Non-inferior
Complete Response – delayed phase	>-7.3 percentage points	-3.5 percentage points	0.00003	Non-inferior
† P-value associated with the 95% confidence interval for the difference (fosaprepitant – aprepitant) in response rates.				

Sponsor's Table 11-2, Summary of Efficacy by Primary and Secondary Hypotheses
Full Analysis Set Patient Population, Study report P017L1, p. 88.

The subpopulation analysis by major demographic factors (e.g., age, gender, race, and concomitant use of highly- or moderately-emetogenic chemotherapy on Day 1 of cisplatin administration) found comparable response rates between the two treatment groups. The subgroup analysis by region (US vs. outside US), however, demonstrated that response rates from the US-based study population (n=58) favored the aprepitant 3-day regimen over the new fosaprepitant regimen (~15% difference in effect size). The very small US sample size prohibits a definitive conclusion that the single day fosaprepitant 150mg regimen would not be comparable to the aprepitant 3-day regimen in the larger US chemotherapy patient population.

Trial P017L1 only provides evidence to support prevention of CINV in patients receiving HEC regimens, such as cisplatin. (b) (4)

6.1 Indication

For the EMEND™ for Injection (fosaprepitant dimeglumine) 150mg single dose regimen, the sponsor proposes the indication of prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin (cisplatin ≥70 mg/m2) (CINV-HEC), (b) (4)

Reviewer's Comment:
The Sponsor submits only one pivotal efficacy trial in patients receiving highly emetogenic cancer chemotherapy to support (b) (4) ***CINV-HEC*** (b) (4) ***Results from one efficacy trial are usually not adequate to support an indication, however, one adequate and well-controlled trial, together with confirmatory evidence may be sufficient to establish effectiveness. This efficacy review evaluates the robustness of the results from clinical trial P017L1 in support of the CINV-HEC indication;*** (b) (4)

Throughout the regulatory history of aprepitant and fosaprepitant, there have been an adequate number of pivotal trials to support the CINV-HEC indication. (b) (4) ***The subsequent approval of fosaprepitant 115mg was primarily based on bioequivalence studies that supported***

fosaprepitant 115mg IV use as an alternative to aprepitant 125mg PO. (b) (4)

[redacted]

6.1.1 Statistical Methods

The design of the clinical study used to support the product efficacy in regards to the proposed indications has been presented in Section 5.3 of this document.

No intent-to-treat population analyses were performed. The FAS population was used for efficacy analysis, with PP population analyses also performed for the primary and secondary endpoints. Although 3.2% of randomized patients were excluded from the full analysis set population, the treatment groups in the FAS population remained balanced. For the FAS population, missing data within the delayed time period were imputed by carrying forward the preceding non-missing data in the same time period. No data were imputed in the acute time period. No missing data imputation was conducted for the PP population.

The primary, secondary, and exploratory endpoint response rates were evaluated for the difference between treatment groups. The primary and secondary endpoints were hypothesis-based; testing if the lower bound of the two-sided 95% CI (adjusted by gender) for the difference in response rates, between fosaprepitant and aprepitant treatment groups, was greater than the non-inferiority margin, then fosaprepitant would be considered non-inferior to aprepitant. Each non-inferiority margin was calculated as half of the treatment differential estimated by the lower 95% confidence bound for the treatment group difference observed in the pivotal clinical trials (P052, P054) of oral aprepitant and are listed in the table below.

Table 9: Non-Inferiority Margins for Primary and Secondary Endpoints

Response Rate	Non-Inferiority Margin
Primary endpoint • **Complete response in the overall phase**	**- 7.0%**
Secondary endpoints • **Complete response in the delayed phase** • **No vomiting in the overall phase**	**- 7.3%** **- 8.2%**

The differences and the 95% CI for the differences were calculated using the methodology of Miettinen and Nurminen. Secondary endpoints were evaluated only if the primary endpoint results were statistically significant.

Reviewer's Comments
The Miettinen and Nurminen method was discouraged by the Agency, however, the Sponsor chose to use the method for the primary analysis, and the Agency preferred method (Koch/Blackwelder) as a confirmatory secondary analysis. The efficacy endpoint analyses by both methods yielded similar statistical values. The adjustment for gender seeks to address the known difference between males and females, whereby, females have a baseline predisposition to emesis in addition to a 16% higher Cmax and 25% slower clearance of aprepitant than males.

6.1.2 Demographics

The demographics of clinical study P017L1 has been presented in Section 5.3 of this document.

6.1.3 Subject Disposition

Patient disposition for clinical study P017L1 has been presented in Section 5.3 of this document.

6.1.4 Analysis of Primary Endpoint

The primary endpoint for clinical efficacy trial P017L1 was patient's complete response (CR) in the overall phase (no vomiting and no use of rescue therapy in the 120 hours following initiation of cisplatin). The lower bound of the 95% CI for the difference between treatment groups had to be greater than -7 percentage points to establish non-inferiority of fosaprepitant compared to aprepitant.

Table 10 provides the results of primary endpoint analysis. The secondary endpoint of complete response in the delayed phase is also displayed in the following table.

Table 10: Number of Patients with Complete Response by Phase and Treatment Group

Phase	Fosaprepitant Regimen (A)		Aprepitant Regimen (B)		Difference (A-B) %
	n/m*	% (95% CI)	n/m*	% (95% CI)	(95% CI)†
Overall Phase	795/1106	71.9 (69.1, 74.5)	820/1134	72.3 (69.6, 74.9)	-0.4 (-4.1, 3.3)
Acute Phase	963/1082	89.0 (87.0, 90.8)	974/1107	88.0 (85.9, 89.8)	1.1 (-1.6, 3.8)
Delayed Phase	822/1106	74.3 (71.6, 76.9)	841/1133	74.2 (71.6, 76.8)	0.1 (-3.5, 3.7)

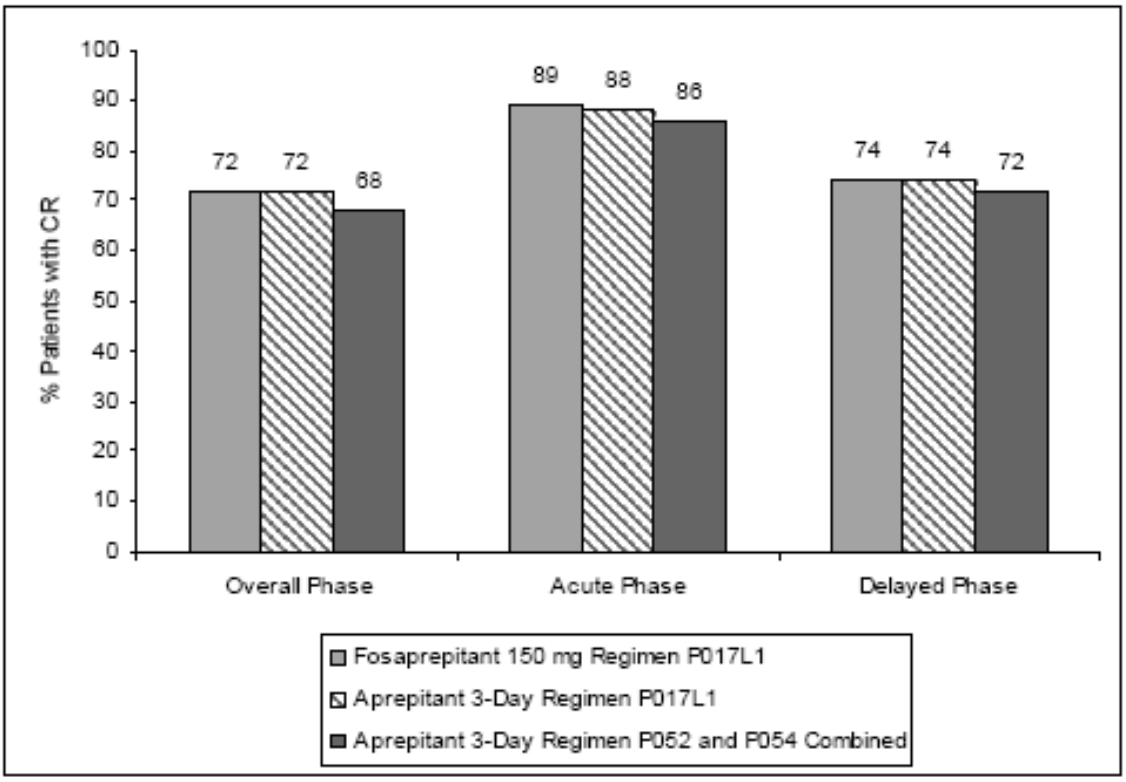
† The difference and the confidence interval (CI) for the difference were calculated using the method proposed by Miettinen and Nurminen and adjusted for Gender.
* n/m = Number of patients with Complete response/number of patients included in the analysis.

Sponsor's Table 11-3, Number (%) of Patients with Complete Response by Phase and Treatment Group with the Difference Between Treatment Groups Full Analysis Set Patient Population, Study Report P017L1, p. 90.

The difference in CR rates between treatment groups, for all phases, was minimal; ranging from -0.4 to 1.1%. The CR overall phase 95% CI lower bound for the difference was -4.1% (NI > -7.0%), while that for CR delayed phase was -3.5% (NI > -7.3%). Both the primary endpoint and secondary endpoint #1 demonstrated non-inferiority to the aprepitant 3-day regimen.

The CR rates in all phases were similar for fosaprepitant and aprepitant treatment groups in the P017L1 study compared to the overall, acute, and delayed pooled CR rates from the oral aprepitant clinical trials (P052 and P054), 68%, 86%, and 74%, respectively. See Figure 2.

Figure 2: Comparison of Complete Response Rates from Current and Historical Trials



Sponsor's Figure 2.5.6 of the Clinical Overview.

Reviewer's Comments
Comparison of the CR rates to the historical studies provides reproducibility of the effect of the active ingredient, aprepitant, in patients receiving HEC therapy.

6.1.5 Analysis of Secondary Endpoints(s)

The results of the secondary endpoint #1: CR delayed phase (no vomiting and no use of rescue therapy 25 to 120 hours following initiation of cisplatin) was described above.

Secondary endpoint #2 was no vomiting - overall (in the 120 hours following initiation of cisplatin). No Vomiting was defined as no vomiting, retching or dry heaves, regardless of whether or not the patient took rescue therapy to treat established nausea and/or vomiting. The lower bound of the 95% CI for the difference between treatment groups had to be greater than -8.2 percentage points to establish non-inferiority of fosaprepitant compared to aprepitant. Table 11 provides the results of this endpoint analysis. Exploratory No Vomiting acute phase and delayed phase endpoints are also demonstrated in the table.

Table 11: Number of Patients with No Vomiting by Phase and Treatment Group

Phase	Fosaprepitant Regimen (A)		Aprepitant Regimen (B)		Difference (A-B) %
	n/m*	% (95% CI)	n/m *	% (95% CI)	(95% CI)†
Overall Phase	806/1106	72.9 (70.2, 75.5)	844/1132	74.6 (71.9, 77.1)	-1.7 (-5.3, 2.0)
Acute Phase	966/1080	89.4 (87.5, 91.2)	983/1105	89.0 (87.0, 90.7)	0.6 (-2.0, 3.2)
Delayed Phase	836/1106	75.6 (72.9, 78.1)	865/1132	76.4 (73.8, 78.9)	-0.8 (-4.3, 2.7)

† The difference and the confidence interval (CI) for the difference were calculated using the method proposed by Miettinen and Nurminen and adjusted for Gender.
* n/m = Number of patients with No Vomiting/number of patients included in the analysis.

Sponsor's Table 11-5 Number (%) of Patients with No Vomiting by Phase and Treatment Group with the Difference Between Treatment Groups Full Analysis Set Patient Population, Study Report P017L1, p. 91.

The difference in No Vomiting rates between treatment groups, for all phases, was minimal; ranging from -1.7 to 0.6%. The No Vomiting overall phase 95% CI lower bound for the difference was -1.7% (NI > - 8.2), demonstrating non-inferiority to the aprepitant 3-day regimen.

6.1.6 Other Endpoints

The following exploratory endpoints were also evaluated:

1. Complete Response - Acute (0 to 24 hours following initiation of cisplatin);
2. No Vomiting - Acute (0 to 24 hours following initiation of cisplatin);
3. No Vomiting - Delayed (25 to 120 hours following initiation of cisplatin);
4. No Significant Nausea (VAS <25 mm) - Overall (0 to 120 hours following initiation of cisplatin);
5. No Impact on Daily Life (FLIE total score >108) - overall;
6. Time to first vomiting/retching episode- Overall (0 to 120 hours following initiation of cisplatin), regardless of use of rescue therapy;
7. No Nausea (VAS <5 mm) - Overall (0 to 120 hours following initiation of cisplatin);
8. Complete Protection- Overall (no vomiting, no use of rescue therapy and maximum nausea VAS <25 mm; evaluated 0 to 120 hours following initiation of cisplatin);
9. Total control – Overall (no vomiting, no use of rescue therapy, and maximum nausea VAS <5 mm; evaluated 0 to 120 hours following initiation of cisplatin);

10. No use of rescue therapy - Overall (0 to 120 hours following initiation of cisplatin);
11. Functional Living Index-Emesis Overall Phase - nausea and vomiting domains.

The fosaprepitant 150mg regimen was shown to be comparable to the aprepitant 3-day regimen for all exploratory endpoints. Analysis results of the difference between treatment groups for exploratory endpoints #1-3 are shown in Tables 10 and 11 above.

Reviewer's Comments
The eleven exploratory endpoints have little additional value to the demonstration of efficacy in this trial relative to the primary and secondary endpoints. Additionally, these exploratory endpoints will not be eligible for inclusion in labeling. Therefore, this reviewer will not present a detailed review of these exploratory endpoints.

6.1.7 Subpopulations

The primary and secondary endpoints were evaluated by major demographic factors to ensure consistency of treatment effect across subpopulations. The fosaprepitant 150mg single day regimen provided similar CR rates as the aprepitant 3-day regimen regardless of age category; gender; White, Black and Asian race groups; and concomitant use of HEC or MEC on Day 1 of cisplatin administration. The major difference in treatment effect was demonstrated by regional group: US compared to outside of the US (Ex-US). While patients enrolled in Ex-US sites showed comparable response rates between treatment groups (72.2% and 72.3%), US patients in the aprepitant treatment group had numerically higher response rates (71%) than those US patients in the fosaprepitant treatment group (55.6%). In both US treatment groups, the numbers of patients were very small (n = ~30) and therefore these results should be interpreted with caution. Table 12 presents the CR rates by treatment group and population subgroup.

Table 12: Complete Response Rates Overall by Subgroup and Treatment Group

	Fosaprepitant Regimen n/m (%)	Aprepitant Regimen n/m (%)
Age Group (years)		
Age < 55 Age >= 55	321/479 (67.0) 474/627 (75.6)	307/459 (66.9) 513/675 (76.0)
Gender Group		
Male	537/698 (76.9)	555/718 (77.3)
Female	258/408 (63.2)	265/416 (63.7)
Race Group		
White Black Asian Multi-Racial Other	470/622 (75.6) 13/18 (72.2) 200/289 (69.2) 92/147 (62.6) 20/30 (66.7)	473/637 (74.3) 15/21 (71.4) 208/292 (71.2) 107/153 (69.9) 17/31 (54.8)
Region Group		
US Ex US	15/27 (55.6) 772/1069 (72.2)	22/31 (71.0) 790/1093 (72.3)
Concomitant Chemotherapy		
Yes	53/76 (69.7)	58/83 (69.9)
No	742/1030 (72.0)	762/1051 (72.5)
Complete Response = No vomiting and no use of rescue therapy. n/m = Number of patients with desired response/number of patients included in subgroup		

Sponsor's Table 11-13, Number (%) of Patients With Complete Response in the Overall Phase by Subgroup and Treatment Group (Full Analysis Set Patient Population), Study Report P017L1, p. 99.

The same pattern of response rates by subpopulation was seen for the No Vomiting Overall endpoint in which all demographic factors except regional group demonstrated similar treatment effects. Patients enrolled in Ex-US sites showed comparable response rates between fosaprepitant and aprepitant treatment groups (73.1% and 74.1%, respectively). However, US patients in the aprepitant treatment group had numerically higher response rates (90.3%) than those US patients in the fosaprepitant treatment group (63%).

The sponsor acknowledges the regional differences in CR rates and provides an evaluation based on recommendations of the ICH E5 guidance and the ability to extrapolate the results from one geographic region to another. The Sponsor reviewed a variety of factors defined in ICH E5 as potentially influencing the ability to extrapolate results from data in various geographic regions, including regional differences in the

medical practice, disease definition, and different aspects of the study population. The Sponsor states that regional differences identified as potentially influencing the drug's efficacy and safety are unlikely, and data generated outside the US in this study is relevant to the US population and medical practice.

Reviewer's Comments
There is a ~15% difference in CR Overall rate and ~27% difference in No Vomiting Overall rate between treatment groups for the US subgroup. This is concerning since fosaprepitant 150 mg single day regimen is being reviewed for marketing in the US population. Unfortunately, because this is a multinational study, each country has only a small to moderately sized patient population, thus making accurate interpretation of the subgroup results difficult.

The Sponsor provided further breakdown of CR Overall and No Vomiting Overall to evaluate grouping of countries. The US was grouped with the EU, Canada, and New Zealand to demonstrate similar results by treatment group. See Table 13***.***

Table 13: Complete Response and No Vomiting Overall by Regional Subgroup and Treatment Group

	Fosaprepitant Regimen	Aprepitant Regimen
	n/m (%)	n/m (%)
Complete Response in Overall Phase		
US, EU, Canada, NZ	333/436 (76.4)	331/444 (74.5)
Other Countries	462/670 (69.0)	489/690 (70.9)
No Vomiting in Overall Phase		
US, EU, Canada, NZ	340/436 (78.0)	347/443 (78.3)
Other Countries	466/670 (69.6)	497/689 (72.1)
No Vomiting = No vomiting or retching or dry heaves.		
n/m = Number of patients with desired response/number of patients included in time point		

Sponsor's Table 2.5: 11, Number (%) of Patients With Complete Response and No Vomiting in the Overall Phase by Subgroup and Treatment Group (Full Analysis Set Patient Population) P017L1, 2.5 Clinical Overview, p.29.

This reviewer does not understand these groupings because there is still too much cultural variability that may affect the results of a clinical study. The EU study sites comprise the countries of Denmark, Germany, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Romania, Spain, and Sweden. This reviewer grouped the results for North American countries compared to Non-North American countries to try to understand if the difference in treatment

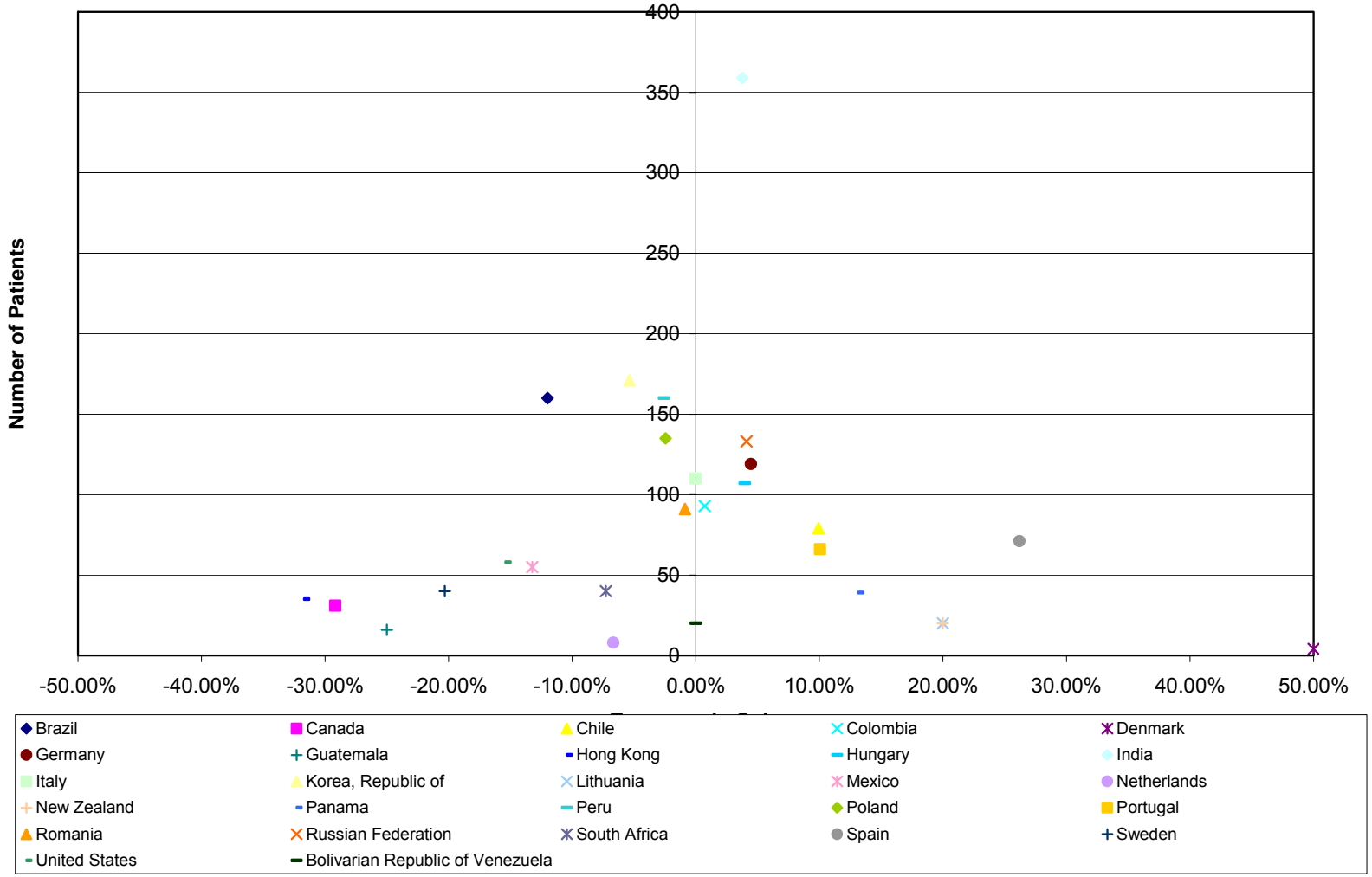
effect by treatment group persisted. This is demonstrated in the Reviewer's Table below.

Table 14: Complete Response and No Vomiting Overall -- North American Subgroup Compared to Non-North American Subgroup

	Fosaprepitant Regimen	**Aprepitant Regimen**
	n/m* (%)	**n/m* (%)**
Complete Response in Overall Phase		
US and Canada	21/43 (48.8)	32/46 (69.6)
US, Canada, Mexico	37/71 (52.1)	51/73 (69.8)
Other Countries	758/1035 (73.2)	769/1061 (72.5)
*n/m = Number of patients with desired response/number of patients included in time point		

Table 14 demonstrates the remaining concern about efficacy results by region because the treatment difference has increased to approximately 20% when the US was grouped, first, with Canada, or, second, with Canada and Mexico. The fact of small sample size still persists. A graphical presentation of each country's CR overall therapeutic gain by sample size shows a normal shaped distribution. The majority of countries with small sample sizes (including the US) had results that favored the aprepitant 3-day regimen over the fosaprepitant regimen, while countries with larger sample sizes tended to favor the fosaprepitant regimen over the aprepitant 3-day regimen and have smaller differences between treatment groups. See Figure 3. Even the removal of outliers such as India (n=359) and Spain (therapeutic gain = 26%), do not change the CR Overall results of this efficacy study; the single-day fosaprepitant regimen is non-inferior to aprepitant 3-day regimen.

Figure 3: Therapeutic Gain by Country and Number of Patients



The Sponsor also provided a breakdown of CR Overall and No Vomiting Overall by baseline demographics, region, and treatment group. Only the demographic factors of gender and age were imbalanced between treatment groups for the US vs. Ex-US-based study sites. Although no conclusion is drawn regarding the age distributions, the sponsor considers the results by gender (% female in U.S.=43% [n=29], % female outside of US =36% [n=813]) to be generally similar in patients treated both within and outside of the US.

Table 15: Baseline Patient Demographics by Region and Treatment Group

	Fosaprepitant Regimen n (%)	**Aprepitant Regimen n (%)**	**Total n (%)**
Ex US population	**1,105**	**1,130**	**2,235**
US population	**32**	**35**	**67**
Ex US Gender Group			
Male	701 (63.4)	721 (63.8)	1,422 (63.6)
Female	404 (36.6)	409 (36.2)	813 (36.4)
US Gender Group			
Male	**16 (50.0)**	22 (62.9)	38 (56.7)
Female	**16 (50.0)**	13 (37.1)	29 (43.3)
Ex US Age Group			
Age < 55	483 (43.7)	467 (41.3)	950 (42.5)
Age >= 55	622 (56.3)	663 (58.7)	1,285 (57.5)
US Age Chemotherapy			
Age < 55	**3 (9.4)**	5 (14.3)	8 (11.9)
Age >= 55	**29 (90.6)**	30 (85.7)	59 (88.1)

From Sponsor's Table 1, Baseline Patient Demographics and Characteristics by Treatment Group EX-U.S. and U.S., Response to Filing Letter, p.3.

Reviewer's Comments

Due to the imbalance of gender distribution between the treatment groups by region, the influence of gender on efficacy results discrepancy by region (US vs. Ex-US) would be probable. However, efficacy results were adjusted for gender. Additionally, a review of CR Overall rates by gender in US patients shows that both male and female response rates favored the aprepitant 3-day regimen over the fosaprepitant single day regimen.

Reviewer's Table: CR Overall Rates by Gender in US Patients*

Gender	*Aprepitant* n/m (%)	*Fosaprepitant* n/m (%)
M	*14/18 (77.8)*	*9/15 (60.0)*
F	*8/13 (61.5)*	*6/12 (50.0)*

*Adapted from table of analysis of complete response by country by Biostatistical reviewer, Dr. WJ Chen.

Again, we are confronted with the issue of how to accurately draw conclusions from small sample sizes. Lastly, there exists a difference in age group distribution between US vs. Ex-US patients. Although difficult to explain, cultural differences may be a contributing factor. Consider that the US has routine preventive medicine and public health measures that support early screening for cancers and reduce exposure to proven carcinogens (i.e., tobacco). The dangers of tobacco use are not similarly emphasized in some nations as in the US. Therefore, the use in adolescents may be less strongly discouraged, and the early exposure to the carcinogens of tobacco leads to early presentation of cancer.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

This NDA efficacy supplement is supported by one pivotal clinical trial and one dosage level of fosaprepitant. Prior clinical studies with various fosaprepitant and aprepitant doses and regimens were performed to assist in dose selection.

A single-day regimen of fosaprepitant 100 mg IV was shown to be less effective in preventing CINV than multiple-day regimens (P004), suggesting that doses higher than 100 mg would be needed to achieve efficacy similar to or greater than that of the aprepitant 3-day regimen. Single doses of fosaprepitant 200 mg IV were tolerated but were associated with a significant incidence (45.5%) of local tolerability reactions that were considered excessive for an alternative to the aprepitant 3-day regimen. Potential doses within this range were evaluated to achieve a comparable NK1 receptor occupancy level (~ 90% or higher) to the aprepitant 3-day regimen. With less adverse tolerability reactions, the Sponsor predicted NK1 receptor occupancy levels would remain greater than 90% through at least Day 3 following a single 150 mg IV fosaprepitant dimeglumine dose administered over 20-30 minutes, and greater than or equal to approximately 80% through at least Day 4. Based on these findings, fosaprepitant 150 mg IV was expected, to provide efficacy for CINV prevention similar to the aprepitant 3-day regimen.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

An analysis of CR Overall and No Vomiting Overall endpoints by treatment day and treatment group was performed using the Per Protocol population. All response rates

for the individual days were >80% and were comparable between the two treatment groups.

Patient tolerance of study drug effects is demonstrated by the high (98%) study drug compliance with fosaprepitant injection, aprepitant and dexamethasone tablets/capsules.

(b) (4)

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7 Review of Safety

Safety Summary

The safety of fosaprepitant 150mg was evaluated in two clinical studies; P017L1 and P018L1. A net total of 1,153 patients and subjects were exposed to a single dose of fosaprepitant 150mg. The incidence of overall adverse events (AE), drug-related AEs, serious AEs, and deaths were similar for both fosaprepitant and aprepitant treatment groups. The fosaprepitant treatment group, however, demonstrated a 40% higher incidence in AEs leading to discontinuation than the aprepitant treatment group.

Table 16: Summary of Overall Adverse Events for Total Exposed Population*

	Fosaprepitant 150mg n (%)	**Aprepitant 3-Day n (%)**	**Difference between Treatment groups**
Study population	1,153	1,169	
with one or more AE	684 (59.3)	718 (61.4)	-2.1
with serious AE	149 (12.9)	157 (13.4)	-0.5
who died	23 (2.0)	26 (2.2)	-0.2
discontinued due to an adverse event	12 (1.0)	7 (0.6)	0.4

* Includes patients/subjects from clinical studies P017L1 and P018L1 exposed to fosaprepitant 150mg.

The common adverse events (>5% incidence) in the fosaprepitant treatment group are similar to those known for the oral aprepitant capsules and include constipation (10.6%), asthenia (8.6%), diarrhea (7.8%), anorexia (6.6%), vomiting (6.6%), nausea (5.9%), and hiccups (5.6%). However, many more infusion site pain reactions were reported with the fosaprepitant group (n=16) than the aprepitant group (n=1).

For nonfatal serious AE, all events were reported in <1% of patients in both treatment arms with the exception of febrile neutropenia, neutropenia, vomiting, and dehydration. However, these SAEs are expected within cancer chemotherapy and were demonstrated to be similar between the two treatment groups. Two patients (P017L1) and one subject (P018L1) experienced pulmonary embolism. None were considered related to the study drug: fosaprepitant (2), aprepitant (1). Only 4 SAEs were considered drug-related: mild constipation (1), hypertensive crisis/SVT (1), and elevated liver enzymes (2).

The incidence of death was comparable between the fosaprepitant group and the aprepitant group. All deaths were considered unrelated to the study drug and due to the natural history of cancer.

The incidence of adverse events leading to discontinuation was slightly higher in the fosaprepitant treatment group (n=11 (1.0%)) compared to the aprepitant treatment group (n=7 (0.4%)). This difference, however, does not appear to be clinically relevant as no incidence pattern was demonstrated by system organ class or treatment group. Two of the eleven AEs leading to discontinuation were considered related to fosaprepitant: hypertensive crisis and immediate hypersensitivity reaction.

Special interest adverse reactions are infusion site reactions and thrombophlebitis, hypersensitivity reactions, hypertension, and elevated liver enzymes.

- Since early clinical development, infusion site reactions have been a known risk with administration of fosaprepitant intravenously and incidence thresholds for these AEs were built into the CINV-HEC study (P017L1) as study stopping criteria. The incidence of all infusion site related AEs was 3.0% in the fosaprepitant treatment group (6x higher than the aprepitant treatment group (0.5%)). The incidence of severe infusion site AEs and thrombophlebitis were also higher in the fosaprepitant group 1.0% compared to the aprepitant group 0.1%. See section 7.3.4 Significant Adverse Events.
- Hypersensitivity has been a concern since postmarketing reports in 2008 demonstrated an increased incidence with aprepitant and fosaprepitant use. The incidence of hypersensitivity AEs in Study P017L1was similar between treatment groups for severity; however, more events occurred in the fosaprepitant treatment group compared to the aprepitant treatment group for Days 1 and 2 of study drug administration. See section 7.3.5 Submission Specific Primary Safety Concerns.
- The reported hypertension AEs show a higher incidence in the fosaprepitant group than in the aprepitant group (fosaprepitant n=17 (1.5%); aprepitant 7 (0.6%)). However, this increased incidence of hypertension in the fosaprepitant treatment group may stem from the imbalance of hypertension as baseline medical history in the treatment groups. Hypertension is also discussed in Section 7.3.5.
- Elevated liver enzymes are known to occur with use of fosaprepitant, aprepitant, and chemotherapy agents. A higher incidence of serum ALT >5X ULN was seen in patients treated with the fosaprepitant single day regimen (1.8%) compared to patients treated with the aprepitant 3-day regimen (0.5%). There were, however, no cases of drug-induced liver injury, or increased ALT >3x ULN associated with increased total bilirubin >2x ULN.

7.1 Methods

Clinical safety data for fosaprepitant 150mg single dose regimen reviewed in this section are provided in Module 2.5 Clinical Overview and Clinical Study Reports for P017L1 and P018L1.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Two studies were provided the clinical safety data for fosaprepitant 150mg single day regimen; the actively-controlled clinical trial P017L1 and the drug interaction study P018L1. Within each major safety result section, the safety from trial P017L1 will be presented first, followed by the same from study P018L1.

7.1.2 Categorization of Adverse Events

Adverse events were coded with MedDRA, version 10.1. Merck has utilized identical coding and verbatim practices in reporting adverse events for sites within and outside the U.S. Any adverse events terms that did not correspond with standard MedDRA terms reported by investigators within and outside of the U.S. were encoded using an identical standardized process.

The analysis of adverse events (AE) was divided into 3 tiers:

- Tier 1 – Infusion-site reactions (e.g., thrombophlebitis, severe pain, severe erythema, and severe induration) were considered events of clinical interest (ECI).
- Tier 2 – AE incidence ≥1%
- Tier 3 – AE incidence <1%

For both Tier 1 and Tier 2 AEs, the difference in incidences (fosaprepitant – aprepitant), corresponding 95% CI for the differences, and associated p-values were calculated using the methodology of Miettinen and Nurminen. The incidence of Tier 3 AEs was summarized by treatment group.

All adverse events were categorized for severity using the NCI Common Toxicity Criteria for Adverse Events v3.0.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The pooling of data across clinical trials P017L1 and P018L1 is appropriate for the evaluation of safety for fosaprepitant 150mg single dose regimen. Details of each trial

are provided above, in section 5.1, Table 4: Clinical Trials in Support of Fosaprepitant 150mg*.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

For clinical trial P017L1, 1131 patients received fosaprepitant; of which 1,128 received fosaprepitant 150mg IV single dose. See Table 17: Fosaprepitant Exposure by Dose. Another 1168 patients received at least 1 dose of oral aprepitant. Thirteen patients received both study drugs and are counted for exposure in both fosaprepitant and aprepitant. For clinical study P018L1, 22 subjects received a single dose of fosaprepitant 150mg on Day 1.

Table 17: Fosaprepitant Exposure by Dose

Fosaprepitant	1 Day	Total Patients†	Duration Range	Mean Duration
Any Dose	1,131	1,131	1 to 1 days	1.0 days
<150mg	3	3	1 to 1 days	1.0 days
150mg	1,128	1,128	1 to 1 days	1.0 days
†There were 13 patients who were randomized to the aprepitant regimen but received active fosaprepitant as well as aprepitant. These patients are included in both the fosaprepitant and aprepitant extent of exposure tables. Additionally, there were 12 patients who were randomized to the fosaprepitant regimen but received the placebo for fosaprepitant instead and did not take active aprepitant. These patients are not on either the fosaprepitant or aprepitant extent of exposure tables because they only received placebo therapy.				
Each patient is counted once on each applicable dosage category row.				

From Sponsor's Table 12-1, Extent of Exposure to Fosaprepitant by Dose, Study Report P017I1, p.104.

7.2.2 Explorations for Dose Response

The sponsor has performed explorations of dose response with aprepitant and fosaprepitant. See section 6.1.8. for a discussion of dose selection. Historical studies of fosaprepitant mannitol injections demonstrated less tolerability than that of the fosaprepitant polysorbate (PS80) formulations. Prior to P017L1, there were 80 normal healthy adult subjects exposed to the fosaprepitant PS80 formulations at single doses of 150 mg or higher. These Phase 1 clinical studies are summarized in the table below. Note that the approved marketed formulation of fosaprepitant is fosaprepitant PS80 (0.05%).

Table 18: Phase 1 Clinical Trials of Fosaprepitant Doses 150mg or 200mg

Protocol Number	No. of Subjects	Dose	Fosaprepitant Formulation	Aprepitant (MK- 0869) Mean Cmax ng/mL	Infusion related reactions
009	16	150 mg	PS80 0.25%	3796	N/A
012	16	150 mg	PS80 0.05%	4569†	7.6%
009	16	200 mg	PS80 0.25%	5317	N/A
016 (TQT study)	32	200 mg	PS80 0.05%:	6300‡	45.5%
Total:	80				
† Cmax value for 150 mg fosaprepitant dimeglumine for P012 is based on n=12. ‡ Cmax value for 200 mg fosaprepitant dimeglumine for P016 is based on n=30. PS = Polysorbate					

Adapted from Sponsor's Table 2.5:1, Clinical Overview, p.9.

Common adverse events in these three Phase 1 trials were headache, tenderness and swelling at the injection site. There were no serious AEs or discontinuations due to AE. However, in P016L1 (the thorough QTc Study), a single fosaprepitant dose of 200 mg IV was associated with a significant incidence (45.5%) of injection site reactions such as local discomfort or thrombophlebitis.

The sponsor reports that the formulation and concentration for administration of the fosaprepitant 150 mg dose is the same as the marketed fosaprepitant 115 mg dose, and consequently, due to the larger volume of the 150 mg dose compared to the 115 mg dose, the infusion time for the 150 mg dose was extended to 20-30 minutes in P017L1 to increase the likelihood that the tolerability profile would be similar to that associated with the 115 mg dose.

7.2.3 Special Animal and/or In Vitro Testing

No additional animal or *in vitro* testing was required to support this application.

7.2.4 Routine Clinical Testing

In order to evaluate safety, the following pre-study and post-study measurements were collected: medical history, physical exam, 12- lead ECG (pre-study only), laboratory tests including hematology, chemistry, urinalysis and pregnancy tests for females of child-bearing potential. Adverse events and tolerability were recorded at all visits during the treatment period and up to 14 days after therapy. Events related to the primary endpoint (vomiting, retching, nausea) were not defined as adverse experiences during the period of data collection with the diary, Day 1 until the morning of Day 6, unless they met the definition of a serious adverse experience.

Adverse events of special interest included severe infusion site reactions and any episode of infusion site thrombophlebitis. These Events of Clinical Interest (ECI) were evaluated at 3 predefined interim analysis time points to determine if incidence was significant to warrant stopping the trial.

Reviewer's Comments
These clinical assessments were adequate to monitor and evaluate the known safety concerns of fosaprepitant and aprepitant.

7.2.5 Metabolic, Clearance, and Interaction Workup

No additional metabolic or clearance workup was required for this current efficacy supplement. Additional evaluation of drug interaction was conducted in Study P018L1 and is summarized in section 4.4 Clinical Pharmacology .

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The drug class of NK1 receptor antagonists is only comprised of fosaprepitant and aprepitant. There are no other chemical entities in the class.

7.3 Major Safety Results

The overall AE incidence in the CINV-HEC trial (P017L1) demonstrated a similar rate between the fosaprepitant and aprepitant treatment groups, 59% and 61%, respectively. The comparability between treatment groups continued through the incidence of drug-related AEs, deaths, and serious AEs. The fosaprepitant treatment group, however, demonstrated a 40% higher incidence in AEs leading to discontinuation than the aprepitant treatment group. See the table below. This difference will be further discussion in section 7.3.3 Dropouts and/or Discontinuations.

Table 19: Adverse Event Summary P017L1*

	Fosaprepitant Regimen (A) n (%)	**Aprepitant Regimen (B) n (%)**	**Difference (A-B) (95% CI)**
Patients in population	**1,143**	**1,169**	
with one or more AE	671 (58.7)	718 (61.4)	-2.7 (-6.7, 1.3)
with drug-related AE	87 (7.6)	87 (7.4)	
with serious AE	148 (12.9)	157 (13.4)	-0.5 (-3.3, 2.3)
who died	23 (2.0)	26 (2.2)	-0.2 (-1.4, 1.0)
Discontinued due to AE	11 (1.0)	7 (0.6)	0.4 (-0.4, 1.2)

*Adapted from Sponsor's Table 12-8, Study Report P017L1, p.109.

The Sponsor also evaluated potential differences in the reporting of adverse events within the Study P017L1 by US and Ex-US sites. Total US patients reported a ~14% higher incidence of reported adverse events (74.2% [n=49]) compared to the total Ex-US patients (60% [n=1336]). However, the AEs reported by Ex-US patients tended to be more disease-related than drug-related. This is revealed by the 2-3x greater incidence of drug-related AE in the US patients than the Ex US patients. The trend of higher AE incidence in the US patients is exhibited with all AE groupings and demonstrated in Table 20.

Table 20 : Adverse Event Summary P017L1 – Ex US vs. US*

	Fosaprepitant Regimen n (%)	**Aprepitant Regimen n (%)**	**Total n (%)**
Ex US population	**1,102**	**1,124**	**2,226**
with one or more AE	646 (58.6)	690 (61.4)	1,336 (60.0)
with drug-related AE	80 (7.3)	81 (7.2)	161 (7.2)
with serious AE	145 (13.2)	150 (13.3)	295 (13.3)
who died	23 (2.1)	25 (2.2)	9 (0.4)
discontinued‡ due to AE	10 (0.9)	5 (0.4)	15 (0.7)
US population	**31**	**35**	**66**
with one or more AE	23 (74.2)	26 (74.3)	49 (74.2)
with drug-related AE	7 (22.6)	5 (14.3)	12 (18.2)
with serious AE	3 (9.7)	7 (20.0)	10 (15.2)
who died	0 (0.0)	1 (2.9)	1 (1.5)
discontinued‡ due to AE	1 (3.2)	2 (5.7)	3 (4.5)
‡ Study drug withdrawn			

*Adapted from Sponsor's Table in the Response to Filing Letter.

With specific focus on the fosaprepitant treatment groups, the proportion of patients with serious adverse events, deaths and discontinuations due to AE are considered comparable between US and Ex-US populations. It should be noted that those Ex-US study sites with patients discontinuing due to AE had the majority of patients discontinuing due a serious AE. Otherwise, when US and Ex-US populations were examined separately, AE incidence was similar across fosaprepitant and aprepitant treatment groups.

The overall AE incidence in the drug interaction study (P018L1) demonstrated a comparable rate for the fosaprepitant treatment groups, 50% and 67%, respectively. Although the pharmacokinetic study sample sizes are very small, the fosaprepitant and

dexamethasone treatment group was the only group to have drug-related AEs and a serious AE. The summary of AEs occurring in Study P018L1 is presented in Table 18.

Table 21: Adverse Event Summary P018L1*

	Fosaprepitant With Dexa n (%)	Dexa alone n (%)	Fosaprepitant With Midazolam n (%)	Midazolam alone n (%)
Patients in population	**12**	**12**	**10**	**10**
with one or more AE	8 (66.7)	8 (66.7)	5 (50.0)	1 (90.0)
with drug-related† AE	4 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
with serious AE	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)
who died	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
discontinued‡ due to AE	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)

† Includes hiccups, gastroesophageal reflux, flatulence, and dystonia.
‡ Study drug withdrawn

*Adapted from Sponsor's Table 12-2, Study Report P018L1, p.74.

Reviewer's Comments
In this age of global clinical research trials, an examination of AE reporting by country is often undertaken to discern if there is any influence by culture. This examination often finds the US study population reporting a higher AE incidence than Ex-US study sites. If substantially different, consideration is given for which AEs are reflected in the labeling. For this trial, it is most interesting to find a 2-3x greater incidence of drug-related AE in US patients compared to Ex-US patients. The pattern may be associated with the various financial incentives provided to patients at the majority of Ex-US study sites. As for labeling, drug-related AEs with incidence greater than the comparator are recommended for inclusion and therefore will appropriately inform US healthcare providers and consumers of the AE risk with fosaprepitant use.

7.3.1 Deaths

In Study P017L1, 49 deaths occurred: 23 (2.0%) in the fosaprepitant treatment group, 26 (2.2%) in the aprepitant treatment group. All the deaths were considered unrelated to the study drug and due to natural history of cancer in these patients.

There were no deaths in Study P018L1.

7.3.2 Nonfatal Serious Adverse Events

Nonfatal serious adverse events (SAE) were reported in 305 patients in Study P017L1. SAE incidence was similar between the fosaprepitant treatment group and the aprepitant treatment group. Each event was reported in <1% of patients in both treatment arms with the exception of febrile neutropenia, neutropenia, vomiting, and dehydration. Table summarizes the SAEs with incidence > 1%.

Table 22: Summary of Serious Adverse Event (Incidence > 1%)

	Fosaprepitant 150mg n (%)	**Aprepitant 3-Day n (%)**
Patients in population	1,143	1,169
with serious adverse events	148 (12.9)	157 (13.4)
with serious drug-related adverse events	4 (0.4)	7 (0.6)
Febrile neutropenia	18 (1.6)	27 (2.3)
Neutropenia	17 (1.5)	13 (1.1)
Vomiting	13 (1.1)	7 (0.6)
Dehydration	12 (1.0)	9 (0.8)

SAEs with an incidence >1% for Fosaprepitant 150mg are expected within the cancer chemotherapy patient population, and are demonstrated above to be similar between the two treatment groups.

Among those SAEs occurring at an incidence <1%, sepsis and septic shock had a slightly higher incidence in the fosaprepitant group (0.4-0.5%) compared to the aprepitant group (0.1%). Sepsis led to death in 3 of the 5 fosaprepitant patients. Septic shock led to death in 3 of the 4 fosaprepitant patients. Sepsis and septic shock led to death of two patients in the aprepitant treatment group.

Additionally, the following designated medical events of pancytopenia, hepatic failure, renal failure, and respiratory failure occurred in this trial. Pancytopenia and hepatic failure were experienced by patients receiving fosaprepitant (n= 3 and 2, respectively), but not by those receiving aprepitant. Conversely, respiratory failure was experienced by patients receiving aprepitant (n= 3), not by those receiving fosaprepitant. The incidence of renal failure was similar between the treatment groups.

Lastly, two patients experienced pulmonary embolism in Study P017L1; one in each treatment group, neither were considered drug-related.

- Patient #06532, Site #0167-- 61 y.o white male, Day 7 onset, severe CTCAE Grade 5. Fatal.
- Patient #07004, Site #0116 -- 46 y.o. white female, Day 6 onset, moderate CTCAE grade 4. Recovered.

Those SAEs considered to be drug-related were reported in four patients receiving fosaprepitant and seven patients receiving aprepitant. The fosaprepitant patients' experiences are recounted below:

- Patient #03083, Site #0026 – 65 y.o White male with constipation of mild intensity, lasting 1.5 weeks; recovered.
- Patient #04265, Site #0183 – 54 y.o. Black female with screening BP 130/90, had a blood pressure of 200/100 after receiving fosaprepitant and after the stop of the ondansetron infusion. At the same time, the patient had an adverse event of supraventricular tachycardia. The patient was treated with captopril 25 mg and BP recovered the same day. Supraventricular tachycardia resolved 2 days later. Patient discontinued the study due to adverse events.
- Patient #06418, Site #0074 – 47 y.o. White male with ALT 14X ULN (ALT 550 IU/L) and a AST 5X ULN (AST 197 IU/L) occurring 7 days after receiving fosaprepitant, cisplatin and epirubicin. On the same day, a normal alkaline phosphatase (113IU/L) and normal total serum bilirubin (0.65 mg/dl) were noted. Normal liver function was demonstrated 4 weeks after dosing study medication. The patient received no intervention and recovered without clinical sequelae.
- Patient #03085, Site#0026 – 55 y.o. white male with ALT 5X ULN (209 IU/L) and AST 3x ULN (109 IU/L) occurring 7 days after receiving fosaprepitant, cisplatin and 5-FU. At that time, the patient had no abnormality of the total serum bilirubin (0.48 mg/dl) and alkaline phosphatase (259 IU/L) was approximately 2X ULN. The patient was treated with Godex 2 capsule (vitamin B complex and carnitine orotate) b.i.d. and Ursa (urosodeoxycholic acid) 100 mg t.i.d. The patient had a normal ALT and AST level 15 days and 30 days after receiving study medication with no clinical sequelae. Cisplatin and 5-FU also suspected.

The 9 serious drug related events for the 7 patients treated with the aprepitant regimen included neutropenia, abdominal pain, flushing, hypertension, fecaloma, diarrhea, erythema, and constipation.

SAEs were reported in 1 patient receiving fosaprepitant and dexamethasone in Part 1 of Study P018L1. The SAEs of pneumonia and pulmonary embolism were reported for 29 y.o. male White Hispanic subject (#AN 0003, in Part 1 of the study), occurring following a car trip from Florida to New Jersey. The subject was discontinued from the study. The clinical investigator reported these events to be severe in intensity, but not related to the study drug. The subject recovered.

Reviewer's Comments
The increased incidence of sepsis and septic shock in the fosaprepitant treatment group is likely related to the intravenous route of administration and the effects of chemotherapy on immune function, rather than fosaprepitant.

For the designated medical events, pancytopenia and hepatic failure occurred only amongst the fosaprepitant treatment group. Due to bone marrow suppression, pancytopenia is not an unusual adverse event in the cancer chemotherapy population. It is unusual that no cases were reported for the aprepitant treatment group.

Many chemotherapy regimens are hepatotoxic and, in addition to fosaprepitant, may have contributed to hepatic failure in the two patients. The hepatic failure patients were:

- ***Patient #03801, site #0032: 65 y.o. multiracial male presented with bacteremia, febrile neutropenia, and hepatic failure 9 days post therapy. Outcome unknown.***
- ***Patient #06181, site #0140: 55 y.o. white male with history of lung cancer, ischemic heart disease, intraatrial block, and urolithiasis, presented with a duodenal ulcer perforation 3 days post therapy. This lead to peritonitis, acute hepatic failure, acute renal failure, thrombocytopenia, granulocytosis, and ended in death.***

For the drug-related SAEs, the events of constipation and elevated liver enzymes are known to the safety profile of aprepitant and chemotherapy agents. However, with the case of patient #04265 (SVT and hypertensive crisis), ondansetron is suspected as the primary cause of the events. Ondansetron labeling states known adverse events of cardiac arrhythmias and hypotension, however, fosaprepitant has been associated with hypertension and may have been the cause of the hypertensive crisis. Further discussion of hypertension is in Section 7.4.3 Vital Signs***.***

7.3.3 Dropouts and/or Discontinuations

For Study P017L1, there was a small proportion of patients who discontinued treatment due to adverse events; 11 (1.0%) patients in fosaprepitant group, 7 (0.6%) patients in aprepitant group. The adverse events demonstrated no incidence pattern by system organ class or treatment group.

The adverse events leading to discontinuation in two of the eleven patients were attributed to fosaprepitant; hypertensive crisis and chest discomfort with flushing and throat tightness.

- Patient #03088, site #0026: 61 y.o. White female experienced chest discomfort after receiving fosaprepitant, dexamethasone, and ondansetron. The adverse events in this patient occurred along with facial flushing and tightness in the throat. The patient received diphenhydramine, cimetidine, and methylprednisolone for these adverse events that occurred 6 minutes after study drug administration. The adverse event lasted for 5 minutes and was characterized as mild in intensity and non serious.
- The case of hypertensive crisis is described in the above section on nonfatal SAE.

Non-drug-related adverse events leading to discontinuation in the fosaprepitant group include cardiopulmonary arrest, erosive gastritis, gastrointestinal hemorrhage, vomiting, chest discomfort, death, somnolence, psychotic disorder, and hydronephrosis.

Drug-related adverse events leading to discontinuation of 4 of the 7 patients in the aprepitant group were diabetes mellitus, abdominal pain, flushing, hypertension, and constipation.

Non-drug-related adverse events leading to discontinuation in the aprepitant group included diplopia, blurred vision, vomiting, and dysuria.

For Study P018L1, one patient with pulmonary embolism and pneumonia discontinued from the study. This patient was described in the above section on nonfatal SAE.

7.3.4 Significant Adverse Events

For Study P017L1, the AEs of severe infusion site erythema, severe infusion site induration, severe infusion site pain, and infusion site thrombophlebitis were considered events of clinical interest (ECI). ECIs were evaluated in interim analyses by an external data monitoring committee to ensure that incidences in the fosaprepitant group were not higher than the aprepitant group; ≥20% higher for severe infusion site pain/erythema/induration or ≥5% higher for thrombophlebitis.

Amongst the ECIs reported, the difference in incidence between treatment groups was significant only for thrombophlebitis. Table 23 displays the ECI incidence. The median start time for thrombophlebitis was 7 days post infusion, with a range of 1 to 16 days. All cases were non-serious and of mild to moderate intensity. Five of the nine cases occurring in the fosaprepitant treatment group, were considered related to the chemotherapy. A post-hoc review of thrombophlebitis demonstrated results were similar regardless of type of intravenous line (peripheral vs. central).

Table 23: Proportion of Patient with ≥ 1% Incidence of ECI*

	Fosaprepitant Regimen n (%)	**Aprepitant Regimen n (%)**	**Difference (A-B) (95% CI)**	**p-value**
Patients in Population	**1,143**	**1,169**		
with one or more injection site AE	11 (1.0)	1 (0.1)		
Severe infusion site pain	2 (0.2)	0 (0.0)	0.2 (-0.15, 0.64)	0.076
Thrombophlebitis	9 (0.8)	1 (0.1)	0.7 (0.21, 1.41)	**0.005**

*There were no reports of severe infusion site erythema and/or severe induration.

Other infusion site-related AEs were non-serious and of mild to moderate severity. Nines cases of infusion site pain and two cases of thrombophlebitis were considered related to fosaprepitant. The table below displays all infusion site-related AEs regardless of level of severity. The incidence of all infusion site related AEs was 6x higher in the fosaprepitant treatment group (3.0%) compared to the aprepitant treatment group (0.5%).

Table 24: Proportion of Patients with Infusion-Site Related Adverse Events

	Fosaprepitant Regimen (A) n (%)	Aprepitant Regimen (B) n (%)	Difference (A-B)	95% CI for Difference† (A-B)
Patients in population	**1,143**	**1,169**		
with one or more AE	34 (3.0)	6 (0.5)		
with no AE	1,109 (97.0)	1,163 (99.5)		
General disorders and administration site conditions	**25 (2.2)**	**5 (0.4)**		
Infusion related reaction	1 (0.1)	0 (0.0)	0.1	(-0.24, 0.49)
Infusion site erythema	6 (0.5)	1 (0.1)	0.4	(-0.01, 1.06)
Infusion site induration	2 (0.2)	1 (0.1)	0.1	(-0.32, 0.56)
Infusion site pain	16 (1.4)	1 (0.1)	1.3	(0.71, 2.19)
Infusion site phlebitis	0 (0.0)	1 (0.1)	-0.1	(-0.48, 0.25)
Infusion site pruritus	3 (0.3)	0 (0.0)	0.3	(-0.07, 0.77)
Infusion site reaction	0 (0.0)	1 (0.1)	-0.1	(-0.48, 0.25)
Infusion site swelling	0 (0.0)	1 (0.1)	-0.1	(-0.48, 0.25)
Injection site pain	1 (0.1)	0 (0.0)	0.1	(-0.24, 0.49)
Vessel puncture site pain	1 (0.1)	0 (0.0)	0.1	(-0.24, 0.49)
Vascular disorders	**9 (0.8)**	**1 (0.1)**		
Thrombophlebitis	9 (0.8)	1 (0.1)	0.7	(0.21, 1.41)

†Calculated using the method of Miettinen and Nurminen. Every patient is counted a single time for each applicable specific adverse event. A patient with multiple adverse events within a system organ class is counted a single time for that system organ class. A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.

Sponsor's Table 1, Patients With Specific Infusion-Site Adverse Events By System Organ Class, Safety Information Amendment -- June 11, 2010, p. 2.

No infusion site related reactions were reported for Study P018L1.

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Hypersensitivity

As a result of the increased risk of hypersensitivity with fosaprepitant and aprepitant use demonstrated in postmarketing reports, hypersensitivity AEs were evaluated for Study P017L1. The incidence of hypersensitivity AEs was similar between treatment groups for severity; however, more events occurred in the fosaprepitant treatment group

compared to the aprepitant treatment group for Days 1 and 2 of study drug administration. Table 25 summarizes the hypersensitivity AEs.

Table 25: Summary of Hypersensitivity Adverse Events by Treatment Group

	Fosaprepitant n (%)	**Aprepitant n (%)**
Number of events of hypersensitivity	46	39
Serious AE	0	2 (5)
AE Related to study medication	8 (9)	7 (18)
AE mild	38 (83)	30 (77)
AE moderate	8 (17)	8 (21)
AE severe	0	1 (2.6)
Number of hypersensitivity adverse events presented on Day 1 of study medication	14 (30)	7 (18)
Number of hypersensitivity adverse events presented on Day 2 of study medication	8 (17)	3 (8)
Number of hypersensitivity adverse events presented on Day 3-17 of study medication	24 (52)	29 (74)

From Sponsor's Table 2.5:14, Number of Potential Hypersensitivity Adverse Events by Treatment Group P017L1, Clinical Overview, p.39.

When the specific hypersensitivity AEs were evaluated by treatment groups, the AE of erythema had an appreciably higher incidence in the fosaprepitant group (1.1%) than the aprepitant group (0.4%). Flushing had a slightly higher rate for the fosaprepitant group (0.6%) compared to the aprepitant group (0.2%). The AEs of drug hypersensitivity (n=2) and wheezing (n=2) where only reported in the fosaprepitant treatment group; however, drug hypersensitivity referred to reactions to chemotherapy agents paclitaxel and docetaxel. All other hypersensitivity AEs were reported at comparable rates between the two groups. See the table below.

Table 26: Hypersensitivity Adverse Events by Treatment Group

Adverse Event Preferred Term	**Treatment Group**	**Incidence n (%)**	**Difference (%)**	**95% CI for Difference**
Patients with ≥ 1 potential hypersensitivity AE	**Fosaprepitant** (N = 1143) **Aprepitant** (N = 1169)	**42 (3.67)** **36 (3.08)**	**0.59**	**(-1.1, 2.7)**
Allergic respiratory symptom	Fosaprepitant Aprepitant	1 (0.1) 0	0.1	(-0.4, 0.9)
Bronchospasm	Fosaprepitant Aprepitant	1 (0.1) 1 (0.1)	0.0	NA
Drug hypersensitivity	Fosaprepitant Aprepitant	2 (0.2) 0	0.2	(-0.4, 1.1)
Erythema	Fosaprepitant Aprepitant	13 (1.1) 5 (0.4)	0.7	(-0.3, 2.1)
Exfoliative rash	Fosaprepitant Aprepitant	0 1 (0.1)	-0.1	(-0.9, 0.4)
Eyelid edema	Fosaprepitant Aprepitant	1 (0.1) 0	0.1	(-0.4, 0.9)
Flushing	Fosaprepitant Aprepitant	7 (0.6) 2 (0.2)	0.4	(-0.3, 1.6)
Hypersensitivity	Fosaprepitant Aprepitant	2 (0.2) 2 (0.2)	0.0	NA
Pharyngeal edema	Fosaprepitant Aprepitant	1 (0.1) 0	0.1	(-0.4, 0.9)
Pruritus	Fosaprepitant Aprepitant	5 (0.4) 9 (0.8)	-0.4	(-1.7, 0.5)
Pruritus generalized	Fosaprepitant Aprepitant	0 1 (0.1)	-0.1	(-0.9, 0.4)
Rash	Fosaprepitant Aprepitant	7 (0.6) 10 (0.9)	-0.3	(-1.6, 0.7)
Rash generalized	Fosaprepitant Aprepitant	0 1 (0.1)	-0.1	(-0.9, 0.4)
Rash papular	Fosaprepitant Aprepitant	2 (0.2) 1 (0.1)	0.1	(-0.5, 1.1)
Swelling face	Fosaprepitant Aprepitant	1 (0.1) 1 (0.1)	0.0	NA
Throat tightness	Fosaprepitant Aprepitant	1 (0.1) 0	0.1	(-0.4, 0.9)
Urticaria	Fosaprepitant Aprepitant	0 4 (0.3)	-0.3	(-1.3, 0.2)
Wheezing	Fosaprepitant Aprepitant	2 (0.2) 0	0.2	(-0.4, 1.1)

Sponsor's Table 2.5:15, Number (%) of Patients with Hypersensitivity Adverse Events with the Difference Between Treatment Groups and 95%CI P017L1, Clinical Overview, p. 41.

The Sponsor reports that hypersensitivity reactions (3%) are rare with fosaprepitant use. However, due to drug-related hypersensitivity AEs occurring in three patients shortly after the start of fosaprepitant administration, the sponsor proposes additional language to the fosaprepitant labeling to emphasize immediate hypersensitivity reactions with fosaprepitant use. Section 8 Postmarket Experience discusses hypersensitivity AEs reported in the postmarketing period for fosaprepitant 115mg and aprepitant 3-day oral regimen.

7.3.5.2 Hypertension

Initiated by a decrease in blood pressure seen in a Phase I drug interaction study of fosaprepitant and diltiazem, additional analyses were performed on patients/subjects throughout the clinical development program of aprepitant and fosaprepitant for blood pressure changes. Data from these Phase 1, 2, and 3 studies in patients/subjects with a wide variety of concomitant conditions were not indicative of an effect on blood pressure.

In light of a prior clinical analysis of blood pressure, the Sponsor has conducted a further evaluation for adverse events related to the effect of aprepitant or fosaprepitant on blood pressure in Study P017L1. In Study P017L1, a comparable rate of hypotensive adverse events was reported for both treatment groups. For hypertensive AEs, the incidence of reported hypertension AEs was higher in the fosaprepitant group than in the aprepitant group (fosaprepitant n=17 (1.5%); aprepitant 7 (0.6%)). For the 17 cases of hypertension in the fosaprepitant group, approximately half (n=9) had a medical history of essential hypertension. All cases of hypertension resolved, except for one considered worsening of essential hypertension. The reported events of hypertensive crisis occurred in two patients treated with fosaprepitant and one patient treated with aprepitant. This AE was considered serious and drug-related for one patient receiving the fosaprepitant single day regimen and was described in section 7.3.2 Nonfatal Serious Adverse Events. The two non-drug-related cases of hypertensive crisis are described below.

- Patient #03430, site #0116 – 47 y.o. Black female was treated with fosaprepitant and experienced hypertensive crisis 5 days after study drug administration; characterized as mild in intensity. The event lasted 1.6 hours; however, the level of blood pressure elevation was not documented.
- Patient #04873, site #0052 – 57 y.o. Multiracial female was treated with aprepitant and experienced hypertensive crisis 14 days after study drug administration; characterized as moderate in intensity. The event lasted 10 hours. The AEs of febrile neutropenia and hematuria occurred around the same time and day as the hypertensive crisis.

Reviewer's Comments

The increased incidence of hypertension in the fosaprepitant treatment group may stem from the imbalance of hypertension as baseline medical history

between the treatment groups. There was a higher prevalence of essential hypertension in the fosaprepitant group (n=16 (1.4%)) compared to the aprepitant group (n= 11 (0.9%)). The Sponsor also suggests possible confounding in the P017L1 aprepitant treatment group based on the fact that hypertension AE incidence for the Phase 3 CINV-HEC trials of oral aprepitant was 1.6% and similar to the hypertension incidence (1.5%) in the P017L1 fosaprepitant treatment group.

7.3.5.3 EDTA and hypotensive adverse events

The Sponsor has conducted a further evaluation for potential adverse events related to the presence of EDTA in the fosaprepitant formulation in Study P017L1. A post-hoc analysis of potential adverse events demonstrated that there were no apparent imbalances in adverse events related to hypocalcaemia (fosaprepitant 0.5%; aprepitant 0.4%), hypomagnesaemia (fosaprepitant 0.1%; aprepitant 0.3%), dizziness (fosaprepitant 3.3%; aprepitant 3.0%), dizziness postural (fosaprepitant 0%; aprepitant 0.1%), loss of consciousness (fosaprepitant 0.1%; aprepitant 0%), presyncope (fosaprepitant 0.1%; aprepitant 0%), syncope (fosaprepitant 0.6%; aprepitant 0.5%), or hypotension (fosaprepitant 1.0%; aprepitant 1.2%) between the fosaprepitant and aprepitant treatment groups. The above findings suggest no clinically relevant consequences due to the presence of EDTA in the fosaprepitant formulation.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common AEs in the fosaprepitant treatment group were predominately seen in the system organ classes (SOC) of gastrointestinal disorders (33%); general disorders and administration site conditions (21%); metabolism and nutrition disorders (12%); respiratory, thoracic and mediastinal disorders (12%); and nervous system disorders (11%). A similar pattern of predominant SOCs were exhibited for the aprepitant treatment group. Table 27 displays the SOCs with incidence >5% by treatment group.

Table 27: Adverse Events by SOC and Treatment Groups (Incidence >5%)

SOC Terms	Fosaprepitant 150mg n (%)	Aprepitant 3-Day n (%)	Difference in % (95% CI)
Patients in population	1,143	1,169	
Blood and lymphatic system disorders	96 (8.4)	98 (8.4)	0.0 (-2.3, 2.3)
Gastrointestinal disorders	381 (33.3)	400 (34.2)	-0.9 (-4.7, 3.0)
General disorders and administration site conditions	243 (21.3)	283 (24.2)	-2.9 (-6.4, 0.5)
Infections and infestations	71 (6.2)	76 (6.5)	-0.3 (-2.3, 1.7)
Investigations	72 (6.3)	84 (7.2)	-0.9 (-3.0, 1.2)
Metabolism and nutrition disorders	142 (12.4)	187 (16.0)	-3.6 (-6.4, -0.7)
Musculoskeletal and connective tissue disorders	50 (4.4)	65 (5.6)	-1.2 (-3.0, 0.6)
Nervous system disorders	121 (10.6)	118 (10.1)	0.5 (-2.0, 3.0)
Respiratory, thoracic and mediastinal disorders	138 (12.1)	140 (12.0)	0.1 (-2.6, 2.8)
Skin and subcutaneous tissue disorders	51 (4.5)	60 (5.1)	-0.7 (-2.4, 1.1)
Vascular disorders	65 (5.7)	45 (3.8)	1.8 (0.1, 3.6)

From Sponsor's Table 12-9, Study Report P017L1, p. 111-112.

The common adverse events (>5% incidence) seen among patients receiving fosaprepitant 150mg single day regimen were associated with the predominant SOCs. These AEs were comparable between treatment groups and not unusual for chemotherapy patients. These common adverse events in the fosaprepitant treatment group include constipation (10.6%), asthenia (8.6%), diarrhea (7.8%), anorexia (6.6%), vomiting (6.6%), nausea (5.9%), and hiccups (5.6%). Interestingly, a slightly higher incidence of asthenia (fosaprepitant 8.6%; aprepitant 11.6%) and anorexia (fosaprepitant 6.6%; aprepitant 9.1) were seen in the aprepitant treatment group compared to patients treated with fosaprepitant. In the present study, the incidence of these adverse events in patients treated with aprepitant was; however, lower than that previously observed in the aprepitant clinical trials supporting the CINV-HEC indications; asthenia 17.8%; anorexia 10.1%. Many more infusion site pain reactions were reported with the fosaprepitant group (n=16) than the aprepitant group (n=1). These reactions are further discussed above in section 7.3.4 Significant Adverse Events. Table 28 (below) demonstrates AE of ≥1% incidence in the fosaprepitant group with an incidence greater than that of the aprepitant treatment group.

Table 28: AEs ≥1% for Fosaprepitant 150mg and greater than Aprepitant 3-day

AE Terms	Fosaprepitant 150mg n (%)	Aprepitant 3-Day n (%)	Difference in % (95% CI)
Patients in population	1,143	1,169	
Anemia	20 (1.7)	10 (0.9)	0.9 (0.0, 1.9)
Tinnitus	19 (1.7)	10 (0.9)	0.9 (-0.1, 1.8)
Constipation	121 (10.6)	112 (9.6)	1.0 (-1.5, 3.5)
Vomiting	75 (6.6)	65 (5.6)	1.0 (-1.0, 3.0)
Urinary tract infections	11 (1.0)	3 (0.3)	0.7 (0.1, 1.5)
Infusion site pain	16 (1.4)	1 (0.1)	1.3 (0.7, 2.2)
Hypertension	17 (1.5)	7 (0.6)	0.9 (0.1, 1.8)
Hypotension	12 (1.0)	14 (1.2)	-0.2 (-1.1, 0.8)

From Sponsor's Table 12-9, Study Report P017L1, p. 111-112.

The AEs of anemia and tinnitus were of 2x higher incidence for the fosaprepitant treatment group (1.7%) compared to the aprepitant treatment group (0.9%). These events, however, have occurred at comparable rates in the Phase 3 CINV-HEC trials for aprepitant (incidence <1%, 3.7%, respectively). The AEs of urinary tract infection (UTI), hypertension and infusion site pain (all severity levels) were 3x higher or more for fosaprepitant group compared to the aprepitant group. No explanation is provided for the AEs of UTI. For the 17 cases of hypertension in the fosaprepitant group, approximately half (n=9) had a medical history of hypertension. All cases of hypertension resolved, except for one considered essential hypertension. One case was considered drug related and has been discussed in section 7.3.2 Nonfatal Serious Adverse Events.

The most commonly reported drug-related AEs were constipation and hiccups for both treatment groups. The incidence of drug related adverse events was similar for both treatment groups, except for where infusion site erythema and infusion site pain occurred at a greater rate in the fosaprepitant group. Table 29 displays this pattern.

Table 29: Drug Related AEs with Incidence Greater for Fosaprepitant 150mg than to Aprepitant 3-day

	Fosaprepitant Regimen		Aprepitant Regimen	
	n	(%)	n	(%)
Patients in population	1,143		1,169	
with one or more drug-related AE	87	(7.6)	87	(7.4)
with no drug-related AE	1,056	(92.4)	1,082	(92.6)
Dyspepsia	5	(0.4)	2	(0.2)
Asthenia	4	(0.3)	0	(0.0)
Infusion site erythema	5	(0.4)	0	(0.0)
Infusion site pain	9	(0.8)	1	(0.1)
Alanine aminotransferase increased	7	(0.6)	4	(0.3)
Aspartate aminotransferase increased	4	(0.3)	1	(0.1)
Flushing	4	(0.3)	1	(0.1)
Thrombophlebitis	3	(0.3)	1	(0.1)

Sponsor's Table.

In P017L1, the severity of adverse events was assessed by the NCI Common Toxicity of Clinical Adverse Event (CTCAE) grading criteria. Those AEs with toxicity grades of 3 and 4 were considered severe or life threatening. Grade 3 and 4 AEs were comparable between the fosaprepitant and the aprepitant treatment group. Those Grade 3 and 4 AEs with incidence ≥1% in both treatment groups were neutropenia (3%) and febrile neutropenia (1.8%). Both of these adverse events are expected in the cancer chemotherapy patient population. Table 30 displays the percentage of study patients with febrile neutropenia and neutropenia by treatment group.

Table 30: Adverse Events with ≥1% Incidence in Toxicity Grades 3 and 4

	Fosaprepitant Regimen		Aprepitant Regimen		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	1,143		1,169		2,312	
with one or more AE	655	(57.3)	695	(59.5)	1,350	(58.4)
with no AE	488	(42.7)	474	(40.5)	962	(41.6)
Blood and lymphatic system disorders	**93**	**(8.1)**	**96**	**(8.2)**	**189**	**(8.2)**
Febrile neutropenia	19	(1.7)	28	(2.4)	47	(2.0)
Grade 1	2	(0.2)	1	(0.1)	3	(0.1)
Grade 2	1	(0.1)	3	(0.3)	4	(0.2)
Grade 3	5	(0.4)	13	(1.1)	18	(0.8)
Grade 4	11	(1.0)	11	(0.9)	22	(1.0)
Neutropenia	44	(3.8)	38	(3.3)	82	(3.5)
Grade 1	2	(0.2)	1	(0.1)	3	(0.1)
Grade 2	6	(0.5)	2	(0.2)	8	(0.3)
Grade 3	13	(1.1)	11	(0.9)	24	(1.0)
Grade 4	23	(2.0)	24	(2.1)	47	(2.0)

Excerpted from Sponsor's Table 12-12, Study Report P017L1, pp. 129-143.

7.4.2 Laboratory Findings

Laboratory safety tests were performed at baseline, once on Day 6 to 8, and once on Day 14 to 29. The Sponsor notes differences from baseline values for many of the laboratory safety tests, which are not unexpected due to the effects of chemotherapy on bone marrow and liver function. Common changes for Days 6 to 8 included decreases in platelet count and alkaline phosphatase and increases in aminotransferase and glucose. Most tests were at or near the baseline value by the Day 14 to 29 visit. Mean changes from baseline were generally comparable among the two treatment groups for both Days 6 and 8 and Days 14 to 29.

7.4.2.1 Liver

Although there was no imbalance in treatment arms with regard to medical history of hepatobiliary disorders or baseline levels of liver enzymes greater than the upper limit of normal, there was a higher incidence of serum ALT >5X ULN in patients treated with the fosaprepitant single day regimen (1.8%) compared to patients treated with the aprepitant 3-day regimen (0.5%). No significant differences were seen for serum AST >5X ULN (fosaprepitant 0.5%; aprepitant 0.2%), serum alkaline phosphatase >5X ULN

(fosaprepitant 0.7%; aprepitant 1.0%) or total serum bilirubin >3X ULN (fosaprepitant 0.5%; aprepitant 1.1%). See Table 31: Patients with Elevated Liver Function Tests by Treatment Group.

Table 31: Patients with Elevated Liver Function Tests by Treatment Group

Liver Function Test	Fosaprepitant	Aprepitant
Serum ALT>10X ULN	4/1112 (0.4%)	0
Serum ALT>5X ULN	20/1112 (1.8%)	6/1137 (0.5%)
Serum AST >5X ULN	5/1112 (0.5%)	2/1136 (0.2%)
Serum Alkaline	8/1110 (0.7%)	11/1139 (1.0%)
Phosphatase >5X ULN		
Total Serum Bilirubin	6/1110 (0.5%)	13/1139(1.1%)
>3XULN		
Serum ALT>3X ULN	58/1112 (5.2%)	42/1137(3.7%)
Serum AST>3X ULN	12/1112 (1%)	7/1136 (0.6%)

Sponsor's Table 12-21, Elevation in Liver Function Tests in Patients Treated with Fosaprepitant and Aprepitant in Protocol 017, Study Report P017L1, p. 169.

For the fosaprepitant group, the majority of ALT elevations >5x ULN persisted 6-8 days post treatment, decreased to ALT>3x ULN by Day 14 post treatment, were not associated with AST elevations >5x ULN or an elevation in total bilirubin >2x ULN. The majority of clinical investigators did not report ALT>5xULN as adverse events; however, 4 cases were reported as AEs. Three of the four cases were considered related to study medication; the last of the four cases occurred in a patient with a history of cholangiocarcinoma.

Table 32: Percentage of Patient with ALT >5x ULN by Treatment Group

Laboratory Test Results	Fosaprepitant	Aprepitant
ALT>5 X ULN	20/1112 (1.8%)	6/1137 (1.3%)
ALT>5 X ULN with baseline ALT>ULN	12/20 (60%)	3/6 (50%)
ALT>5 X ULN with an underlying hepatobiliary disease	6/20 (30%)	2/6 (33%)
ALT>5 X ULN with an AE related to increase liver function tests	4/20 (20%)	1/6 (17%)
ALT>5 X ULN Day 6-8 post treatment	15/20 (75%)	6/6 (100%)
ALT>5 X ULN Day 9-13 post treatment	3/20 (15%)	0
ALT>5 X ULN Day 14-29 post treatment	2/20 (10%)	0
ALT>5 X ULN with ALT ≤ 3 X ULN on Day 14-29	15/20 (75%)	6/6 (100%)
ALT>5 X ULN with Total serum bilirubin >2 X ULN	0	1
ALT>5 X ULN with AST >5 X ULN	4/20 (20%)	1/6 (17%)

From Table 2.5:18, Clinical Overview, p. 46.

Reviewer's Comments:
Although there were sizeable elevations in ALT, the elevation of liver enzymes could be attributed to fosaprepitant, chemotherapy agents or patient history of hepatobiliary disease. There, however, were no clear cut cases of drug-induced liver injury, or increased ALT >5x ULN or >3x ULN associated with increased total bilirubin >2x ULN.

7.4.3 Vital Signs

The mean changes from baseline were comparable between the two treatment groups. During the safety monitoring period (Day 6-28), the incidence of clinically significant vital sign changes were also similar between treatment groups. See Table 33.

Table 33: Number (%) of Patients With Clinically Significant Vital Sign Abnormalities (CSVA) Days 6 to 29

Vital Sign		Number (%) with CSVA				Difference † (A-B)	95% CI for Difference † (A-B)
		Fosaprepitant Regimen (A)		Aprepitant Regimen (B)			
Measurement	Criteria	n/m	(%)	n/m	(%)		
Systolic BP (mmHg)	≥180 mmHg and ≥20 mmHg increase	7/1111	(0.6)	4/1132	(0.4)	--	--
	≤90 mmHg and ≥20 mmHg decrease	42/1111	(3.8)	38/1132	(3.4)	0.3	(-1.2, 1.9)
Diastolic BP (mmHg)	≥105 mmHg and ≥15 mmHg increase	5/1111	(0.5)	5/1132	(0.4)	--	--
	≤50 mmHg and ≥15 mmHg decrease	12/1111	(1.1)	9/1132	(0.8)	0.3	(-0.6, 1.2)
Pulse Rate (beats/min)	≥120 bpm and ≥15 bpm increase	11/1111	(1.0)	19/1132	(1.7)	-0.7	(-1.7, 0.3)
	≤50 bpm and ≥15 bpm decrease	4/1111	(0.4)	1/1132	(0.1)	--	--
Respiratory Rate (breaths/min)	>18 rpm	543/1102	(49.3)	560/1120	(50.0)	-0.7	(-4.9, 3.4)
	<8 rpm	1/1102	(0.1)	0/1120	(0.0)	--	--

† Calculated by the method of Miettinen and Nurminen. The difference and confidence interval (CI) for the difference displayed only if the incidence is ≥1% in at least one treatment group.

n/m = Number of randomized patients in each treatment group with a CSVA/number of randomized patients in each treatment group with vital sign data.

Sponsor's Table 12-25, Study Report P017L1, p. 176.

7.4.4 Electrocardiograms (ECGs)

The QT prolongation potential for fosaprepitant IV was evaluated in a previous study whereby no QT prolongation was detected for fosaprepitant 200 mg infused over 15 minutes.

7.4.5 Special Safety Studies/Clinical Trials

N/A

7.4.6 Immunogenicity

Hypersensitivity adverse events are special safety concerns for fosaprepitant and are discussed in sections 7.3.5Submission Specific Primary Safety Concerns and 8 Postmarket Experience.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

N/A

7.5.2 Time Dependency for Adverse Events

Hypersensitivity adverse events have been demonstrated immediately following fosaprepitant infusion. These AEs are discussed in 7.3.5 Submission Specific Primary Safety Concerns.

7.5.3 Drug-Demographic Interactions

There are no apparent drug-demographic interactions.

7.5.4 Drug-Disease Interactions

For the clinical efficacy trial P017L1, patient medical histories were comparable between the two treatment groups, except for the condition of essential hypertension; (fosaprepitant n=16 (1.4%); aprepitant n= 11 (0.9%)).

7.5.5 Drug-Drug Interactions

See section 4.4 Clinical Pharmacology of this document.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There is no additional human carcinogenicity data other than that originally submitted with oral aprepitant.

7.6.2 Human Reproduction and Pregnancy Data

There is no additional human reproduction data other than that originally submitted with oral aprepitant.

7.6.3 Pediatrics and Assessment of Effects on Growth

No studies have been performed in pediatric patients for either fosaprepitant or aprepitant. However, the Sponsor has outstanding Written Requests and PREA obligations for both drug products.

(b) (4)

Additionally, the Division has revised the pediatric plan to include the entire pediatric population. The revised plan is outlined below:

Study 1: PK/PD study to characterize aprepitant PK parameters following administration of a single dose of fosaprepitant I.V. in combination with a 5HT3 antagonist and dexamethasone in pediatric cancer patients ages 0 to 17 years undergoing treatment with highly and moderately emetogenic chemotherapy.

Study 2: An adequate, double-blinded, placebo controlled, randomized, parallel-group, add-on design, superiority study to evaluate the safety and efficacy of a single dose of fosaprepitant I.V. in combination with a 5HT3 antagonist as compared to standard therapy (a 5HT3 antagonist) in pediatric cancer patients ages 0 to 17 years undergoing treatment with highly and moderately emetogenic chemotherapy.

The plan was reviewed by PeRC on July 7, 2010, and found acceptable. (b) (4) this pediatric plan has been modified to restrict study of a single dose of fosaprepitant IV to the pediatric patient population receiving highly emetogenic chemotherapy.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Within Study P017L1, 13 patients received both a single dose of fosaprepitant 150mg IV and at least one dose of aprepitant. Nine patients reported AEs. The following is a listing of adverse events reported:

Table 34: Adverse Events in Patient Who Received Both Study Drugs*

	Drug-Related	Not Drug-Related
Onset Day of Drug Administration	abdominal pain, constipation, hiccups, flushing, hypertension, erythema	fatigue, abdominal discomfort, chills, anorexia, musculoskeletal pain, headache, peripheral edema
Onset Days Post Therapy		tumor hemorrhage, headache, hot flush, syncope, rash, hemoptysis, peripheral coldness, dizziness, asthenia, upper abdominal pain, confusional state, dyspnea, hyponatremia, leukopenia, neutropenia, underweight, insomnia.

*Adapted from Sponsor's Table 12-10, Listing of Adverse Events Patients Who Received Both Study Therapies, Study Report P017L1, pp. 113-122.

Two patients who received fosaprepitant had serious adverse events due to an accidental overdose.

- One patient received both the fosaprepitant and the aprepitant regimen; he experienced facial flushing, abdominal pain and reactive hypertension (BP maximum 170/92). The intravenous study medication was discontinued and symptoms resolved within 30 minutes without additional intervention.
- The second patient received both the fosaprepitant and the aprepitant regimen. He experienced facial redness two days after receiving study medication. The adverse events was considered related to the administration of 5-fluorouracil by the investigator, and resolved without intervention.

There is no additional overdose or drug abuse potential data other than the original NDA submissions with fosaprepitant 115mg IV and oral aprepitant.

7.7 Additional Submissions / Safety Issues

There are no additional safety submissions or issues.

8 Postmarket Experience

Since March 2003 through June 2009, (b) (4) individual courses of aprepitant have been distributed worldwide. From August 2007 to June 2009, approximately (b) (4) doses of fosaprepitant have been distributed worldwide. The table below summarizes the most common (>10%) worldwide adverse event reports occurring in the postmarketing period for fosaprepitant and aprepitant.

Table 35: Worldwide Spontaneous Reports by SOC (>10% of the total) †ǂ

System Organ Class	Aprepitant		Fosaprepitant	
	Total Number of Reports	% of Total Reports	Total Number of Reports	% of Total Reports
Gastrointestinal disorders	192	23	10	8
General disorders and administration site conditions	264	31	73	60
Injury, poisoning and procedural complications	134	16	8	7
Nervous system disorders	184	22	14	11
Respiratory, thoracic and mediastinal disorders	115	13	17	14
Skin and subcutaneous tissue disorders	84	10	28	23
Vascular disorders	41	5	21	17
DISTINCT NUMBER OF REPORTS*	853		122	

* A single report may include adverse events in one or more System Organ Classes. Therefore, the sum of reports from all System Organ Classes can be greater than the total distinct number of reports received. Percentages are the percent of distinct number of reports for events in that System Organ Class.
†It is not possible to ascertain when a patient was exposed to only one or both products. This presentation of the data is based on the reported primary suspect therapy to potentially avoid duplicate reporting.

ǂ From Sponsor's Table 2.5:20, Aprepitant and Fosaprepitant: Market introduction (aprepitant: 26-Mar-2003; fosaprepitant: 20-Aug-2007) through 30-Jun-2009 Summary Tabulation of Spontaneous Reports by SOC, in 2.5 Clinical Overview, p. 51.

Aprepitant demonstrated the most postmarketing adverse event reports in the SOCs of general disorders and administration site conditions, gastrointestinal disorders, and nervous system disorders with 31%, 23% and 22%, respectively. The SOC of General disorders and administration site conditions included no adverse event, fatigue, drug ineffective, drug interaction, and asthenia. Events of "no adverse event" can be captured as an AE when it is reported along with a medication/administration error. This preferred term "no adverse event" represented the largest percent (21%) of events within this SOC. The most common AEs within the gastrointestinal disorders SOC were nausea and vomiting. The most common AEs within the nervous system disorders SOC were dizziness and headache. The sponsor concludes that the majority of the reports were consistent with the expected AEs associated with aprepitant: nausea and diarrhea, drug interactions, headache, and dyspnea.

Fosaprepitant demonstrated most postmarketing adverse event reports in the SOCs of general disorders and administration site conditions, skin and subcutaneous tissue disorders, and vascular disorders, 60%, 23% and 17%, respectively. The SOC for General disorders and administration site conditions included infusion or injection site pain, edema peripheral, and infusion site phlebitis. The most common AEs within the skin and subcutaneous tissue disorders SOC were erythema, blister, and skin discoloration. The most common AE within the vascular disorders SOC was flushing. The sponsor concludes that the majority of the reports were consistent with the expected AEs associated with fosaprepitant: infusion site reactions (infusion/injection site pain).

Reports in the SOC of immune disorders comprised 2% and 8% of total reports for aprepitant and fosaprepitant, respectively. Hypersensitivity is believed to be greater in fosaprepitant due to the excipients of the intravenous formulation (e.g., Polysorbate 80) versus the aprepitant molecule itself; however, the relative contribution of fosaprepitant and/or excipients cannot be fully determined. The sponsor cites publications where polysorbate 80 has been reported to be a mediator of hypersensitivity reactions for other agents such as docetaxel and etoposide. A search of the Worldwide Adverse Event System for reports with the terms anaphylactic reaction, angioedema, asthma/bronchospasm and severe cutaneous adverse reactions yielded 42 reports for fosaprepitant. Twenty-six hypersensitivity reactions were reported in association with fosaprepitant administration on Day 1. Most hypersensitivity reactions consisted of flushing, erythema and dyspnea, and responded to discontinuation of fosaprepitant and clinical management. The table below summarizes these reports.

Table 36: Summary of Fosaprepitant Hypersensitivity Reactions from Worldwide Adverse Event Database

Fosaprepitant hypersensitivity reactions	
Total	42
Infusion site reactions	11
Day 1 hypersensitivity reactions	26
• occurring within minutes of administration	12
○ only fosaprepitant given, no oral aprepitant	9
○ previously tolerated oral aprepitant	1
○ tolerated oral aprepitant after reaction to fosaprepitant	2
○ cases of anaphylaxis	6
Unknown onset time of hypersensitivity reaction	5

Reviewer's Comments

Based on the above described hypersensitivity reports, the sponsor believes and this reviewer concurs that inclusion of hypersensitivity language is important for the fosaprepitant labeling.

9 Appendices

9.1 Literature Review/References

- Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4:213-26.
- Blackwelder WC. "Proving the null hypothesis" in clinical trials. Control Clin Trials 1982;3:345-53.

9.2 Labeling Recommendations

- Throughout the labeling, the Sponsor needs to clearly distinguish the single day fosaprepitant 150mg regimen versus the 3-day fosaprepitant 115mg/oral aprepitant regimen.
- In section 6, Adverse Reactions,
    - Infusion-site reactions are (b) (4) the exact incidence should be reported in the labeling
    - Further emphasis on immediate hypersensitivity reactions may be added in regards to fosaprepitant

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was required.

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/s/

TAMARA N JOHNSON
10/15/2010

NANCY C SNOW
10/17/2010
acting CDTL agrees with Clinical Reviewer recommendations; CDTL review to follow

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology Products

MEMORANDUM

DATE: January 25, 2010

TO: Donna Griebel, MD, Division Director

THROUGH: Nancy Snow, DO, MPH, Acting Team Leader

FROM: Tamara Johnson, MD, MS, Medical Officer

SUBJECT: Request for Waiver of 4-Month Safety Update

Drug Name:	EMEND (fosaprepitant dimeglumine) for Injection
Application Type/Number:	NDA 22023/S004
Sponsor:	Merck & Co. Inc.
Indications:	1) Prevention of nausea and vomiting associated with highly emetogenic chemotherapy [redacted] (b) (4)
Dose:	150mg single dose
Route of Administration:	Intravenous
Submission Stamp Date:	October 13, 2009
PDUFA Goal Date:	**August 13, 2010**

Purpose

Merck & Co., Inc. has requested that a waiver of the 4-month safety update be granted for NDA 22-023/S-004, reporting that there are no additional non-clinical or clinical studies that would impact the safety information already provided with this efficacy supplement.

Recommendation

This reviewer recommends allowing a waiver of the 4-month safety update because clinical safety data to support the current efficacy application have been submitted and no new safety information has been found from an interim safety review of an ongoing Japanese study. Merck will provide further safety data from the Japanese study when it becomes available. This is projected to occur around September 2010, which is after the PDUFA date (August 13, 2010) for the current efficacy application.

Background

In their request for waiver, Merck stated that no additional nonclinical studies had been conducted and that all available nonclinical information on EMEND for Injection was included in the NDA supplement. They reported no extensions to the clinical studies conducted in support of the application and that all safety data from these studies were submitted. Merck also disclosed that a study evaluating the PK, safety and tolerability of the EMEND 150mg IV single dose in Japanese patients had been initiated in Japan. In a review of the blinded safety data, Merck did not identify any information from the Japanese study that would impact on the draft labeling for EMEND for injection.

On January 21, 2010, via email communication to the Agency, Merck provided the below description regarding the ongoing Japanese study of EMEND 150mg IV.

> *As referenced in the submission dated January 8, 2010, in which [Merck] requested a waiver for submission of a 4-month safety update report for NDA 22023/S-004, there is one clinical study with the 150 mg formulation of fosaprepitant ongoing. This study is being conducted by our development partner in Japan, Ono Pharmaceuticals, who has the rights to commercialize both aprepitant and fosaprepitant in Japan and this study was designed in consultation with the PMDA [Pharmaceuticals and Medical Devices Agency of Japan]. This study is being conducted in Japan and not under a US IND, and is a multi-center double blind placebo controlled, parallel group study to evaluate the efficacy and safety of a single intravenous (150 mg) dose of IV EMEND in 340 patients (170 patients per treatment arm) for the prevention of CINV in patients with a malignant tumor who receive cisplatin chemotherapy at ≥70 mg/m2. All patients randomized in the study also receive dexamethasone and granisetron. The study is being to conducted to support a marketing application in Japan for the use of a single intravenous dose of fosaprepitant 150mg, dosed concomitantly with a 5HT3 RA and a corticosteroid, as an alternative for the approved 3-day oral aprepitant regimen (aprepitant 125 mg on Day 1 followed by aprepitant 80 mg on Days 2 and 3, dosed concomitantly with a 5HT3 RA and a corticosteroid) for the indication of the prevention of CINV.*
>
> *Ono has informed us that LPLV (last patient last visit) occurred on 18th December 2009 and they are currently targeting final data to be available around September 2010. We will provide results from this study to FDA once final data are available.*

Rationale

Upon review of the sponsor's request for waiver and their email response with further description of the Japanese study, this reviewer finds that the sponsor will not have adequate information to comprise a 4-month safety update. All available clinical safety data to support the current efficacy application have been submitted. The Japanese study is in fact a randomized, controlled trial for safety and efficacy and not a PK, safety and

tolerability study. Merck reports that after review of the blinded safety data the data did not reveal any safety information to affect the current supplement. As no further conclusions can be drawn about drug-related adverse reactions until the final study data is available (September 2010--after the PDUFA date for the current efficacy supplement), this reviewer deems a 4-month safety update unnecessary.

Conclusion

Upon review of the sponsor's request and description of the ongoing Japanese safety and efficacy study, this reviewer agrees to allow waiver of the 4-month safety update because clinical safety data to support the current efficacy supplement have been submitted and there appears to be no safety information from the Japanese study that would contribute to this supplement until after the final safety data analysis is completed.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

TAMARA N JOHNSON
01/25/2010

NANCY C SNOW
01/26/2010

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22-023/S-004 Applicant: Merck & Co., Inc Stamp Date: 10/13/2009

Drug Name: EMEND NDA/BLA Type: Standard

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?		X		Draft labeling not in PLR format.
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			Clinical Summary mislabeled as Clinical Overview in section 2.5 instead of 2.7
9.	Has the applicant submitted the integrated summary of safety (ISS)?		X		However, complies with *Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within The Common Technical Document.*
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		X		Same as above.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(1) supplement
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission: 5.3.5.1:724	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 = Protocol 017 Design: multicenter, randomized, double-blind non-inferiority Indication: Prevention of CINV (b) (4) HEC) Pivotal Study #2 None		X		One trial, would prefer 2 however sponsor claims that the one has robust evidence; 150mg IV single-dose v. 125/80mg oral 3-day regimen
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			1 Study
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		Clin Summary 2.5.4.4 pp.28-29 However, sponsor compared US/CAN/NZ/EU to other countries to show similarities in Tx group rates; only 68 US patients out of 2322 in study
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?		X		Adverse event incidence tables in 5.3.5 in clinical study report for P017L1.
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			QTc study = P016L1 in section 5.3.4.1
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			N/A	N= 1143 on 150mg single dose in P017L1, not combined with Phase 1: 150 subjects exposed to ≥150mg of current formulation
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?				TBD

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?		X		Missing coding dictionary
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			Infusion site reaction, hypersensitivity
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Drug interaction studies of fosaprepitant with midazolam, as well as with dexamethasone
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			N/A	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Deferral 6mo-17yrs. Waiver <6mo. not justified in current submission
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			N/A	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		96.7% of patients were outside of US
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			Difficult to find files, located in 5.3.5.1.25.3; format not previously agreed upon.
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			N/A	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			N/A	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			Section 5 of Study Report P017L1

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __YES_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- Applicant needs to submit draft labeling in PLR format.
- One trial is presented in this submission, although Agency prefers two adequate and well-controlled studies; the second to provide confirmatory evidence.
- Applicant needs to submit a rationale for assuming the applicability of foreign data to the U.S. population and US practice of medicine. The applicant must address the potential effects of regional differences (e.g. medical practice, follow-up of patients, incidence of adverse events, coding and verbatim practices in reporting of adverse events) that may influence the drug's efficacy and safety. Supportive evidence (i.e. tables, figures) should be included. Please see ICH Guidance *E5 – Ethinic Factors in the Acceptability of Foreign Clinical Data* and the related *Guidance for Industry: E5 – Ethinic Factors in the Acceptability of Foreign Clinical Data – Questions and Answers, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065004.htm*
- If applicant is referencing original NDA for additional safety patient exposures to doses ≥150mg in Phase 1, safety data from Phase 1 subjects should be summarized in Clinical Summary or Integrated Summary of Safety.
- We are unable to locate coding dictionary. Please submit or clarify location.
- Justification of pediatric study waiver for infants <6months-old is not provided in current submission. Please provide.

Tamara Johnson, MD, MS — November 30, 2009

Reviewing Medical Officer — Date

Nancy Snow, MD, MPA

Clinical Team Leader

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

TAMARA N JOHNSON
12/09/2009

NANCY C SNOW
12/09/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022023/S-004

CHEMISTRY REVIEW(S)

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER
	ONDQA Div IV, Branch VIII and HFD-180	22-203

3. NAME AND ADDRESS OF APPLICANT	4. COMMUNICATION, DATE
Merck & Co., Ltd. P. O. Box 2000 RY 33-200 Rahway, NJ 07065	S-004 dated 10-12-2009 Efficacy, PA Goal date is 8-12-2010

5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
EMEND®	Fosaprepitant dimeglumine for injection	N/A

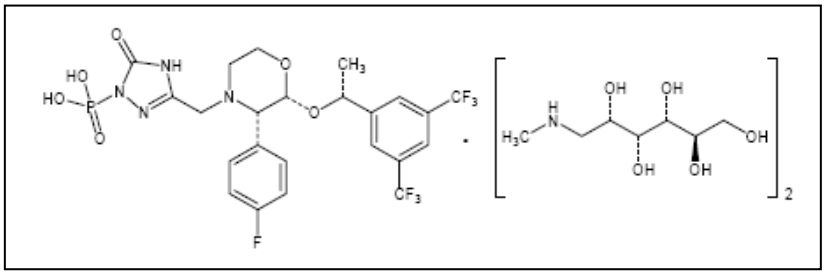
8. COMMUNICATION PROVIDES FOR:

A new dosing regimen for the drug product along with the development of a new dosage strength, a 150-mg "for injection" presentation.

9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Intended for prevention of nausea and vomiting with (b) (4) high emetogenic chemotherapy	Rx	none
12. DOSAGE FORM	**13. POTENCY**	
Lyophilized powder for injection	Each mL provides 115 mg or 150 mg of fosaprepitant (as the free acid)	

14. CHEMICAL NAME AND STRUCTURE

Fosaprepitant dimeglumine (a prodrug of aprepitant)
1-Deoxy-1-(methylamino)-D-glucito[[3[[(*2R,3S*)-2-[(*1R*)-1-[3,5-bis(trifluromethyl)phenyl) ethoxy]-3-(4-flurophenyl)-4-morpholinyl)methyl]-2,5-dihydro-5-oxo-*1H*-triazol-1-yl] phosphonate (2:1) salt
$C_{23}H_{22}F_7N_4O_6P \bullet 2(C_7H_{17}NO_5)$, molecular weight is 1004.83 grams per mole
Structure:



15. COMMENTS

This prior-approval supplement provides a new dosing regimen for the drug product, EMEND® (fosaprepitant dimeglumine) for injection, involving the use of a single 150-mg injection to be administered concurrently with a 5-HT3 receptor antagonist. The currently-approved dosing regimen for fosaprepitant dimeglumine for injection involves the administration of a 115-mg injection on Day 1 followed by oral aprepitant on Days 2 and 3.

This CMC review addresses the development, manufacture, control, and stability of the new dosage unit, a vial of EMENED® (fosaprepitant dimeglumine) for Injection, designed to provide a dose of 150 mg fosaprepitant (as the free acid).

The injectable EMEND product is a lyophilized powder for injection. (b) (4) .

Issues of sterility assurance were evaluated by the microbiology staff, and are recommended for approval (microbiology review dated 29-JUNE-2010, S. Fong, Ph.D., reviewer).

Several issues, including drug substance, drug product solution compounding, specifications, analytical methods, and container closure system, involved CMC information identical (unchanged) from the original NDA 22-023 application, and were adequate by reference. This review focused on pharmaceutical development, justification of specifications, analytical results (release and stability), and labeling.

The labeling (container label, carton label, and package insert) was evaluated in this review. The applicant added en entry for the new higher-strength presentation. All labeling statements regarding quantity and quality of ingredients matched the information provided within the supplemental application.

16. CONCLUSION AND RECOMMENDATION

The application is recommended for APPROVAL from the standpoint of CMC. This application is OND-managed, and ONDQA will not draft the action letter.

17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
DAVID LEWIS	See appended electronic signature sheet	30-JUNE-2010

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

DAVID B LEWIS
07/12/2010
recommend approval from standpoint of CMC

HASMUKH B PATEL
07/12/2010

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

NDA Number: 22-023	**Supplement Number and Type: SE2-004**	**Established/Proper Name: EMEND (fosaprepitant dimeglumine) for Injection**
Applicant: Merck & Co., Inc.	**Letter Date: 13-OCTOBER-2009**	**Stamp Date: 13-OCTOBER-2009**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			N/A; this is a post-approval supplement

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		Section entitled "Statement of PAI Readiness – 150mg, in Module 1". However, no new facilities are provided.
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			N/A; the API is derived from chemical synthesis

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		Facility is listed along with point of contact. This facility is NOT new to the application.
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)			Facility is listed along with point of contact. This facility is NOT new to the application. DMF (b) (4) is referenced.

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	x		Categorical exclusion per 21 CFR 25.31(b)

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	x		By reference to approved NDA 21-549
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	x		See above
14.	Does the section contain information regarding the characterization of the DS?	x		See above
15.	Does the section contain controls for the DS?	x		See above
16.	Has stability data and analysis been provided for the drug substance?	x		See above
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	N/A
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	N/A

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?		x	N/A; the reference product is the marketed lower-strength product, 115 mg per vial. This is a higher-strength version.
23.	Have any biowaivers been requested?			
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?		x	(b) (4) [redacted] .

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	x		

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4) [redacted]					

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Describe filing issues here or on additional sheets
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?			Describe potential review issues here or on additional sheets

{See appended electronic signature page}

Name of
Pharmaceutical Assessment Lead or CMC Lead / CMC Reviewer — Date
Division of Pre-Marketing Assessment #
Office of New Drug Quality Assessment

{See appended electronic signature page}

Name of
Branch Chief — Date
Division of Pre-Marketing Assessment #
Office of New Drug Quality Assessment

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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

/s/

DAVID B LEWIS
11/30/2009
The application is fileable regarding CMC

HASMUKH B PATEL
11/30/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022023/S-004

PHARMACOLOGY REVIEW(S)

Pharmacologist's Review of NDA 22-023
(Sequence # 004, Dated October 12, 2009)

Sponsor and Address: Merck & Co., Inc.
Rahway, NJ 07054

Reviewer: Sushanta Chakder, Ph. D.
Supervisory Pharmacologist, HFD-180

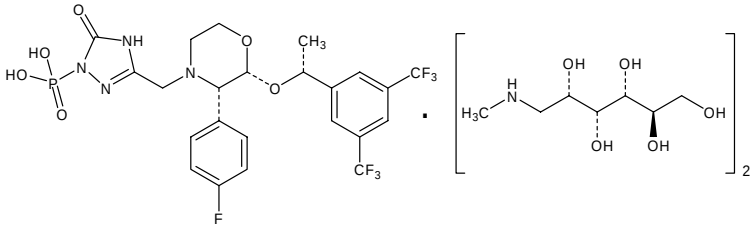
Date of Submission: October 12, 2009

Date of HFD-180 Receipt: October 12, 2009

Date of Review: July 01, 2010

Drug: Emend™ (Fosaprepitant dimeglumide; MK-0517) for Injection

Chemical Name: 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).



Molecular Formula/Molecular Weight: $C_{23}H_{22}F_7N_4O_6P \cdot 2(C_7H_{17}NO_5)/1004.83$

Category: NK-1 receptor antagonist/Anti-emetic

Clinical Formulation:
Each vial of EMEND for Injection 115 mg for intravenous administration contains 188 mg of fosaprepitant dimeglumine equivalent to 115 mg of fosaprepitant free acid and the following inactive ingredients: edetate disodium (14.4 mg), polysorbate 80 (57.5 mg), lactose anhydrous (287.5 mg), sodium hydroxide and/or hydrochloric acid (for pH adjustment). Each vial of EMEND for Injection 150 mg for intravenous administration contains 245.3 mg of fosaprepitant dimeglumine equivalent to 150 mg of fosaprepitant free acid and the following inactive ingredients: edetate disodium (18.8 mg), polysorbate 80 (75 mg), lactose anhydrous (375 mg), sodium hydroxide and/or hydrochloric acid (for pH adjustment).

Submission Contents: Prior approval supplement

Fosaprepitant dimeglumide (Emend) for Injection was approved by the FDA on January 25, 2008 for use as part of the 3-day dosage regimen. In the CINV dosage regimen, Emend for Injection (115 mg) is substituted for oral Emend (125 mg) on Day 1 that includes a corticosteroid and a 5-HT_3 antagonist. In the current prior approval supplement, the sponsor is seeking approval of a single dose fosaprepitant dosage regimen as an alternative to the approved oral 3-day regimen of Emend. This supplemental application is submitted to support the use of a single IV 150 mg dose of fosaprepitant, dosed concomitantly with a 5-HT_3 receptor antagonist and a corticosteroid.

Executive Summary

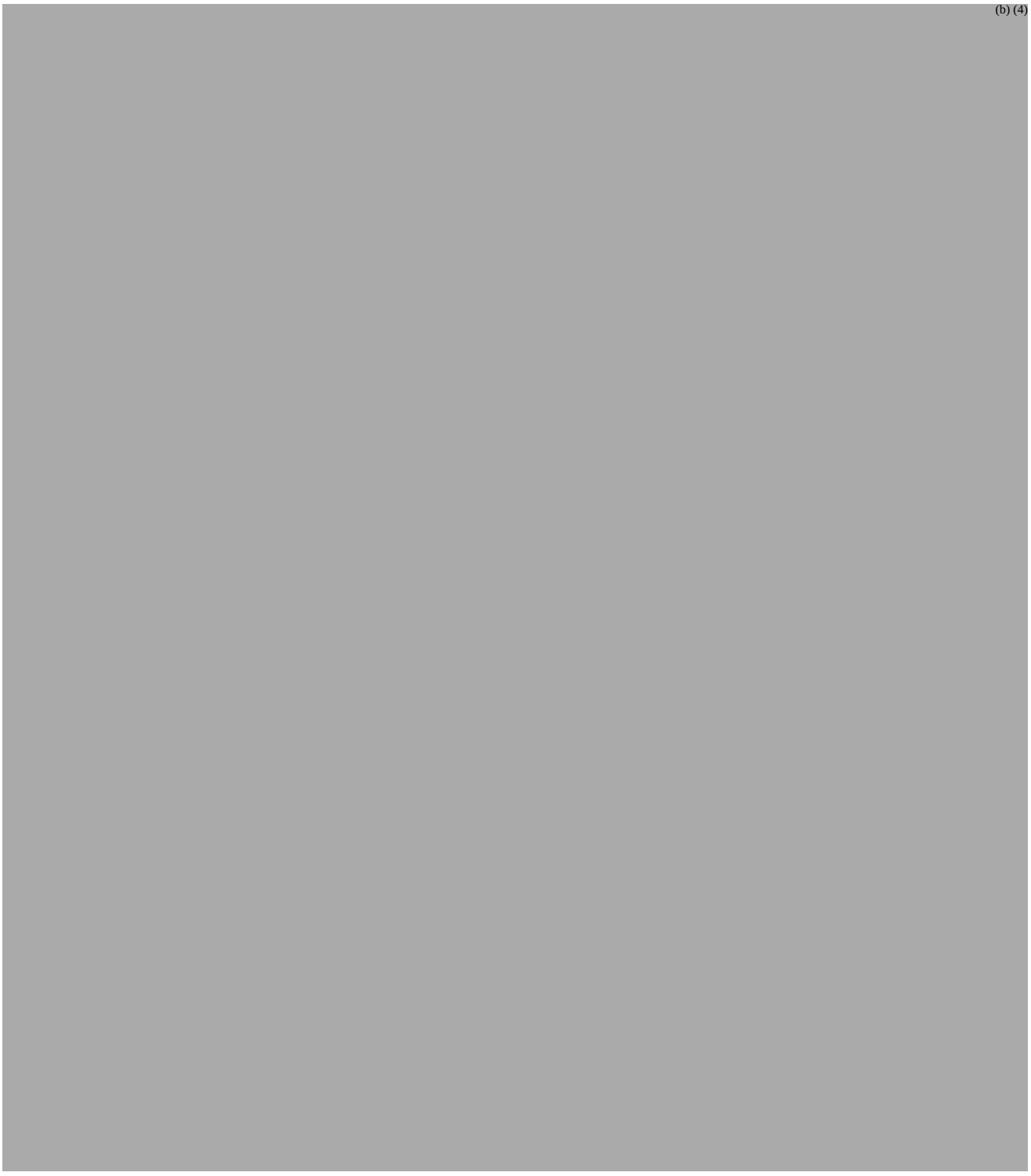
I. Recommendations

A. **Recommendation on Approvability:** From a nonclinical standpoint, an approval of the NDA Prior Approval Supplement is recommended.

B. **Recommendation for Nonclinical Studies:** None.

C. **Recommendations on Labeling:** (b) (4)

(b) (4)



II. Summary of Nonclinical Findings:

A. Brief overview of nonclinical findings:

Fosaprepitant dimeglumide (Emend) for Injection is currently approved for use as part of the 3-day CINV dosage regimen. The nonclinical safety of fosaprepitant was established in toxicology studies submitted in the original NDA application. In the current prior approval supplement, the sponsor submitted a nonclinical study report in which the local tolerability of the commercial formulation of MK-0517 (fosaprepitant dimeglumide for injection containing 1 mg/mL of MK-0517) was assessed following single intravenous, intramuscular, paravenous and subcutaneous administration to male and female rabbits. Following administration of a single dose of the fosaprepitant commercial formulation to rabbits, the severity of physical signs and the incidences and severity of histomorphologic changes observed at the injection sites were slightly higher for fosaprepitant, as compared with the vehicle. In previous repeat dose toxicity studies in rats, treatment with fosaprepitant was associated with injection site changes (cellular proliferation of venous intima, venous necrosis or thrombosis, skin necrosis, subcutaneous edema, cellular infiltration and degeneration of muscle fibers). In dogs, the injection site was also the target organ of toxicity (venous thrombosis, fibroplasia and necrosis).
In a 39-week oral toxicity study with aprepitant in dogs, the target organs of toxicity were the testes (tubular degeneration) and prostate (atrophy). Testicular degeneration and an atrophy of the prostate and thymus were also observed in a 5-week oral toxicity study in dogs. However, in a 53-week oral toxicity study with a 27-week interim sacrifice, no target organ of toxicity was identified. In monkeys, intravenous dosing of L-758, 298 for up to 240 mg/kg/day for 17 days, and up to 10 mg/kg/day for 5 weeks was not associated with any adverse effects, and no target organs of toxicity were identified. Thus, repeated intravenous administration of fosaprepitant/aprepitant in rodents and non-rodents was not associated with any toxic effects other than the injection site reactions.

B. Pharmacologic Activity:

Fosaprepitant is a prodrug of aprepitant, and when administered intravenously, it is rapidly converted to aprepitant. Aprepitant is a selective high affinity antagonist of substance P/neurokinin 1 (NK_1) receptor. Aprepitant has very low or no affinity for serotonin ($5\text{-}HT_3$), dopamine and corticosteroid receptors. In animal models, aprepitant has been shown to inhibit emesis induced by cytotoxic chemotherapeutic agents, such as cisplatin. 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 showed that aprepitant augments the antiemetic activity of the $5\text{-}HT_3$ receptor antagonist ondansetron and the corticosteroid dexametahsone.

C. **Nonclinical Safety Issues Relevant to Clinical Use:** None

TOXICOLOGY:

LOCAL TOLERABILITY:

Study title: Single-Dose Intravenous/Paravenous/Subcutaneous/Intramuscular Local Tolerability Study in Rabbits

Key findings: Following intravenous, paravenous, subcutaneous and intramuscular administration of a single dose of fosaprepitant commercial formulation to male and female rabbits, the severity of physical signs and the incidences and severity of histomorphologic changes observed at the injection sites were slightly higher for fosaprepitant as compared with the vehicle.

Study no: TT#08-7590
Conducting laboratory and location: Merck Research Laboratories, Merck & Co., Inc., West Point, PA 19486.
Date of study initiation: November 03, 2008
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, radiolabel, and % purity**: Fosaprepitant (MK-0517, L-000758298), Lot # L-000758298-014J001 also known as WL00017620**

Formulation/vehicle**: The composition of Fosaprepitant Dimeglumide for Injection is provided in the sponsor's Table below.**

Ingredients	Quantity	Final Concentration
MK-0517 (Fosaprepitant Dimeglumine [free acid])	115 mg	1 mg/mL
Inactive Ingredients:[a]		
Edetate disodium	14.4 mg	0.125 mg/mL
Polysorbate 80	57.5 mg	0.5 mg/mL
Lactose anhydrous	287.5 mg	2.5 mg/mL
[a] Contains sodium hydroxide and/or hydrochloric acid for pH adjustment.		

The formulation was supplied as a lyophilized product in 10 mL glass vials, and each vial was reconstituted with 4 mL of sterile saline. The reconstituted material was then diluted with 110 mL of sterile saline to yield a total volume of 115 mL and a final concentration of 1 mg/mL of fosaprepitant.

Methods:
The study was conducted to assess the local tolerability of the commercial formulation of MK-0517 (fosaprepitant dimeglumide for injection containing 1 mg/mL of MK-0517) when administered as single intravenous, intramuscular, paravenous and subcutaneous doses to male and female rabbits. The first 5 rabbits/sex/group were sacrificed approximately 24 hours after the single injections on Study Day 2, and the remaining 5 rabbits/sex/group were sacrificed on Study Day 8. Assessment of irritation and tolerability was based on mortality, physical examinations, and gross and histopathological examinations of the injection sites.

Doses: Two groups of rabbits each consisting of 10 females and 10 males were used in the study. One group received MK-0517 in a 0.5 mL (0.5 mg) bolus IV injection into the left marginal ear vein and a 0.5 mL bolus IM injection in the left sacrospinalis muscle. The second group received MK-0517 in a 0.5 mL bolus paravenous injection next to the left marginal ear vein, and a 0.5 mL bolus SC injection into the left lateral thoracic area overlying the rib cage. Both groups also received the placebo control formulation (0.9% saline; 0.125 mg/mL edetate sodium, 0.5 mg/mL polysorbate 80, 2.5 mg/mL lactose monohydrate, 9 mg/mL sodium chloride, with minor sodium hydroxide and/or hydrochloric acid, for pH adjustment) by the same routes on the right side of the animal.

Species/strain: New Zealand White rabbits.

Number/sex/group or time point (main study): 10 animals/sex/group

Route, formulation, volume, and infusion rate: 0.5 mL of the above-mentioned formulation was administered by the different routes by a bolus injection.

Satellite groups used for toxicokinetics or recovery: None

Age: Approximately 19 weeks

Weight: 2020 – 2755 g

Sampling times: N/A

Unique study design or methodology (if any): None

Observation and Times:

Clinical signs: The animals were observed daily for clinical signs and mortality. On the day of dosing, injection sites were observed prior to dosing and twice post-dosing.

Body weights: Body weights were measured pretest.

Gross and Histopathology: Animals sacrificed at interim necropsy or at study termination underwent a complete necropsy examination. Samples of the injection sites (shown in the Table below) were collected and placed in 10% neutral buffered formalin for histopathologic examination.

	Animal #08-1327-1336 Animal #08-1347-1356	Animal #08-1337-1346 Animal #08-1357-1366
Intravenous injection sites	Site 1- control: Marginal ear vein, right ear. Site 2- MK-0517: Marginal ear vein, left ear.	
Intramuscular injection sites	Site 3- control: Intramuscular, right sacrospinalis muscle. Site 4- MK-0517: Intramuscular, left sacrospinalis muscle.	
Paravenous injection sites		Site 5- control: Paravenous to marginal ear vein, right ear. Site 6- MK-0517: Paravenous to marginal ear vein, left ear.
Subcutaneous injection sites		Site 7- control: Right subcutaneous dorsum. Site 8- MK-0517: Left subcutaneous dorsum.

Results:

Mortality: There were no mortalities in any group.

Clinical signs:The incidence of physical signs (purple red discoloration) at the intravenous and paravenous injection sites was comparable between the MK-0517 and placebo formulations, but the severity was slightly greater at the MK-0517-treated sites. The incidence and severity of purple/red discoloration at the intramuscular and subcutaneous was comparable between the MK-0517 and placebo formulations.

Body weights: Body weights were measured only pretest.

Gross and Histopathology: At interim necropsy (Day 2), treatment-related gross and histomorphologic changes were in MK-0517-treated injection sites, which were generally of greater incidence and severity as compared with the controls injection sites. The histomorphologic changes observed in the control and MK-0517 group are summarized in the Table below.

Test Article-Related Postmortem Findings - Histomorphology
MK-0517, Sexes Combined

Dose (0.5 mL/site)	Control[a]	MK-0517[b]
Interim (Study Day 2) Final (Study Day 8)	n=10 n=10	n=10 n=10
IV Injection Site		
Interim		
Hemorrhage	7	9
Inflammation, acute	3	9
Final		
Inflammation, subacute	2	2
IM Injection Site		
Interim		
Inflammation, acute, focal	2	5
Muscle fiber, degeneration, focal	8	8
Muscle fiber, necrosis, focal	-	6
Final		
Inflammation, subacute, focal	-	6
Muscle regeneration, focal	1	7
Muscle fiber, degeneration, focal	-	6
Muscle fiber, mineralization, focal	-	6
Muscle fiber, necrosis, focal	-	6
PV Injection Site		
Interim		
Hemorrhage	7	6
Inflammation, acute	6	9
Final		
Hemorrhage	2	-
Inflammation, subacute	2	5
SC Injection Site		
Interim		
Hemorrhage	1	3
Inflammation, acute	-	4
Final		
Muscle Fiber, regeneration	-	2

[a] Control = Placebo contains 0.125 mg/mL edetate disodium, 0.5 mg/mL polysorbate 80, 2.5 mg/mL lactose anhydrous, 9 mg/mL sodium chloride, with minor sodium hydroxide and/or hydrochloric acid (for pH adjustment) in water.
[b] 0.5 mL of 1 mg/mL formulation.
IM = Intramuscular.
IV = Intravenous.
PV = Paravenous.
SC = Subcutaneous.
- = No test article-related change.

Single-Dose Intravenous/Paravenous/Subcutaneous/Intramuscular Local Tolerability Study in Rabbits.

On **Study Day 2** (interim sacrifice), histomorphologic changes observed at the injection sites of MK-0517-treated animals were of increased incidence and severity as compared with those receiving the vehicle. MK-0517-treated intravenous, paravenous and subcutaneous injection sites had very slight to moderate acute inflammation, and very slight to moderate hemorrhage in the subcutis, which correlated with the grossly observed focal red discoloration. The inflammation was characterized by a diffuse infiltrate of small number of neutrophils associated with edema. At the intramuscular injection sites, the changes consisted of very slight to moderate focal skeletal muscle degeneration and necrosis with associated focal areas of neutrophilic inflammation. Histomorphologic changes observed in different groups at interim necropsy are shown in the sponsor's Tables below.

TABLE B-4. MK-0517: Single Dose Intravenous/Paravenous/Subcutaneous/Intramuscular Local Tolerability Study in Rabbits. TT #08-7590
Histomorphology - Interim Necropsy

	Female	
	DC 014	DC 024
ANIMAL NUMBER	0 0 0 0 0 8 8 8 8 8 1 1 1 1 1 3 3 3 3 3 2 2 2 3 3 7 8 9 0 1	0 0 0 0 0 8 8 8 8 8 1 1 1 1 1 3 3 3 3 3 3 3 3 4 4 7 8 9 0 1
DEATH STATUS	S S S S S	S S S S S
WEEKS ON STUDY	1 1 1 1 1	1 1 1 1 1
Site 1	N	
Hemorrhage	1 1 1 1	
Inflammation, Acute	- 2 - -	
Site 2	N	
Hemorrhage	2 2 2 2	
Inflammation, Acute	2 2 1 3	
Site 3	N N	
Muscle Fiber, Degeneration, Focal	1 1 1	
Site 4	N	
Inflammation, Focal Acute	1 - - -	
Muscle Fiber, Degeneration, Focal	3 1 2 2	
Muscle Fiber, Necrosis, Focal	1 1 1 -	
Site 5		
Hemorrhage		2 1 1 2 -
Inflammation, Acute		2 - - 1 1
Site 6		
Hemorrhage		3 - 2 - 1
Inflammation, Acute		2 2 - 2 2
Site 7		N N N N N
Site 8		N
Hemorrhage		3 1 - 2
Inflammation, Acute		1 1 1 2

KEY: N = NOT REMARKABLE
A = AUTOLYSIS
B = TISSUE NOT PRESENT IN SECTION(S)
L = TISSUE LOST OR MISSING
K = EARLY SACRIFICE
1 = VERY SLIGHT
2 = SLIGHT OR SMALL
3 = MODERATE
4 = MARKED
S = SCHEDULED SACRIFICE
5 = SEVERE
X = PRESENT
- = NOT PRESENT
D = FOUND DEAD

* AUTOLYSIS DOES NOT PRECLUDE EXAMINATION FOR NEOPLASTIC AND OBVIOUS NON-NEOPLASTIC CHANGES.
NO ORGAN ENTRY = GROSSLY NORMAL, NO MICROSCOPIC EXAMINATION

Site 1 = IV Control
Site 2 = IV Treated
Site 3 = IM Control
Site 4 = IM Treated
Site 5 = PV Control
Site 6 = PV Treated
Site 7 = SC Control
Site 8 = SC Treated

TABLE B-4. MK-0517: Single Dose Intravenous/Paravenous/Subcutaneous/Intramuscular Local Tolerability Study in Rabbits. TT #08-7590
Histomorphology - Interim Necropsy

	Male	
	DC 014	DC 024
ANIMAL NUMBER	0 0 0 0 0 8 8 8 8 8 1 1 1 1 1 3 3 3 3 3 4 4 4 5 5 7 8 9 0 1	0 0 0 0 0 8 8 8 8 8 1 1 1 1 1 3 3 3 3 3 5 5 5 6 6 7 8 9 0 1
DEATH STATUS	S S S S S	S S S S S
WEEKS ON STUDY	1 1 1 1 1	1 1 1 1 1
Site 1	N N	
Hemorrhage	1 1 1	
Inflammation, Acute	1 - 1	
Site 2		
Hemorrhage	1 1 1 1 2	
Inflammation, Acute	1 2 1 1 1	
Site 3		
Inflammation, Focal Acute	- 1 - - 1	
Muscle Fiber, Degeneration, Focal	1 1 1 1 2	
Site 4	N	
Inflammation, Focal Acute	1 1 1 1	
Muscle Fiber, Degeneration, Focal	3 3 3 3	
Muscle Fiber, Necrosis, Focal	1 - 1 1	
Site 5		N N
Hemorrhage		1 1 1
Inflammation, Acute		1 1 1
Site 6		
Hemorrhage		2 - 2 1 -
Inflammation, Acute		2 2 1 1 2
Site 7		N N N N
Hemorrhage		3
Site 8		N N N N N

KEY: N = NOT REMARKABLE
A = AUTOLYSIS
B = TISSUB NOT PRESENT IN SECTION(S)
L = TISSUE LOST OR MISSING
K = EARLY SACRIFICE
1 = VERY SLIGHT
2 = SLIGHT OR SMALL
3 = MODERATE
4 = MARKED
S = SCHEDULED SACRIFICE
5 = SEVERE
X = PRESENT
- = NOT PRESENT
D = FOUND DEAD

* AUTOLYSIS DOES NOT PRECLUDE EXAMINATION FOR NEOPLASTIC AND OBVIOUS NON-NEOPLASTIC CHANGES.
NO ORGAN ENTRY = GROSSLY NORMAL, NO MICROSCOPIC EXAMINATION

Site 1 = IV Control
Site 2 = IV Treated
Site 3 = IM Control
Site 4 = IM Treated
Site 5 = PV Control
Site 6 = PV Treated
Site 7 = SC Control
Site 8 = SC Treated

On **Study Day 8** (final necropsy), histomorphologic changes at the intramuscular and subcutaneous injection sites were also increased in animals receiving MK-0517 compared to the vehicle-treated animals. Changes at the intramuscular injection sites consisted of focal skeletal muscle necrosis (very slight to moderate) with mineralization (very slight to moderate) bordered by subacute inflammation, and correlated with pale discoloration noted grossly. The subacute inflammatory infiltrate consisted of macrophages, lymphocytes and fibroblasts at the periphery of the muscle necrosis. In addition, MK-0517-treated injection sites had an increased incidence and severity of skeletal muscle fiber regeneration on Study Day 8. At the subcutaneous injection sites, MK-0517-related hemorrhagic changes, on Day 8, consisted of very slight, focal skeletal muscle regeneration in the subcuticular panniculus muscle. Histomorphologic changes at intravenous and paravenous injection sites at final necropsy were similar between MK-0517 and vehicle treatment groups, and consisted of very slight to slight subacute inflammation. Histomorphological changes observed at final necropsy (Day 8) in different treatment groups are shown in the sponsor's Tables below.

TABLE B-6. MK-0517: Single Dose Intravenous/Paravenous/Subcutaneous/Intramuscular Local Tolerability Study in Rabbits. TT #08-7590
Summary Incidence of Histomorphology - Final Necropsy

Group Number	Female 1	Female 2	Male 1	Male 2
NUMBER NECROPSIED	5	5	5	5
Site 1				
NO. EXAMINED MICROSCOPICALLY	5	0	5	0
Not Remarkable	4		4	
Inflammation, Subacute	1		1	
Site 2				
NO. EXAMINED MICROSCOPICALLY	5	0	5	0
Not Remarkable	4		4	
Inflammation, Subacute	1		1	
Site 3				
NO. EXAMINED MICROSCOPICALLY	5	0	5	0
Not Remarkable	4		5	
Muscle, Regeneration, Focal	1		-	
Site 4				
NO. EXAMINED MICROSCOPICALLY	5	0	5	0
Not Remarkable	1		2	
Inflammation, Focal Subacute	3		3	
Muscle, Regeneration, Focal	4		3	
Muscle Fiber, Degeneration, Focal	3		3	
Muscle Fiber, Mineralization, Focal	3		3	
Muscle Fiber, Necrosis, Focal	3		3	
Site 5				
NO. EXAMINED MICROSCOPICALLY	0	5	0	5
Not Remarkable		4		3
Hemorrhage		-		2
Inflammation, Subacute		1		1
Site 6				
NO. EXAMINED MICROSCOPICALLY	0	5	0	5
Not Remarkable		2		3
Inflammation, Subacute		3		2
Site 7				
NO. EXAMINED MICROSCOPICALLY	0	5	0	5
Not Remarkable		5		5
Site 8				
NO. EXAMINED MICROSCOPICALLY	0	5	0	5
Not Remarkable		4		4
Muscle, Regeneration		1		1

KEY: GROUP 1 = DC 014 GROUP 2 = DC 024
- = NOT PRESENT.
Site 1 = IV Control Site 5 = PV Control
Site 2 = IV Treated Site 6 = PV Treated
Site 3 = IM Control Site 7 = SC Control
Site 4 = IM Treated Site 8 = SC Treated

TABLE B-8. MK-0517: Single Dose Intravenous/Paravenous/Subcutaneous/Intramuscular Local Tolerability Study in Rabbits. TT #08-7590
Histomorphology - Final Necropsy

	Female	
	DC 014	DC 024
ANIMAL NUMBER	0 0 0 0 0 8 8 8 8 8 1 1 1 1 1 3 3 3 3 3 3 3 3 3 3 2 3 4 5 6	0 0 0 0 0 8 8 8 8 8 1 1 1 1 1 3 3 3 3 3 4 4 4 4 4 2 3 4 5 6
DEATH STATUS	S S S S S	S S S S S
WEEKS ON STUDY	2 2 2 2 2	2 2 2 2 2
Site 1	N N N N	
Inflammation, Subacute	1	
Site 2	N N N N	
Inflammation, Subacute	1	
Site 3	N N N N	
Muscle, Regeneration, Focal	1	
Site 4	N	
Inflammation, Focal Subacute	3 3 1 -	
Muscle, Regeneration, Focal	3 3 2 1	
Muscle Fiber, Degeneration, Focal	1 3 2 -	
Muscle Fiber, Mineralization, Focal	3 3 2 -	
Muscle Fiber, Necrosis, Focal	3 2 1 -	
Site 5		N N N N
Inflammation, Subacute		1
Site 6		N N
Inflammation, Subacute		1 1 2
Site 7		N N N N N
Site 8		N N N N
Muscle, Regeneration		1

KEY: N = NOT REMARKABLE
A = AUTOLYSIS
B = TISSUE NOT PRESENT IN SECTION(S)
L = TISSUE LOST OR MISSING
K = EARLY SACRIFICE
1 = VERY SLIGHT
2 = SLIGHT OR SMALL
3 = MODERATE
4 = MARKED
S = SCHEDULED SACRIFICE
5 = SEVERE
X = PRESENT
- = NOT PRESENT
D = FOUND DEAD
* AUTOLYSIS DOES NOT PRECLUDE EXAMINATION FOR NEOPLASTIC AND OBVIOUS NON-NEOPLASTIC CHANGES.
NO ORGAN ENTRY = GROSSLY NORMAL, NO MICROSCOPIC EXAMINATION
Site 1 = IV Control
Site 2 = IV Treated
Site 3 = IM Control
Site 4 = IM Treated
Site 5 = PV Control
Site 6 = PV Treated
Site 7 = SC Control
Site 8 = SC Treated

Continued
TABLE B-8. MK-0517: Single Dose Intravenous/Paravenous/Subcutaneous/Intramuscular Local Tolerability Study in Rabbits. TT #08-7590
Histomorphology - Final Necropsy

	Male	
	DC 014	DC 024
ANIMAL NUMBER	0 0 0 0 0 8 8 8 8 8 1 1 1 1 1 3 3 3 3 3 5 5 5 5 5 2 3 4 5 6	0 0 0 0 0 8 8 8 8 8 1 1 1 1 1 3 3 3 3 3 6 6 6 6 6 2 3 4 5 6
DEATH STATUS	S S S S S	S S S S S
WEEKS ON STUDY	2 2 2 2 2	2 2 2 2 2
Site 1	N N N N	
Inflammation, Subacute	1	
Site 2	N N N N	
Inflammation, Subacute	1	
Site 3	N N N N N	
Site 4	N N	
Inflammation, Focal Subacute	3 3 3	
Muscle, Regeneration, Focal	3 3 3	
Muscle Fiber, Degeneration, Focal	1 1 1	
Muscle Fiber, Mineralization, Focal	1 3 1	
Muscle Fiber, Necrosis, Focal	3 1 3	
Site 5		N N N
Hemorrhage		1 1
Inflammation, Subacute		1 -
Site 6		N N N
Inflammation, Subacute		1 1
Site 7		N N N N N
Site 8		N N N N
Muscle, Regeneration		1

KEY: N = NOT REMARKABLE
A = AUTOLYSIS
B = TISSUE NOT PRESENT IN SECTION(S)
L = TISSUE LOST OR MISSING
K = EARLY SACRIFICE
1 = VERY SLIGHT
2 = SLIGHT OR SMALL
3 = MODERATE
4 = MARKED
S = SCHEDULED SACRIFICE
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- = NOT PRESENT
D = FOUND DEAD
* AUTOLYSIS DOES NOT PRECLUDE EXAMINATION FOR NEOPLASTIC AND OBVIOUS NON-NEOPLASTIC CHANGES.
NO ORGAN ENTRY = GROSSLY NORMAL, NO MICROSCOPIC EXAMINATION
Site 1 = IV Control
Site 2 = IV Treated
Site 3 = IM Control
Site 4 = IM Treated
Site 5 = PV Control
Site 6 = PV Treated
Site 7 = SC Control
Site 8 = SC Treated

Summary: To determine the local tolerability of the commercial formulation of fosaprepitant dimeglumine for injection (MK-0517, 1 mg/mL), it was administered as a single bolus 0.5 mL injection to male and female rabbits by intravenous, paravenous, intramuscular and subcutaneous routes. There were no unscheduled deaths. The incidence of physical signs (purple red discoloration) at the intravenous and paravenous injection sites was comparable between the

MK-0517 and placebo formulations, but the severity was slightly greater at the MK-0517-treated sites. The incidence and severity of purple/red discoloration at the intramuscular and subcutaneous injection sites were comparable between the MK-0517 and placebo formulations. Histomorphologic changes observed on **Study Day 2** (interim sacrifice) at the injection sites of MK-0517-treated animals were of increased incidence and severity as compared with those receiving the vehicle. MK-0517-treated intravenous, paravenous and subcutaneous injection sites had very slight to moderate acute inflammation, and very slight to moderate hemorrhage in the subcutis. The inflammation was characterized by a diffuse infiltrate of small number of neutrophils associated with edema. At the intramuscular injection sites, the changes consisted of very slight to moderate focal skeletal muscle degeneration and necrosis with associated focal areas of neutrophilic inflammation.
On **Study Day 8** (final necropsy), histomorphologic changes at the intramuscular and subcutaneous injection sites were also increased in animals receiving MK-0517 compared to the vehicle-treated animals. Changes at the intramuscular injection sites consisted of focal skeletal muscle necrosis (very slight to moderate) with mineralization (very slight to moderate) bordered by subacute inflammation, and correlated with pale discoloration noted grossly. The subacute inflammatory infiltrate consisted of macrophages, lymphocytes and fibroblasts at the periphery of the muscle necrosis. In addition, MK-0517-treated injection sites had an increased incidence and severity of skeletal muscle fiber regeneration on Study Day 8. At the subcutaneous injection sites, MK-0517-related hemorrhagic changes, on Day 8, consisted of very slight, focal skeletal muscle regeneration in the subcuticular panniculus muscle.

SUMMARY AND EVALUATION:

Fosaprepitant dimeglumide (Emend) for Injection was approved by the FDA on January 25, 2008 for use as part of the 3-day dosage regimen. In the approved CINV dosage regimen, Emend for Injection (115 mg) is substituted for oral Emend (125 mg) on Day 1 that includes a corticosteroid and a 5-HT_3 antagonist. In the current prior approval supplement, the sponsor is seeking approval of a single dose fosaprepitant dosage regimen as an alternative to the approved oral 3-day regimen of Emend. This supplemental application is submitted to support the use of a single IV 150 mg dose of fosaprepitant, dosed concomitantly with a 5-HT_3 receptor antagonist and a corticosteroid.

The nonclinical safety of fosaprepitant was established in toxicology studies submitted in the original NDA application. In the current prior approval supplement, the sponsor submitted a nonclinical study report in which the local tolerability of the commercial formulation of MK-0517 (fosaprepitant dimeglumide for injection containing 1 mg/mL of MK-0517) was assessed following single intravenous, intramuscular, paravenous and subcutaneous administration to male and female rabbits. Following intravenous, paravenous, intravenous and subcutaneous administration of the commercial formulation of fosaprepitant dimeglumide to male and female rabbits, the severity of physical signs at the injection sites was slightly higher than that for the vehicle. Histomorphologic changes were also of increased incidence and severity as compared with those receiving the vehicle, on both study day 2 and 8. MK-0517-treated intravenous, paravenous and subcutaneous injection sites had very slight to moderate acute inflammation, and very slight to moderate hemorrhage in the subcutis.

In previous repeat dose toxicity studies of fosaprepitant in rats and dogs, injection site was also a target organ of toxicity, and the injection site changes included cellular proliferation of venous intima, venous necrosis or thrombosis, skin necrosis, subcutaneous edema, cellular infiltration and degeneration of muscle fibers in rats, and venous thrombosis, fibroplasia and necrosis in dogs.
Nonclinical studies conducted with fosaprepitant (reviewed under the original NDA application) support the safety of the use of a single 150 mg dose of fosaprepitant. Thus, from a nonclinical standpoint, the sponsor's proposed 150 mg dosage regimen does not appear to have any safety concerns.

Recommendations: From a nonclinical standpoint, the Prior Approval Supplement is recommended for approval, with incorporation of the proposed labeling changes.

_____ _____

Sushanta Chakder, Ph.D. Date
Supervisory Pharmacologist, HFD-180

cc:
NDA
HFD- 180
HFD- 180/RPM
HFD- 180/Dr. Chakder

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

SUSHANTA K CHAKDER
07/01/2010

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22-023 **Applicant:** (b) (4) **Stamp Date: 10/12/2009**

Drug Name: EMEND (fosaprepitant dimeglumide) for Injection **NDA/BLA Type: Prior Approval Supplement**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		No nonclinical data were submitted.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			N/A
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)		X	
11	Has the applicant addressed any abuse potential issues in the submission?		X	
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?		N/A	

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Sushanta Chakder, Ph.D. November 30, 2009

Reviewing Pharmacologist Date

Sushanta Chakder, Ph.D. November 30, 2009

Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

SUSHANTA K CHAKDER
11/30/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022023/S-004

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA/Serial Number:	22023/S-004
Drug Name:	EMEND (fosaprepitant dimeglumine) for Injection (MK-0517)
Indication(s):	Prevention for acute and delayed nausea and vomiting with (b) (4) high emetogenic chemotherapy
Applicant:	Merck
Date(s):	Electronic submission received October 12, 2009
Review Priority:	Standard; PDUFA date: November 13, 2010
Biometrics Division:	Division of Biometrics 3
Statistical Reviewer:	Wen-Jen Chen, Ph.D.
Concurring Reviewer:	Mike Welch, Ph.D. Team leader
Medical Division:	Gastroenterology Products (HFD-180)
Clinical Team:	Tamara Johnson, MD., Nancy Snow, MD, Team leader (Actg)
Project Manager:	Jagjit Grewal, M.P.H.

Statistical Keywords: Non-inferiority, Single study, Clinical studies; NDA review.

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

The purpose of this supplemental application is to support the use of a single intravenous dose of fosaprepitant 150 mg (dosed concomitantly with a 5HT3 receptor antagonist and a corticosteroid) for the prevention of acute and delayed nausea and vomiting in cancer patients undergoing [redacted] (b) (4) highly emetogenic chemotherapy (HEC).

The sponsor conducted a single, multi-national trial, Study P017L1, and results of analyses of the primary endpoint (complete response in the overall phase) and secondary endpoints (complete response in the delayed phase and no vomiting in the overall phase) support the intended indication but only for cancer patients undergoing HEC, as the study enrolled patients only in that category. [redacted] (b) (4)

However, based on this reviewer's treatment-by-country analysis of the primary endpoint, the study does not show convincing evidence that clinical benefit is consistent across different countries. In addition, for the findings of treatment by region analyses, US versus Non-US and US/Canada versus Non-(US/Canada), Study P017L1 does not provide clear efficacy evidence to support the use of the fosaprepitant regimen in US patients for the proposed claim. However, since only 2.6% of patients were enrolled in US sites, no formal conclusion can be made regarding the efficacy of fosaprepitant regimen in US patients.

1.2 Brief Overview of Clinical Studies

This was a worldwide, multi-center, phase 3, randomized, double-blind, active controlled, parallel-group study (conducted under in-house blinding) to assess the safety, tolerability, and efficacy of a single dose of 150 mg IV fosaprepitant dimeglumine for the prevention of chemotherapy induced nausea and vomiting (CINV) in patients who were naïve to cisplatin chemotherapy and who were treated with a chemotherapy regimen that included cisplatin $\geq$ 70 mg/m^2.

The primary objective of Study P017L1 was to compare the single-dose fosaprepitant dimeglumine regimen and the aprepitant regimen with respect to efficacy in the first cycle of cisplatin-based HEC and evaluate the safety and tolerability of the single-dose fosaprepitant dimeglumine regimen for CINV. The associated efficacy hypothesis was the single-dose fosaprepitant dimeglumine regimen is non-inferior to the aprepitant regimen with respect to the proportion of patients with a complete response (no vomiting and no use of rescue therapy) in the overall phase (in the 120 hours following initiation of cisplatin). If the above is established, the following will be evaluated: the single-dose fosaprepitant dimeglumine regimen is superior to the aprepitant regimen with respect to the proportion of patients with a complete response overall.

The secondary objectives were to (1) compare the single-dose fosaprepitant dimeglumine regimen and the aprepitant regimen in terms of the proportion of patients with a complete response in the delayed phase (25 to 120 hours following initiation of cisplatin) and (2) compare the single-dose fosaprepitant dimeglumine regimen and the aprepitant regimen in terms of the proportion of patients with no vomiting overall (in the 120 hours following initiation of cisplatin). The two secondary objective comparisons were based upon non-inferiority analyses.

A total of 2322 cisplatin-naïve patients with a confirmed solid malignancy were randomized into one of two treatment arms: fosaprepitant regimen (fosaprepitant dimeglumine 150 mg IV, ondansetron 32 mg IV, and dexamethasone 12 mg PO on Day 1, dexamethasone 8 mg PO on Day 2, and dexamethasone 16 mg PO on Days 3 and 4) or aprepitant regimen (aprepitant 125 mg PO, ondansetron 32 mg IV, and dexamethasone 12 mg PO on Day 1, aprepitant 80 mg PO and dexamethasone 8 mg PO on Days 2 and 3, dexamethasone 8 mg PO on Day 4).

Of the 2322 randomized patients, 2241 were evaluable (based on the full analysis set definition, section 9.7.1.2). Allocation to study treatment was pre-stratified by clinical study site. Within each clinical study site, patients were assigned to one of the two treatment regimens according to an allocation schedule of random numbers supplied by the applicant. Both treatment arms included concomitant administration of the 5HT3 antagonist ondansetron and dexamethasone.

The primary endpoint was the complete response (no vomiting and no use of rescue therapy) in the overall phase (120 hours following initiation of cisplatin).

1.3 Statistical Issues and Findings

The comments given below are based upon the primary endpoint (complete response in the overall phase).

- This reviewer's efficacy analysis by investigator-site based upon the complete response in the overall phase using the FAS population indicates that for the two sites (42205 and 44487), it seems that the complete response rates for the fosaprepitant regimen were unusually higher than that of the aprepitant regimen and for one site (41975), only one patient in fosaprepitant regimen was identified as failure in complete reponse.

  However, the sensitivity analyses by excluding data from all of the three sites do not reflect that the non-inferiority of the fosaprepitant regimen to the aprepitant regimen is dominated by these three sites. Accordingly, the non-inferiority of the fosaprepitant regimen to the aprepitant regimen is supported.

- Since a single study was submitted to support fosaprepitant regimen used for the proposed indication, this study should be of high quality with substantial demonstration of efficacy. Based upon this requirement, this study should show clear clinical benefit and efficacy results that are internally consistent among different endpoints and subgroups as recommended in the Guidance for Industry: Providing Clinical Evidence of Effectiveness for

Human Drug and Biological Products, May 1998.

- The efficacy difference analysis by country shows that of the twenty-seven countries in the study, seven countries (Brazil, Canada, Guatemala, Hong Kong, Mexico, Sweden, and United States) showed complete response rates in the overall phase, for the fosaprepitant regimen, that were less than that of aprepitant regimen by more than 7% (non-inferiority margin). This indicates that the treatment effects of the fosaprepitant regimen might not be internally consistent in the sense of non-inferiority to aprepitant regimen across country. Thus, the efficacy data provided by this single study is not indicative of clear clinical benefit for the entire study population.

  In addition, for the US patients (enrolled 2.6%), the efficacy result of region analysis by US vs. Non-US indicated that the complete response rate for fosaprepitant regimen in US region was 15% less than that of aprepitant regimen (56% vs. 71%). Furthermore, it is also noted that the complete response rate for fosaprepitant regimen is more than 16% less in the North America region (US/Canada) than that in the Non-North America region (but this regional difference is not shown for the aprepitant regimen). This raises a concern that the study drug might not have sufficient treatment benefit for US patients for the proposed indication.

2.0 INTRODUCTION

2.1 Overview

The purpose of this supplemental application is to support the use of a single intravenous dose of fosaprepitant 150 mg (dosed concomitantly with a 5HT3 receptor antagonist and a corticosteroid) for the prevention of acute and delayed nausea and vomiting associated with (b) (4) highly emetogenic chemotherapy (HEC).

The primary objective for Study P017L1 was to compare the single-dose fosaprepitant dimeglumine regimen and the aprepitant regimen with respect to efficacy in the first cycle of cisplatin-based HEC and evaluate the safety and tolerability of the single-dose fosaprepitant dimeglumine regimen for CINV. The associated efficacy hypothesis was the single-dose fosaprepitant dimeglumine regimen is non-inferior to the aprepitant regimen with respect to the proportion of patients with a complete response (no vomiting and no use of rescue therapy) in the overall phase (in the 120 hours following initiation of cisplatin). If the above is established, the following will be evaluated: the single-dose fosaprepitant dimeglumine regimen is superior to the aprepitant regimen with respect to the proportion of patients with a complete response overall.

The secondary objectives were to (1) compare the single-dose fosaprepitant dimeglumine regimen and the aprepitant regimen in terms of the proportion of patients with a complete response in the delayed phase (25 to 120 hours following initiation of cisplatin) and (2) compare the single-dose fosaprepitant dimeglumine regimen and the aprepitant regimen in terms of the proportion of patients with no vomiting overall (in the 120 hours following initiation of cisplatin).

The two secondary objective comparisons were based upon non-inferiority analysis.

This was a worldwide, multi-center, phase III, randomized, double-blind, active controlled, parallel-group study (conducted under in-house blinding) to assess the safety, tolerability, and efficacy of a single dose of 150 mg IV fosaprepitant dimeglumine for the prevention of CINV in patients who were naïve to cisplatin chemotherapy and who were treated with a chemotherapy regimen that included cisplatin ≥ 70 mg/m^2.

A total of 2322 cisplatin-naïve patients with a confirmed solid malignancy were randomized into one of two treatment arms: fosaprepitant regimen (Fosaprepitant dimeglumine 150 mg IV, ondansetron 32 mg IV, and dexamethasone 12 mg PO on Day 1, dexamethasone 8 mg PO on Day 2, and dexamethasone 16 mg PO on Days 3 and 4) or aprepitant regimen (Aprepitant 125 mg PO, ondansetron 32 mg IV, and dexamethasone 12 mg PO on Day 1, aprepitant 80 mg PO and dexamethasone 8 mg PO on Days 2 and 3, dexamethasone 8 mg PO on Day 4).

The allocation of patients across treatment groups (~50% in each arm) was based on the power for the primary hypothesis. Of the 2322 randomized patients, 2241 were evaluable (based on the full analysis set definition, section 9.7.1.2). Allocation to study treatment was pre-stratified by clinical study site. Within each clinical study site, patients were assigned to one of the two treatment regimens according to an allocation schedule of random numbers supplied by the SPONSOR. Both treatment arms included concomitant administration of the 5HT3 antagonist ondansetron and dexamethasone.

The primary endpoint was the complete response (no vomiting and no use of rescue therapy) in the overall phase (120 hours following initiation of cisplatin).

2.2 Data Sources

To assess the clinical efficacy of fosaprepitant regimen used in the prevention for acute and delayed nausea and vomiting (b) (4) high emetogenic chemotherapy, this reviewer reviewed electronic NDA supplement (SNDA) submission, dated 10/12/09, located at "\\CDSESUB1\EVSPROD\NDA022023\022023.enx (sequence #0044)". Data used by this reviewer for the efficacy analysis was submitted by applicant on 01/27/2010, located at "\\CDSESUB1\EVSPROD\NDA022023\022023.enx (sequence #0052)".

3.0 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

This was a worldwide, multi-center, phase III, randomized, double-blind, active controlled, parallel-group study (conducted under in-house blinding) to assess the safety, tolerability, and efficacy of a single dose of 150 mg IV fosaprepitant dimeglumine for the prevention of CINV in

patients who were naïve to cisplatin chemotherapy and who were treated with a chemotherapy regimen that included cisplatin ≥ 70 mg/m^2.

The primary objective for Study P017L1 was to compare the single-dose fosaprepitant dimeglumine regimen and the aprepitant regimen with respect to efficacy in the first cycle of cisplatin-based HEC and evaluate the safety and tolerability of the single-dose fosaprepitant dimeglumine regimen for CINV. The associated efficacy hypothesis was the single-dose fosaprepitant dimeglumine regimen is non-inferior to the aprepitant regimen with respect to the proportion of patients with a complete response (no vomiting and no use of rescue therapy) overall (in the 120 hours following initiation of cisplatin). If the above is established, the following will be evaluated: the single-dose fosaprepitant dimeglumine regimen is superior to the aprepitant regimen with respect to the proportion of patients with a complete response overall.

The secondary objectives were to (1) compare the single-dose fosaprepitant dimeglumine regimen and the aprepitant regimen in terms of the proportion of patients with a complete response in the delayed phase (25 to 120 hours following initiation of cisplatin) and (2) compare the single-dose fosaprepitant dimeglumine regimen and the aprepitant regimen in terms of the proportion of patients with no vomiting overall (in the 120 hours following initiation of cisplatin). The two secondary objective comparisons were based upon non-inferiority analysis.

The primary endpoint was the complete response (no vomiting and no use of rescue therapy) in the overall phase (120 hours following initiation of cisplatin).

There were two secondary endpoints: 1) complete response in the delayed phase (25 to 120 hours following initiation of cisplatin) and 2) no vomiting in the overall phase.

There were eleven exploratory endpoints:
1. Complete Response in the acute phase (0 to 24 hours following initiation of cisplatin);
2. No Vomiting in the acute phase;
3. No Vomiting in the delayed phase;
4. No Significant Nausea (VAS <25 mm) in the overall phase;
5. No Impact on Daily Life (FLIE total score >108) in the overall phase;
6. Time to first vomiting/retching episode in the overall phase;
7. No Nausea (VAS <5 mm) in the overall phase;
8. Complete Protection (no vomiting, no use of rescue therapy and maximum nausea VAS <25 mm) in the overall phase;
9. Total control (no vomiting, no use of rescue therapy, and maximum nausea VAS <5 mm) in the overall phase;
10. No use of rescue therapy in the overall phase;
11. Functional Living Index-Emesis - nausea and vomiting domains.

3.1.2 Statistical Methodologies

The applicant indicated that there were three types of patient populations analyzed in the study:

full analysis set, per-protocol population, and all treated population.

Full Analysis Set (FAS) population consisted of patients to have received cisplatin chemotherapy, taken a dose of study drug, and had at least 1 post-treatment assessment. FAS population was used for all efficacy analyses.

Per-Protocol (PP) population consisted of patients who adhered to the protocol. PP population was also used to address the primary and secondary efficacy hypotheses. Protocol violation criteria and protocol violators were identified prior to un-blinding of the study data.

All Treated (AT) population consisted of patients who were randomized to double-blind therapy and received at least 1 dose of study drug. AT population was used for safety analyses.
The applicant indicated that patients were included in the treatment group corresponding to the study therapy actually received. However, patients who received both fosaprepitant and aprepitant were included in the treatment group to which they were randomized.

To analyze the primary efficacy endpoint, the proportion of patients with a complete response in the 120 hours following initiation of chemotherapy is displayed with its 95% confidence interval (CI) by treatment group. In addition, the difference in response rates between the 2 treatment groups (fosaprepitant – aprepitant) and its 95% CI are displayed. The 95% CIs for the individual proportions were calculated using the normal approximation to the binomial distribution. The treatment difference and the 95% CI for the treatment difference in response rates were calculated using a methodology proposed by Miettinen and Nurminen ("Comparative analysis of two rates", Statistics in Medicine Vol. 4, 213-226, 1985) to account for the post-randomization stratification adjusted for gender. If the 95% CI for the treatment difference in response rates had a lower limit greater than –7 percentage points, then fosaprepitant would be considered at least as effective as aprepitant for complete response in the overall phase.

If the lower limit of the 95% CI for the treatment difference in response rates between the 2 treatment groups was greater than –7 percentage points, then a subsequent test would be performed to determine whether or not the fosaprepitant regimen was superior to the aprepitant regimen (i.e., the lower limit of the 95% CI for the treatment difference in response rates between the 2 treatment groups was greater than zero). The sponsor's choice of a 7% non-inferiority margin was based on the data from the two HEC studies P052 and P054 submitted through NDA 21549 in 2002.

Efficacy results are displayed within each treatment group by gender, as well as combined over gender. A test of treatment-by-stratum interaction was performed to make sure the results could be combined across gender. A significance level of 0.10 was used for the test of treatment by-gender interaction.

The treatment comparisons with respect to the secondary efficacy variables were made in the same fashion as those described for the primary efficacy analyses. If the confidence interval for the difference in response rates had a lower limit >–7.3 percentage points (for the Complete

Response in the delayed phase endpoint) or >–8.2 percentage points (for the No Vomiting overall endpoint), then fosaprepitant would be considered at least as effective as aprepitant with respect to these endpoints.

The 95% CI for the exploratory efficacy variables were calculated using the same methodology as that described for the primary and secondary efficacy analyses, where appropriate. However, the non-inferiority margin was not predefined for these endpoints. For the analysis of time to first vomiting episode, Kaplan-Meier curves (survival analysis using a product-limit approach) are displayed by treatment group. Kaplan-Meier curves depict the percentage of patients with no vomiting episodes since the initiation of cisplatin therapy. For the analysis of the FLIE questionnaire, the proportions of patients with a total FLIE score >108 points, a FLIE nausea score >54 points, and a FLIE vomiting score >54 points are displayed by treatment group.

For the efficacy analyses using the FAS patient population, missing data within the delayed time period were imputed by carrying forward the preceding non-missing data in the same phase. No data were imputed in the acute time period. For example, if the only data available for the patient was from Day 1, then the patient was only included in the acute analysis and excluded from the delayed and overall analyses. Conversely, if the only data available for the patient was within Days 2 to 5, then the patient was only included in the delayed analysis and excluded from the acute and overall analyses. For the per-protocol patient population, no imputation for missing data was made. All data handling rules were established before un-blinding of the database.

Any vomiting or use of rescue therapy within a phase (acute or delayed) defined a patient as having an unfavorable response for that phase and for the overall analysis (regardless of missing data at other time points) for both efficacy patient populations (FAS, PP). In the FAS, response to therapy in a particular phase was assessed based on the observed data in that phase. If all efficacy data for an endpoint was missing in a particular phase, then the patient was excluded from the analysis of that phase. In the PP population, any missing data (in the absence of vomiting or use of rescue therapy at another time point) excluded the patient from the analysis for that phase and for the overall analysis.

For the FLIE data, when there were missing data, the domain score was calculated by multiplying the average item score for the non-missing items by 9. At least 5 of the 9 FLIE domain items must be non-missing to calculate a FLIE domain score. At least 12 of the 18 FLIE items and both the vomiting and nausea domain must be non-missing to calculate a FLIE total score.

In addition to analyzing the primary, secondary, and exploratory (as appropriate) endpoints using the methodology proposed by Miettinen and Nurminen, these endpoints were also analyzed using the methodology by Blackwelder [16.1.12.11] utilizing the same CMH weights as for the Miettinen and Nurminen method. The latter methodology was applied as a result of correspondence with the Agency. The results using the Blackwelder method are in [16.1.9.2].

Three interim un-blinded safety analyses and 1 interim un-blinded futility analysis were performed by a statistician not connected with the project. Safety analyses were performed when at least 10%, 40%, and 60% of the total number of patients completed the study. The futility analysis was performed when at least 40% of the total number of patients completed the study.

The external Data Management Committee (DMC) reviewed the analysis results and recommend whether the study should continue. The analyses provided to this DMC consisted of the incidence rates, by treatment group, of all severe instances of 1) infusion site pain, 2) infusion site erythema, 3) infusion site induration and 4) all instances of infusion site thrombophlebitis of any severity.

If 1) the combined incidence of severe pain, severe erythema and severe induration was ≥ 20% in the fosaprepitant group, was at least twice the incidence in the aprepitant group, and was significantly different from the incidence in the aprepitant group, or 2) the incidence of infusion site thrombophlebitis in the fosaprepitant group was ≥ 5 percentage points higher than that of the aprepitant group and was significantly different from the incidence in the aprepitant group, then it would be determined that the rate of significant infusion-site reactions was excessive, and the study should be stopped.

The above criteria were provided as guidelines for the DMC to assist them in recommending whether the study should be continued or stopped for safety reasons. The DMC had more specific safety information about the patients that could have led them to make recommendations outside of these guidelines.

The applicant indicated that in the three un-blinded safety interim analyses, none of the safety endpoints that would have been used to stop the study pertained to the efficacy endpoints of the study. That is, adverse events such as vomiting or nausea were not part of the stopping criteria. As a result, the safety analyses did not inflate the overall Type I error for the study. In addition, the safety analysis results showed that none of the safety interim analyses demonstrated any reason to stop the study.

The applicant indicated that a statistician not connected with the project performed the futility analysis so that the project statistician can remain blinded until the time of the final analysis. The stopping boundaries for the futility analysis were based on the Gamma spending function with a parameter of 3 [See Study Report section 16.1.12.12]. The study would have been stopped with early rejection of the alternative hypothesis (i.e., fosaprepitant dimeglumine will not be considered at least as effective as aprepitant) if the test statistic crossed these pre-specified stopping boundaries (i.e., the value of the test statistic is greater than the value of the Gamma stopping boundary at the time of the interim analysis, suggesting that fosaprepitant is inferior to aprepitant). The study was not to be stopped early if non-inferiority was demonstrated, therefore the futility analysis did not inflate the Type I error. The external DMC reviewed the analysis results and recommended the study should continue.

For the primary efficacy hypothesis (Complete Response overall), the applicant indicated that no multiplicity adjustment was needed since there was only one primary efficacy endpoint and time point. There were two secondary efficacy hypotheses (Complete Response in the delayed phase and No Vomiting in the overall phase). These hypotheses were tested only after the primary efficacy hypothesis was found to be significant. Hochberg's Procedure was used to preserve the overall Type I error rate at 0.05 for the secondary efficacy hypothesis tests. Specifically, the p-values for the two secondary efficacy hypothesis tests were ranked in ascending order ($P(1) \leq P(2)$). A two-step approach was planned.

1) For the hypothesis associated with the maximum p-value (P(2)), if the 95% CI ($\alpha = 0.05$) for the difference in response rates (fosaprepitant – aprepitant) had a lower limit greater than the corresponding non-inferiority margin (–7.3 percentage points for the Complete Response in the delayed phase endpoint or –8.2 percentage points for the No Vomiting overall endpoint), then fosaprepitant was to be considered at least as effective as aprepitant with respect to both of the secondary efficacy endpoints. (2) If the 95% CI for the difference in response rates had a lower limit less than the non-inferiority margin corresponding to the hypothesis associated with the maximum p-value (P(2)), then the conclusion would have been that it had not been demonstrated that fosaprepitant was at least as effective as aprepitant with respect to this endpoint. For the hypothesis associated with the minimum p-value (P(1)), if the 97.5% CI (⟨/2 = 0.025) for the difference in response rates had a lower limit not less than the corresponding non-inferiority margin, then fosaprepitant would be considered at least as effective as aprepitant with respect to this endpoint. If the 97.5% CI for the difference in response rates had a lower limit less than the non-inferiority margin corresponding to the hypothesis associated with the minimum p-value (P(1)), then it was to be concluded that it had not been demonstrated that fosaprepitant was at least as effective as aprepitant with respect to either of the two secondary efficacy endpoints.

This multiplicity strategy would strongly control the overall Type I error rate at 0.05 across all primary and secondary efficacy hypotheses.

To address the primary hypothesis, a total of 2292 patients were planned to be enrolled in the study to yield approximately 2226 evaluable patients. It was anticipated that 1113 evaluable patients per regimen, assuming a 2-sided 5% significance level for testing the primary efficacy hypothesis and an expected response rate of 67.7% in each treatment regimen, would yield 90% power to declare non-inferiority for the single-dose fosaprepitant regimen, using a non-inferiority margin of 7 percentage points.

The applicant indicated that if the study design had not included a futility analysis, 1876 evaluable patients would have been needed to have 90% power for the primary efficacy hypothesis. However, the inclusion of the futility analysis is accompanied by a slight loss of power. In order to maintain 90% power for the primary efficacy hypothesis, the sample size of the study was increased from 1876 to 2226 evaluable patients.

3.1.3 Patient Disposition

A total of 2322 cisplatin-naïve patients with a confirmed solid malignancy were randomized into one of two treatment arms: fosaprepitant regimen (Fosaprepitant dimeglumine 150 mg IV, ondansetron 32 mg IV, and dexamethasone 12 mg PO on Day 1, dexamethasone 8 mg PO on Day 2, and dexamethasone 16 mg PO on Days 3 and 4) or aprepitant regimen (Aprepitant 125 mg PO, ondansetron 32 mg IV, and dexamethasone 12 mg PO on Day 1, aprepitant 80 mg PO and dexamethasone 8 mg PO on Days 2 and 3, dexamethasone 8 mg PO on Day 4).

Of the 2322 randomized patients, 2241 were evaluable (based on the full analysis set definition, section 9.7.1.2). Allocation to study treatment was pre-stratified by clinical study site. Within each clinical study site, patients were assigned to one of the two treatment regimens according to an allocation schedule of random numbers supplied by the applicant. Both treatment arms included concomitant administration of the 5HT3 antagonist ondansetron and dexamethasone.

The disposition of the 2,322 patients who met the inclusion criteria and were randomized is in Table 3.1.3.1; 94.2% of patients in the fosaprepitant group and 93.1% in the aprepitant group completed the study. The applicant indicated that there were no clinically meaningful differences between treatment groups in the percentage of patients who completed the study.

The study medication disposition indicates that 97.4% of patients in the fosaprepitant group and 98.0% in the aprepitant group completed study medication. Reasons for discontinuation were also comparable between treatment groups.

Table 3.1.3.1 (Applicant's) Disposition of Patients

	Fosaprepitant Regimen		Aprepitant Regimen		Total	
	n	(%)	n	(%)	n	(%)
Not Randomized					232	
Patients in population	1,147		1,175		2,322	
Study Disposition						
COMPLETED	1,080	(94.2)	1,094	(93.1)	2,174	(93.6)
DISCONTINUED	67	(5.8)	81	(6.9)	148	(6.4)
ADVERSE EVENT	32	(2.8)	36	(3.1)	68	(2.9)
LOST TO FOLLOW-UP	12	(1.0)	16	(1.4)	28	(1.2)
PHYSICIAN DECISION	0	(0.0)	7	(0.6)	7	(0.3)
PROGRESSIVE DISEASE	3	(0.3)	1	(0.1)	4	(0.2)
PROTOCOL VIOLATION	1	(0.1)	1	(0.1)	2	(0.1)
WITHDRAWAL BY SUBJECT	19	(1.7)	20	(1.7)	39	(1.7)
Study Medication Disposition						
COMPLETED	1,117†	(97.4)	1,151	(98.0)	2,268	(97.7)
DID NOT TAKE STUDY MEDICATION	4	(0.3)	6	(0.5)	10	(0.4)
DISCONTINUED	25	(2.2)	18	(1.5)	43	(1.9)
ADVERSE EVENT	10	(0.9)	7	(0.6)	17	(0.7)
LACK OF EFFICACY	1	(0.1)	0	(0.0)	1	(0.0)
LOST TO FOLLOW-UP	4	(0.3)	2	(0.2)	6	(0.3)
PHYSICIAN DECISION	1	(0.1)	1	(0.1)	2	(0.1)
PROGRESSIVE DISEASE	1	(0.1)	0	(0.0)	1	(0.0)
PROTOCOL VIOLATION	3	(0.3)	0	(0.0)	3	(0.1)
WITHDRAWAL BY SUBJECT	4	(0.3)	8	(0.7)	12	(0.5)

Each patient is counted once for Study Disposition, Study Medication Disposition based on the latest corresponding disposition record.
† One patient (AN 04865) listed as Completed Study Medication did not complete all study doses per protocol and discontinued due to an Adverse Event.

In addition, all efficacy analyses were based on the Full Analysis Set (FAS) patient population. The FAS population included patients who received at least one dose of study therapy, received cisplatin chemotherapy, and had at least one post-treatment efficacy assessment.

Of the 2322 patients randomized, 2247 patients (3.2% exclusion from total randomized population) were included in the FAS population. Of the 75 patients excluded from FAS population, thirty seven patients on the aprepitant regimen and 38 patients on the fosaprepitant regimen were excluded.

The Per Protocol (PP) patient population was used for the primary and secondary efficacy endpoints and was supportive to the FAS population. The PP population excluded patients with important deviations from the protocol that might have substantially affected the results of the efficacy analyses. Of the 2247 patients included in the FAS population, 2203 (2.0% exclusion from FAS) patients were included in the PP population.

3.1.4 Demographics and Baseline Characteristics

Table 3.1.4.1 displayed the baseline demographics while Table 3.1.4.2 was for baseline characteristics of all randomized patients.

Table 3.1.4.1 (Applicant's) Displayed baseline demographics of all randomized patients by treatment group

	Fosaprepitant Regimen		Aprepitant Regimen		Total	
	n	(%)	n	(%)	n	(%)
Patients in population	1,147		1,175		2,322	
Gender						
Male	722	(62.9)	748	(63.7)	1,470	(63.3)
Female	425	(37.1)	427	(36.3)	852	(36.7)
Age (YEARS)						
< 55	491	(42.8)	475	(40.4)	966	(41.6)
≥ 55	656	(57.2)	700	(59.6)	1,356	(58.4)
17 and under	0	(0.0)	0	(0.0)	0	(0.0)
18 to 34	67	(5.8)	68	(5.8)	135	(5.8)
35 to 54	424	(37.0)	407	(34.6)	831	(35.8)
55 to 64	402	(35.0)	418	(35.6)	820	(35.3)
65 to 74	226	(19.7)	246	(20.9)	472	(20.3)
Over 74	28	(2.4)	36	(3.1)	64	(2.8)
Mean	55.2		55.9		55.6	
SD	11.9		12.0		12.0	
Median	56.0		57.0		57.0	
Range	19 to 86		19 to 82		19 to 86	
Race						
AMERICAN INDIAN OR ALASKA NATIVE	32	(2.8)	33	(2.8)	65	(2.8)
ASIAN	296	(25.8)	306	(26.0)	602	(25.9)
BLACK OR AFRICAN AMERICAN	21	(1.8)	22	(1.9)	43	(1.9)
MULTI-RACIAL	149	(13.0)	157	(13.4)	306	(13.2)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1	(0.1)	2	(0.2)	3	(0.1)
WHITE	648	(56.5)	655	(55.7)	1,303	(56.1)
Ethnicity						
HISPANIC OR LATINO	370	(32.3)	393	(33.4)	763	(32.9)
NOT HISPANIC OR LATINO	777	(67.7)	782	(66.6)	1,559	(67.1)

Based on Table 3.1.4.1, the applicant indicated that there were more males (63.3%) than females (36.7%) randomized, with a similar proportion between the two treatment groups. Greater than half of the patients were over the age of 55 and this age group along with other age groups under the age of 55 was also similar between the two treatment groups. The majority of the patients were of the white race, but approximately one third of patients were representative of other races;

the proportions of patients of specific ethnic origin were similar between the two treatment groups.

Table 3.1.4.2 (Applicant's) Displayed baseline characteristics of all randomized patients by treatment group

	Fosaprepitant Regimen		Aprepitant Regimen		Total	
	n	(%)	n	(%)	n	(%)
Type of malignancy						
Breast Cancer	33	(2.9)	26	(2.2)	59	(2.5)
Endocrine Cancer	1	(0.1)	10	(0.9)	11	(0.5)
Gastrointestinal Cancer	251	(21.9)	247	(21.0)	498	(21.4)
Hepatic and Biliary Cancer	8	(0.7)	16	(1.4)	24	(1.0)
Lymphoma	10	(0.9)	13	(1.1)	23	(1.0)
Miscellaneous or Site Unspecified	60	(5.2)	57	(4.9)	117	(5.0)
Nervous System Cancer	1	(0.1)	1	(0.1)	2	(0.1)
Renal and Urinary Tract Cancer	49	(4.3)	41	(3.5)	90	(3.9)
Reproductive and Genitourinary Cancer	172	(15.0)	178	(15.1)	350	(15.1)
Respiratory and Mediastinal Cancer	530	(46.2)	558	(47.5)	1,088	(46.9)
Skeletal Cancer	8	(0.7)	7	(0.6)	15	(0.6)
Skin Cancer	21	(1.8)	15	(1.3)	36	(1.6)
History of motion sickness						
Yes	0	(0.0)	3	(0.3)	3	(0.1)
No	1,143	(99.7)	1,166	(99.2)	2,309	(99.4)
History of vomiting associated with Pregnancy						
Yes	3	(0.3)	3	(0.3)	6	(0.3)
No	420	(36.6)	421	(35.8)	841	(36.2)
Region						
US	31	(2.7)	35	(3.0)	66	(2.8)
EX-US	1,112	(96.9)	1,134	(96.5)	2,246	(96.7)
Concomitant HEC or MEC on Day 1						
	Fosaprepitant Regimen		Aprepitant Regimen		Total	
	n	(%)	n	(%)	n	(%)
Yes	78	(6.8)	84	(7.1)	162	(7.0)
No	1,065	(92.9)	1,085	(92.3)	2,150	(92.6)

Patients are counted a single time for Type of Malignancy, Motion Sickness and Vomiting Associated with Pregnancy.
Treated patients are considered for the categories: Type of Malignancy, History of motion sickness and History of vomiting associated with pregnancy.
Only female patients are considered for History of vomiting associated with pregnancy.
HEC= highly emetogenic chemotherapy
MEC=moderately emetogenic chemotherapy

From Table 3.1.4.2, the applicant indicated that the most common primary tumor types were respiratory and mediastinal cancer (46.9%), gastrointestinal cancer (21.4%), reproductive and genitourinary (15.1%). In general, the treatment groups were balanced with regard to tumor types.

3.1.5 Applicant's Efficacy Analysis Results and Conclusions

The applicant indicated that the efficacy results presented are those for the Full Analysis Set (FAS) patient population. In addition, results based on the per-protocol patient population are presented for the primary and secondary endpoints only.

3.1.5.1 Primary and secondary endpoint analyses

The primary (Complete Response in the overall phase) and secondary (Complete Response in the delayed phase and No Vomiting in the overall phase) hypothesis tests were based on the comparison of the lower bound of the 95% CI for the difference between treatment groups (fosaprepitant – aprepitant) to the pre-defined non-inferiority margin. The criterion used to establish non-inferiority of fosaprepitant with aprepitant for the primary endpoint of Complete Response in the overall phase, was that the lower bound of the 95% CI for the treatment difference was greater than -7 percentage points. In addition, since there were two secondary hypotheses, Hochberg's multiple comparison procedure was used to preserve the overall Type I error rate at 0.05. Table 3.1.5.1 summarized the analysis results for the primary and secondary endpoints.

Table 3.1.5.1 (Applicant's) Summary of efficacy by primary and secondary hypotheses using FAS Population

Hypothesis Level and Endpoint	Lower Bound Needed For Non-inferiority	Actual Lower Bound	Actual P-Value†	Conclusion
Primary				
Complete Response – overall phase	>-7 percentage points	-4.1 percentage points	--	Non-inferior
Secondary				
No Vomiting – overall phase	>-8.2 percentage points	-5.3 percentage points	0.0002	Non-inferior
Complete Response – delayed phase	>-7.3 percentage points	-3.5 percentage points	0.00003	Non-inferior
† P-value associated with the 95% confidence interval for the difference (fosaprepitant – aprepitant) in response rates.				

Based upon the results of Table 3.1.5.1, the applicant indicated that with a lower bound of -4.1 percentage points larger than the non-inferiority margin of -7 percentage points, it was concluded that fosaprepitant was non-inferior to aprepitant assessed by complete response in the overall phase using FAS population analysis.

For the secondary endpoints, no vomiting in the overall phase is displayed first since it was associated with the largest p-value of 0.0002. For the lower bound of the two sided 95% confidence interval was -5.3% greater than -8.2%, it was concluded that fosaprepitant is non-inferior to aprepitant assessed by no vomiting in the overall phase using FAS population analysis. Since fosaprepitant was considered non-inferior to aprepitant for the secondary endpoint with the largest p-value, by Hochberg multiplicity adjustment procedure, fosaprepitant was also concluded non-inferior to aprepitant assessed by complete response in the delayed phase.

In addition, the proportions of patients with complete response in the overall, acute, and delayed phases, along with the treatment group difference are displayed in Table 3.1.5.2 for the FAS population while the proportions of patients with no vomiting in the overall, acute, and delayed phases are presented in Table 3.1.5.3. The 95% CI for each proportion and for the treatment difference is also displayed.

Table 3.1.5.2 (Applicant's) Proportion of patients with complete response by phase using FAS Population

Phase	Fosaprepitant Regimen (A)		Aprepitant Regimen (B)		Difference(A-B)
	n/m	% (95% CI)	n/m	% (95% CI)	% (95% CI)†
Overall Phase	795/1106	71.9 (69.1, 74.5)	820/1134	72.3 (69.6, 74.9)	-0.4 (-4.1, 3.3)
Acute Phase	963/1082	89.0 (87.0, 90.8)	974/1107	88.0 (85.9, 89.8)	1.1 (-1.6, 3.8)
Delayed Phase	822/1106	74.3 (71.6, 76.9)	841/1133	74.2 (71.6, 76.8)	0.1 (-3.5, 3.7)

† The difference and the confidence interval (CI) for the difference 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 phase = 0 to 120 hours post-initiation of cisplatin chemotherapy.

Acute phase = 0 to 24 hours post-initiation of cisplatin chemotherapy.

Delayed phase = 25 to 120 hours post-initiation of cisplatin chemotherapy.

n/m = Number of patients with Complete response/number of patients included in the analysis.

Similar to the FAS population analysis, the applicant indicated that the non-inferiority of fosaprepitant regimen over aprepitant regimen assessed by complete response was also shown for the overall and delayed phases when analyzed using per protocol population.

Table 3.1.5.3 (Applicant's) Proportion of patients with no vomiting by phase using FAS Population

Phase	Fosaprepitant Regimen (A)		Aprepitant Regimen (B)		Difference(A-B)
	n/m	% (95% CI)	n/m	% (95% CI)	% (95% CI)†
Overall Phase	806/1106	72.9 (70.2, 75.5)	844/1132	74.6 (71.9, 77.1)	-1.7 (-5.3, 2.0)
Acute Phase	966/1080	89.4 (87.5, 91.2)	983/1105	89.0 (87.0, 90.7)	0.6 (-2.0, 3.2)
Delayed Phase	836/1106	75.6 (72.9, 78.1)	865/1132	76.4 (73.8, 78.9)	-0.8 (-4.3, 2.7)

† The difference and the confidence interval (CI) for the difference were calculated using the method proposed by Miettinen and Nurminen and adjusted for Gender.

Overall phase = 0 to 120 hours post-initiation of cisplatin chemotherapy.

Acute phase = 0 to 24 hours post-initiation of cisplatin chemotherapy.

Delayed phase = 25 to 120 hours post-initiation of cisplatin chemotherapy.

n/m = Number of patients with No Vomiting/number of patients included in the analysis.

Similar to the FAS population analysis, the applicant indicated that the non-inferiority of fosaprepitant regimen over aprepitant regimen assessed by no vomiting was also demonstrated for the overall phase when analyzed using per protocol population.

The results of the efficacy comparisons of fosaprepitant versus aprepitant based upon primary and secondary endpoints using per protocol population were presented in Appendix.

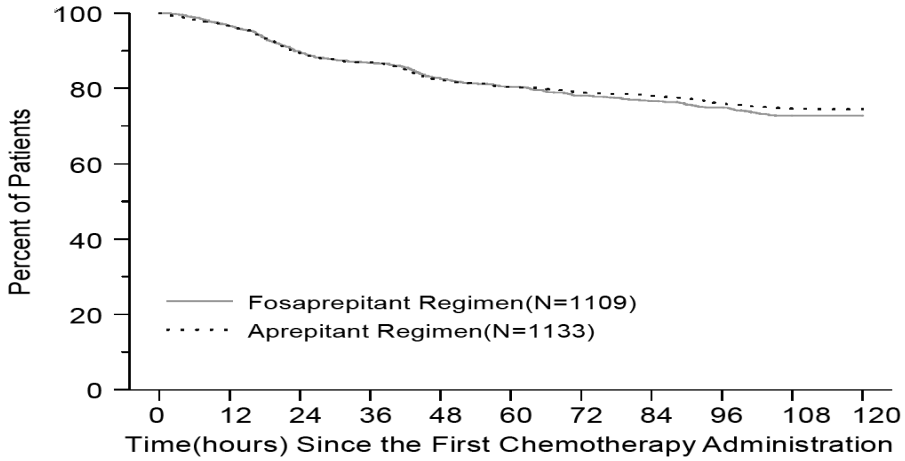
3.1.5.2 Exploratory endpoint analysis

The following exploratory endpoint analysis results are copied from the applicant study report.

i) Time to First Vomiting – Overall Phase

Kaplan-Meier curves for the time to first vomiting, regardless of use of rescue therapy, in the overall phase for the FAS population, were displayed in Figure 3.1.5.1. The Kaplan-Meier curves showed that the time to first vomiting was numerically identical for patients on the fosaprepitant regimen as for those on the aprepitant regimen.

Figure 3.1.5.1 (Applicant's) Kaplan-Meier curves for time to first vomiting episode from start of chemotherapy administration in the overall phase using FAS population



ii) Functional Living Index-Emesis (FLIE) – Overall Phase

The FLIE is a self-administered, validated emesis- and nausea-specific questionnaire. Patients completed the questionnaire 5 days after receiving chemotherapy (Day 6). The questionnaire had 9 questions (items) on nausea (nausea domain) and 9 questions on vomiting (vomiting domain).

For the purpose of this study, impact of CINV on daily life was defined as an average item score of >6 on the 7-point scale (i.e., >108 total score or > 54 domain score). The percent of patients with no impact of CINV on daily life by treatment group was summarized in Table 3.1.5.4.

The applicant indicated that for the total score, nausea domain score, vomiting domain score, and the specific items mentioned in the table, the 95% confidence intervals for the differences in the percent of patients with "no impact" from chemotherapy on their daily lives suggest that the effect of fosaprepitant was numerically similar to that of aprepitant in controlling nausea and vomiting in the overall phase.

Table 3.5.1.4 (Applicant's) Percent of patients with no Impact of CINV on daily life† by treatment group – overall phase using FAS population

	FLIE Domain or Item Number	Fosaprepitant Regimen (A) n/m (%)	Aprepitant Regimen (B) n/m (%)	Difference‡ (A-B)	95% CI‡ Difference
Total Score					
Nausea and Vomiting Specific	Total Score	748/1083 (69.1)	776/1108 (70.0)	-1.0	(-4.8, 2.9)
Domain and Item Scores					
Nausea-specific	Nausea Domain	710/1084 (65.5)	708/1108 (63.9)	1.6	(-2.4, 5.6)
Nausea-specific 'ability to enjoy daily meal'	Item 4	731/1084 (67.4)	738/1107 (66.7)	0.8	(-3.2, 4.7)
Nausea-specific 'daily functioning'	Item 7	773/1084 (71.3)	771/1108 (69.6)	1.7	(-2.1, 5.5)
Nausea-specific 'personal hardship'	Item 8	742/1084 (68.5)	747/1107 (67.5)	1.0	(-2.9, 4.9)
Vomiting-specific	Vomiting Domain	852/1084 (78.6)	904/1108 (81.6)	-3.0	(-6.3, 0.4)
Vomiting-specific 'ability to enjoy daily meal'	Item 13	889/1084 (82.0)	941/1107 (85.0)	-3.0	(-6.1, 0.1)
Vomiting-specific 'daily functioning'	Item 16	898/1081 (83.1)	961/1105 (87.0)	-3.9	(-6.9, -0.9)
Vomiting-specific 'hardship on other people'	Item 18	899/1081 (83.2)	951/1105 (86.1)	-2.9	(-5.9, 0.1)

† No Impact of CINV on Daily Life is defined as an average item score of >6 on the 7 point scale.

‡ The difference and the confidence interval (CI) for the difference were calculated using the method proposed by Miettinen and Nurminen and adjusted for Gender.

Overall phase = 0 to 120 hours post-initiation of cisplatin chemotherapy.

CINV = Chemotherapy-induced nausea and vomiting.

FLIE = Functional Living Index-Emesis.

n/m = Number of patients with No Impact of CINV on Daily Life/number of patients included in the analysis of the item.

iii) No Use of Rescue Therapy – Overall, Acute, and Delayed Phases

Patients were allowed to take rescue therapy if needed for established nausea or vomiting. No rescue was defined as no use of rescue therapy. Table 3.1.5.5 displays the proportion of patients who did not use rescue therapy by phase and treatment group.

Table 3.1.5.5 (Applicant's) Number of patients with no use of rescue medication by phase and treatment group using FAS Population

	Fosaprepitant Regimen (A)		Aprepitant Regimen (B)		Difference(A-B)
Phase	n/m	% (95% CI)	n/m	% (95% CI)	% (95% CI)†
Overall Phase	999/1109	90.1 (88.2, 91.8)	1024/1138	90.0 (88.1, 91.7)	0.1 (-2.4, 2.6)
Acute Phase	1081/1109	97.5 (96.4, 98.3)	1105/1138	97.1 (96.0, 98.0)	0.4 (-1.0, 1.8)
Delayed Phase	1005/1109	90.6 (88.8, 92.3)	1035/1138	90.9 (89.1, 92.6)	-0.3 (-2.7, 2.1)

† The difference and the confidence interval (CI) for the difference were calculated using the method proposed by Miettinen and Nurminen and adjusted for Gender.

Overall phase = 0 to 120 hours post-initiation of cisplatin chemotherapy.

Acute phase = 0 to 24 hours post-initiation of cisplatin chemotherapy.

Delayed phase = 25 to 120 hours post-initiation of cisplatin chemotherapy.

n/m = Number of patients with no use of rescue/number of patients included in the analysis.

Based upon Table 3.1.5.5, the applicant indicated that for the three phases, patients who received fosaprepitant used rescue therapy numerically to the same extent as patients who received aprepitant.

iv) No Significant Nausea and No Nausea in the Overall Phase

Nausea was self-assessed by the patient using a 100-mm horizontal VAS (0 = no nausea and 100 = maximum nausea). At each scheduled rating time, the patient recorded his/her assessment of the degree of nausea experienced during the preceding 24 hours by placing a vertical mark on the scale.

The proportion of patients with no significant nausea (maximum nausea VAS <25 mm) in the overall phase by treatment group, regardless of whether or not the patient took rescue therapy, was displayed in Table 3.1.5.6 while the results of patients without no nausea was summarized by Table 3.1.5.7.

Table 3.1.5.6 (Applicant's) Number of patients with no significant nausea in the overall phase by treatment group using FAS population

Phase	Fosaprepitant Regimen (A)		Aprepitant Regimen (B)		Difference(A-B)
	n/m	% (95% CI)	n/m	% (95% CI)	% (95% CI)†
Overall Phase	772/1102	70.1 (67.3, 72.7)	797/1132	70.4 (67.7, 73.1)	-0.3 (-4.1, 3.5)

† The difference and the confidence interval (CI) for the difference were calculated using the method proposed by Miettinen and Nurminen and adjusted for Gender.

Overall phase = 0 to 120 hours post-initiation of cisplatin chemotherapy.

n/m = Number of patients with No Significant Nausea/number of patients included in the analysis.

The applicant indicated that the control of significant nausea in the overall phase was numerically comparable between the two treatment groups.

Table 3.1.5.7 (Applicant's) Number of patients with no nausea in the overall phase by treatment group using FAS population

Phase	Fosaprepitant Regimen (A)		Aprepitant Regimen (B)		Difference(A-B)
	n/m	% (95% CI)	n/m	% (95% CI)	% (95% CI)†
Overall Phase	585/1104	53.0 (50.0, 56.0)	577/1133	50.9 (48.0, 53.9)	2.1 (-2.0, 6.2)

† The difference and the confidence interval (CI) for the difference were calculated using the method proposed by Miettinen and Nurminen and adjusted for Gender.

Overall phase = 0 to 120 hours post-initiation of cisplatin chemotherapy.

n/m = Number of patients with No Nausea/number of patients included in the analysis.

Similar to no significant nausea, the applicant indicated that fosaprepitant seemed numerically as effective as aprepitant in controlling nausea in the overall phase.

v) Complete Protection – Overall Phase

Complete Protection was defined as no vomiting, no use of rescue therapy, and no significant nausea (VAS <25 mm). Table 3.1.5.8 displayed the proportion of patients with complete protection in the overall phase by treatment group.

Table 3.1.5.8 (Applicant's) Number of patients with complete protection in the overall phase by treatment group using FAS population

Phase	Fosaprepitant Regimen (A)		Aprepitant Regimen (B)		Difference(A-B)
	n/m	% (95% CI)	n/m	% (95% CI)	% (95% CI)†
Overall Phase	683/1102	62.0 (59.0, 64.9)	711/1133	62.8 (59.9, 65.6)	-0.7 (-4.7, 3.2)

† The difference and the confidence interval (CI) for the difference were calculated using the method proposed by Miettinen and Nurminen and adjusted for Gender.

Complete protection = no vomiting, no use of rescue therapy, and no significant nausea (VAS <25 mm).

Overall phase = 0 to 120 hours post-initiation of cisplatin chemotherapy.

n/m = Number of patients with Complete Protection/number of patients included in the analysis.

The applicant indicated that the complete protection in the overall phase was numerically comparable between the two treatment groups.

vi) Total Control – Overall Phase

Total control was defined as no vomiting, no use of rescue therapy, and no nausea (VAS <5 mm). Table 3.1.5.9 displayed the proportion of patients with Total Control in the overall phase by treatment group.

Table 3.1.5.7 (Applicant's) Number of patients with total control in the overall phase by treatment group using FAS population

Phase	Fosaprepitant Regimen (A)		Aprepitant Regimen (B)		Difference(A-B)
	n/m	% (95% CI)	n/m	% (95% CI)	% (95% CI)†
Overall Phase	562/1105	50.9 (47.9, 53.8)	558/1134	49.2 (46.3, 52.2)	1.7 (-2.4, 5.8)

† The difference and the confidence interval (CI) for the difference were calculated using the method proposed by Miettinen and Nurminen and adjusted for Gender.

Total control = no vomiting, no use of rescue therapy, and no nausea (VAS <5 mm).

Overall phase = 0 to 120 hours post-initiation of cisplatin chemotherapy.

n/m = Number of patients with Total control/number of patients included in the analysis.

The applicant indicated that fosaprepitant seemed numerically as effective as aprepitant with respect to total control in the overall phase.

3.1.6 Statistical Reviewer's Analysis and Comments

In order to validate the applicant's claim on the efficacy of fosaprepitant regimen not inferior to that of aprepitant regimen assessed by the proportion of complete response in the overall phase, in this section, this reviewer has performed the following three analyses based upon the complete response in the overall phase 1) efficacy analysis using CMH weight 2) efficacy comparison by investigator site, 3) treatment difference by country, and 4) efficacy comparison by region. Following the efficacy analyses, this reviewer makes comments on the efficacy strength of the single study.

3.1.6.1 Statistical Reviewer's Analysis

3.1.6.1.1 Efficacy analysis using CMH weight

In order to validate the method proposed by Miettinen and Nurminen (MN) and used by the applicant in this NDA submission, this reviewer applies the method proposed by Koch et al with CMH weight to compare the efficacy of fosaprepitant regimen versus standard regimen. For detail information for MN method, refer to Koch, G.G., Carr, G.J., Amara, I.A., Stokes, M.E., and Uryniak, T.J., (1989) entitled Categorical Data Analysis of Chapter 13 in "Statistical Methodology in Pharmaceutical Sciences, Marcel Dekker, New York, pp. 414-421".

The result for the efficacy comparison performed by this reviewer is presented by Table 3.1.6.1.

Table 3.1.6.1 (Reviewer's) Efficacy comparisons assessed by the complete response in the overall phase using FAS population

ENDPOINT	TREATMENT GROUPS	
	Fosaprepitnat Regimen N= 1106	Aprepitant Regimen N = 1134
Complete Response, n (% = n/N)	795 (71.9%)	820 (72.3%)
Therapeutic Gain (TG), %‡		-0.4%
95.0% two-sided CI for TG†		(-4.1%, 3.3%)

The efficacy results from Table 3.1.6.1 is numerically identical to that of the applicant's method presented by Table 3.1.5.2. Accordingly, the non-inferiority of fosaprepitant regimen versus standard regimen claimed by the applicant is supported.

3.1.6.1.2 Efficacy comparison by investigator-site

In order to explore whether the non-inferiority of fosaprepitant regimen to aprepitant regimen assessed by the complete response in the overall phase was dominated by certain investigator-sites, this reviewer compares the efficacy of fosaprepitant regimen versus aprepitant regimen by investigator-site based upon the complete response in the overall phase using the FAS population.

Since a small site has no capability to dominate the non-inferiority of fosaprepitant regimen to aprepitant regimen, in this large clinical trail with more than two thousand patients, the numbers of patients for sites with no less than twenty patients are explored and presented in Table 3.1.6.2.

Table 3.1.6.2 (Reviewer's) proportions of complete response in the overall phase by site using FAS population

SITE NUMBER	FOSAPREPITANT (F) % (n/N)	APREPITANT (A) % (n/N)	DIF. F –A	SITE NUMBER	FOSAPREPITANT (F) % (n/N)	APREPITANT (A) % (n/N)	DIF. F –A
Site 12823	53.0 (9/17)	67.0 (12/18)	-14.0%	**Site 42029**	83.0 (19/23)	92.0 (23/25)	-9.0%
Site 12993	53.0 (20/38)	57.0 (21/37)	-4.0%	**Site 42030**	75.0 (9/12)	92.0 (12/13)	-17.0%
Site 15417	80.0 (8/10)	80.0 (8/10)	0.0%	**Site 42032**	81.0 (17/21)	82.0 (18/22)	-1.0%
Site 22654	90.0 (9/10)	90.0 (9/10)	0.0%	**Site 42033**	75.0 (12/16)	83.0 (15/18)	-8.0%
Site 22750	74.0 (14/19)	70.0 (14/20)	4.0%	**Site 42075**	52.0 (12/23)	54.0 (13/24)	-2.0%
Site 25357	36.0 (4/11)	92.0 (11/12)	-56.0%	**Site 42105**	50.0 (7/14)	47.0 (7/15)	3.0%
Site 30458	91.0 (21/23)	92.0 (22/24)	-1.0%	***Site 42205***	*69.0 (11/16)*	*33.0 (5/15)*	*36.0%*
Site 30739	88.0 (15/17)	78.0 (14/18)	10.0%	**Site 42210**	92.0 (11/12)	83.0 (10/12)	9.0%
Site 30971	82.0 (18/22)	80.0 (16/20)	2.0%	**Site 43365**	69.0 (9/13)	58.0 (7/12)	11.0%
Site 33816	64.0 (7/11)	70.0 (7/10)	-6.0%	**Site 43480**	88.0 (14/16)	93.0 (14/15)	-5.0%
Site 35741	58.0 (7/12)	54.0 (7/13)	4.0%	**Site 43481**	100.0 (14/14)	93.0 (13/14)	7.0%
Site 39862	64.0 (4/11)	67.0 (8/12)	-3.0%	**Site 43482**	100.0 (16/16)	75.0 (12/16)	25.0%
Site 40866	69.0 (11/16)	87.0 (13/15)	-18.0%	**Site 43714**	89.0 (32/36)	79.0 (27/34)	10.0%
Site 41868	63.0 (12/19)	50.0 (10/20)	13.0%	***Site 44487***	*80.0 (8/10)*	*30.0 (3/10)*	*50.0%*
Site 41918	92.0 (12/13)	75.0 (9/12)	17.0%	**Site 45061**	56.0 (5/9)	60.0 (9/15)	-4.0%
Site 41975	***95.0 (18/19)***	***77.0 (17/22)***	***18.0%***	**Site 45605**	71.0 (12/17)	59.0 (10/17)	12.0%
Site 41976	80.0 (8/10)	82.0 (9/11)	-2.0%	**Site 45068**	75.0 (30/40)	68.0 (27/40)	7.0%
Site 42025	57.0 (8/14)	60.0 (9/15)	-3.0%	**Site 46154**	91.0 (21/23)	100.0 (23/23)	-9.0%
Site 42028	73.0 (8/11)	58.0 (7/12)	15.0%	**Overall**	71.9 (795/1106)	72.3 (820/1134)	-0.4%

Based upon the results from Table 3.1.6.2, for most sites, the proportions of complete response of fosaprepitant regimen were similar to that of aprepitant regimen. However, for the two sites

42205 (69.0% vs. 32.0%) and 44487 (80.0% vs. 30.0%), it seems that the complete response rates for the fosaprepitant regimen were unusually higher than that of the aprepitant regimen and for one site 41975 (95.0% vs. 77.0%), only one patient in fosaprepitant regimen was identified as failure in complete reponse.

In order to explore whether the three sites dominate the non-inferiority of fosaprepitant regimen to aprepitant regimen, this reviewer performs the sensitivity analyses by excluding data from all of the three sites to compare the efficacy of fosaprepitant regimen versus that of aprepitant regimen. However, the sensitivity analyses do not reflect that the non-inferiority of the fosaprepitant regimen to the standerd regimen is dominated by the three sites. Accordingly, one may deem that the non-inferiority of aprepiatnt regimen to aprepitant regimen is not dominated by certain investigator-sites.

The result of the sensitivity analysis is presented in Table 3.1.6.3.

Table 3.1.6.3 (Reviewer's) Efficacy comparisons assessed by the complete response in the overall phase using FSA population without three sites

ENDPOINT	TREATMENT GROUPS	
	Fosaprepitnat Regimen N= 1061	Aprepitant Regimen N = 1087
Complete Response, n (% = n/N)	758 (71.0%)	795 (73.0%)
Therapeutic Gain (TG), %‡		-2.0%
95.0% two-sided CI for TG†		(-5.5%, 2.1%)

3.1.6.1.3 Treatment difference analysis by country

In order to explore whether the therapeutic gains (defined as the complete response rate of fosaprepitant regimen minus that of aprepitant regimen) for fosaprepitant regimen versus aprepitant regimen were affected by country, this reviewer tabulates the proportions on the complete response in the overall phase by country using the FAS population.

The complete responses in the overall phase by country are presented in Table 3.1.6.4.

Table 3.1.6.4 (Reviewer's) Complete response rate in the overall phase by country using FAS population

COUNTRY	FOSAPREPITANT (F) % (n/N)	APREPITANT (A) % (n/N)	THERAPEUTIC GAIN† % (F - A)
Bolivarian	80.0 (8/10)	80.0 (8/10)	0.0%
Brazil	65.0 (51/79)	77.0 (62/81)	-12.0%
Canada	38.0 (6/16)	67.0 (10/15)	-29.0%
Chile	*61.0 (22/36)*	*51.0 (22/43)*	*10.0%*
Colombia	66.0 (31/47)	65.0 (30/46)	1.0%
Denmark	*100.0 (2/2)*	*50.0 (1/2)*	*50.0%*
Germany	75.4 (43/57)	71.0 (44/62)	4.0%
Guatemala	50.0 (4/8)	75.0 (6/8)	-25.0%
Hong Kong	29.0 (5/17)	61.0 (11/18)	-32.0%
Hungary	89.0 (47/53)	82.0 (44/54)	7.0%
India	77.0 (135/175)	73.0 (135/184)	4.0%
Italy	85.5 (47/55)	85.5 (47/55)	0.0%
Korea	63.0 (55/88)	69.0 (57/83)	-6.0%
Lithuania	*100.0 (10/10)*	*80.0 (8/10)*	*20.0%*
Mexico	*57.0 (16/28)*	*70.0 (19/27)*	*-13.0%*
Netherlands	33.0 (1/3)	40.0 (2/5)	-7.0%
New Zealand	*70.0 (7/10)*	*50.0 (5/10)*	*20.0%*
Panama	*63.0 (12/19)*	*50.0 (10/20)*	*13.0%*
Peru	64.0 (50/78)	66.0 (54/82)	-2.0%
Poland	87.0 (60/69)	89.0 (59/66)	-2.0%
Portugal	91.0 (29/32)	85.0 (29/34)	6.0%
Romania	60.0 (27/45)	61.0 (28/46)	-1.0%
Russian Federation	89.0 (59/66)	87.0 (58/67)	2.0%
South Africa	74.0 (14/19)	81.0 (17/21)	-7.0%
Spain	*83.0 (30/36)*	*57.0 (20/35)*	*26.0%*
Sweden	43.0 (9/21)	63.0 (12/19)	-20.0%
United States	56.0 (15/27)	71.0 (22/31)	-15.0%
Overall	71.9 (795/1106)	72.3 (820/1134)	-0.4%

†: defined as proportion of complete response of Fosaprepitant regimen minus that of Aprepitant regimen.

Based upon the results from Table 3.1.6.4, the complete response rates in the overall phase for the seven countries (Brazil, Canada, Guatemala, Hong Kong, Mexico, Sweden, and United States) out of twenty seven, for the fosaprepitant regimen, are less than that of aprepitant regimen by more than 7% (non-inferiority margin); however, the complete response rates in the overall phase for the six countries (Chile, Denmark, Lithuania, New Zeland, Panama, and Spain) out of twenty seven, for the fosaprepitant regimen, are higher than that of aprepitant regimen by more than 7% (non-inferiority margin).

The therapeutic gains (defined as the complete response rate of fosaprepitant regimen minus that of aprepitant regimen) less than -7% (7%: non-inferiority margin) generated by the seven countries raise a concern that the efficacy of fosaprepitant regimen may be influenced by country/region. It appears that the treatment effects of the fosaprepitant regimen versus that of the aprepitant regimen might not be internally consistent across countries. Thus, the efficacy data provided by this single study might be unable to demonstrate a clear/consistent clinical benefit across countries.

3.1.6.1.4 Efficacy comparison by region

Noted by this reviewer, only 2.8% of patients were enrolled from United States by the clinical study, in order to further assess the efficacy of the study drug fosaprepitant regimen to the patients in US and Canada (deemed to have similar clinical practice to US), this reviewer performs the following two efficacy comparisons:

i) Efficacy comparison by US versus Non-US;
ii) Efficacy comparison by North America (US & Canada) versus Non-North America.

i) Efficacy comparison by US and Non-US

Table 3.1.6.5 presents the efficacy comparison for the fosaprepitant regimen versus aprepitant regimen by US versus Non-Us while Table 3.1.6.6 presents efficacy comparison by US+Canada (North America) versus Non-NorthAmerica.

Table 3.1.6.5 (Reviewer's) Efficacy comparisons by US Vs. Non-US region assessed by the complete response in the overall phase using FAS population

US (2.60%=58/2240)

ENDPOINT	TREATMENT GROUPS	
	Fosaprepitnat Regimen N= 27	Aprepitant Regimen N = 31
Complete Response, n (% = n/N)	15 (56.0%)	22 (71.0%)
Therapeutic Gain (TG), %‡		-15.0%
95.0% two-sided CI for TG†		(-40.0%, 9.0%)

Non-US (97.4%=2182/2240)

ENDPOINT	TREATMENT GROUPS	
	Fosaprepitnat Regimen N= 1079	Aprepitant Regimen N = 1103
Complete Response, n (% = n/N)	780 (72.3%)	798 (72.4%)
Therapeutic Gain (TG), %‡		-0.1%
95.0% two-sided CI for TG†		(-3.8%, 3.7%)

†: 95.0% two-sided confidence interval for the Therapeutic Gain without using stratum factor;
‡: Therapeutic Gain defined as the Complete response rate of Aprepitant minus that of Standard;

Table 3.1.6.5 shows that the complete response rate for fosaprepitant regimen in US region is 56%, 15% less than that of aprepitant regimen (71%). In addition, it is also noted that the complete response rate (56%) for fosaprepitant regimen in US is also 16.3% less than that of fosaprepitant in Non-US while the complete response rate (71%) for aprepitant in US is close to that (72%) of aprepitant regimen in Non-US. Furthermore, the signal of more than 15% less complete response rate for fosaprepitant regimen shown in US than that in Non-US but not shown for aprepitant regimen raises a concern that the study drug may not be supported by substantial evidence to use for US patients for the proposed indication.

Table 3.1.6.6 (Reviewer's) Efficacy comparisons by North America Vs. Non-North America assessed by the complete response in the overall phase using FAS population

North America (4.0%=89/2240)

ENDPOINT	TREATMENT GROUPS	
	Fosaprepitnat Regimen N= 43	Aprepitant Regimen N = 46
Complete Response, n (% = n/N)	21 (49.0%)	32 (70.0%)
Therapeutic Gain (TG), %‡		-21.0%
95.0% two-sided CI for TG†		(-41%, -0.7%)

Non- North America (96.0%=2151/2240)

ENDPOINT	TREATMENT GROUPS	
	Fosaprepitnat Regimen N= 1063	Aprepitant Regimen N = 1088
Complete Response, n (% = n/N)	774 (72.8%)	788 (72.4)
Therapeutic Gain (TG), %‡		0.4%
95.0% two-sided CI for TG†		(-4.0%, 3.0%)

†: 95.0% two-sided confidence interval for the Therapeutic Gain without using stratum factor;
‡: Therapeutic Gain defined as the Complete response rate of Aprepitant minus that of Standard;

From Table 3.1.6.6, it is noted that for North America (US+Canada) region, the two-sided 95% confidence interval for the treatment difference of fosaprepitant regimen minus aprepitant regimen does not cover zero. Therefore, the complete response rate for fosaprepitant regimen is statistically significantly less than that of aprepotant regimen. Furthermore, the complete response rate (49.0%) for fosaprepitant regimen in North America region is also 23.8% less than that of fosaprepitant in Non-North America region while the complete response rate (70%) for aprepitant in North America region is close to that (72.4%) of aprepitant region in Non-North America region.

Since the clinical practice of Canda is deemed close to that of USA, the significantly less effect size for fosaprepitant regimen than that of aprepitnat regimen shown in North America region provide more evidence not in favor of using the study drug fosaprepitant regimen in US patients for the proposed indication.

3.1.6.2 Comments on the efficacy strength of the single study

Based upon the statistical analysis results performed by the applicant and this reviewer, the non-inferiority of fosaprepitant regimen versus aprepitant regimen assessed by the complete response in the overall phase is not dominated by certain sites. The non-inferiority of fosaprepitant to aprepitant claimed by the applicant is supported.

However, since single study was submitted to support fosaprepitant regimen used for the proposed indication, the study should be of high quality with substantial demonstration of efficacy. Based upon this requirement, the study should show clear clinical benefit and efficacy results that are internally consistent among different endpoints and subgroups as recommended in the Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and

Biological Products, May 1998. Now, based upon the result for the "treatment difference by country", it shows that the complete response rates in the overall phase for the seven countries (Brazil, Canada, Guatemala, Hong Kong, Mexico, Sweden, and United States) out of twenty seven, for the fosaprepitant regimen, are less than that of aprepitant regimen by more than 7% (non-inferiority margin). It appears that the treatment effects of the fosaprepitant regimen may not be internally consistent across country in the sense of non-inferiority to aprepitant regimen. Thus, the efficacy data provided by this single study might not be able to demonstrate a clear clinical benefit for the entire study population.

In addition, the result of region analysis by US vs. Non-US indicated that the complete response rate for fosaprepitant regimen in US region is 15% less than that of aprepitant regimen (56% vs. 71%). In the meanwhile, it is also noted that the complete response rate for fosaprepitant regimen is more than 15% less in US region than that in Non-US region. This raises a concern that the study drug might not have efficacy effect to US patients for the proposed indication. The less effect of fosaprepitant regimen in US than in Non-US is further shown in the region analysis by combining patients form US and Canada (North America) versus patients not from US and Canada.

However, due to small proportion (2.6%) of patients enrolled from US, no formal conclusion is made regarding the efficacy issue of fosaprepitant used in US patients.

3.2 Evaluation of Safety

The adverse event profile is summarized by treatment group in Table 3.2.1. The applicant indicated that adverse events were reported by 1,389 (60.1%) of the 2,312 patients included in the safety population and were generally comparable between the fosaprepitant and aprepitant groups. In general, the adverse event profile observed was typical of a patient population with cancer receiving highly emetogenic chemotherapy.

Table 3.2.1 (Applicant's) Adverse Event Summary

	Fosaprepitant Regimen (A)		Aprepitant Regimen (B)		Difference[§] (A-B)	95% CI[§] for the Difference
	n	(%)	n	(%)		
Patients in population	1,143		1,169			
with one or more adverse events	671	(58.7)	718	(61.4)	-2.7	(-6.7, 1.3)
with no adverse event	472	(41.3)	451	(38.6)		
with drug-related[†] adverse events	87	(7.6)	87	(7.4)	0.2	(-2.0, 2.3)
with serious adverse events	148	(12.9)	157	(13.4)	-0.5	(-3.3, 2.3)
with serious drug-related adverse events	4	(0.4)	7	(0.6)	-0.2	(-0.9, 0.4)
who died	23	(2.0)	26	(2.2)	-0.2	(-1.4, 1.0)
discontinued[‡] due to an adverse event	11	(1.0)	7	(0.6)	0.4	(-0.4, 1.2)
discontinued due to a drug-related adverse event	2	(0.2)	3	(0.3)	-0.1	(-0.6, 0.4)
discontinued due to a serious adverse event	8	(0.7)	4	(0.3)	0.4	(-0.3, 1.1)
discontinued due to a serious drug-related adverse event	1	(0.1)	2	(0.2)	-0.1	(-0.5, 0.3)

[†] Determined by the investigator to be related to the drug.

[‡] Study medication withdrawn.

[§] Calculated using the method of Miettinen and Nurminen.

The applicant further indicated that the adverse event profile for intravenous fosaprepitant 150 mg regimen was generally consistent with the safety data on the three day formulation of aprepitant and the day one intravenous fosaprepitant 115 mg substitute for 125 mg oral aprepitant on Day 1. Although a slightly higher incidence of thrombophlebitis in patients treated with fosaprepitant compared to patients treated with aprepitant was observed, the cases were rare in occurrence (0.8%), all non-serious, mild to moderate in intensity, and patients recovered from the adverse event. The occurrence of infusion site reactions in Protocol 017 is consistent with the post-marketing experience from the Day 1 intravenous fosaprepitant 115 mg as cases of infusion related thrombophlebitis are mild to moderate and not associated with significant clinical sequela.

In addition, infusion site pain occurred at a higher incidence in patients receiving the fosaprepitant regimen (1.4%) compared to patients receiving the aprepitant regimen (0.4%).
Urinary tract infections occurred at a higher incidence in patients in the fosaprepitant regimen group (1%) compared to patients in the aprepitant regimen group (0.3%). There were overall no difference in the incidence of infections and infestations between patients treated with fosaprepitant and aprepitant regimens. It is unlikely that the observation in the differences observed in adverse events of urinary tract infections is clinically significant since overall infections were not increased in patients treated with fosaprepitant.

A slight numerical increase in the incidence of hypertension was noted for patients treated with fosaprepitant group (1.5%) compared to patients treated with aprepitant (0.6%) in Protocol 017. The majority of these events were also mild and self-limited. Of note, the overall incidence of hypertension adverse events in the fosaprepitant arm of Protocol 017 was highly similar to that previously reported in the Phase III HEC trials for aprepitant (1.6%), conducted in a similar patient population. Overall, the data do not suggest that the numerical increase in adverse events related to hypertension in patients treated with fosaprepitant observed in Protocol 017 is substantially different from the previous experience of patients treated with aprepitant.

There was a higher incidence of asthenia (fosaprepitant 8.6%; aprepitant 11.6%) and anorexia (fosaprepitant 6.6%; aprepitant 9.1) in patients treated with aprepitant compared to patients treated with fosaprepitant. However, the incidence of these adverse events in patients treated with aprepitant in the present study were lower than previously observed in patients treated with aprepitant receiving HEC (asthenia 17.8%; anorexia 10.1%).

There were more incidences of serum alanine aminotransferase >5X ULN in patients treated with the fosaprepitant regimen (1.8%) compared to patients treated with the aprepitant regimen (0.5%). Many patients in this study had baseline elevations in their ALT and comorbid illnesses including their cancer diagnoses which can be associated with significant increases in liver function tests over time. In addition, all patients received chemotherapy at the time they received study medication which may have contributed to significant increases in liver function tests. Of note, the increases in ALT >3 ULN were not associated with increases in total serum bilirubin >2 XULN and there was no significant imbalance noted in AST increases in patients treated with fosaprepitant compared to patients treated with aprepitant. In addition, the majority of the increases were transient and resolved by the last study visit, and only patients with an underlying

hepatobiliary diseases continued to have elevated ALT levels Therefore, although a weak association between fosaprepitant use and mild, transient and asymptomatic ALT elevations cannot be definitely excluded, it is unlikely that a single dose of fosaprepitant is associated with significant long term liver toxicity.

In conclusion, the applicant emphasized that the overall data support the conclusion that the single day fosaprepitant regimen (fosaprepitant 150 mg I.V., ondansetron 32 mg I.V., and dexamethasone 12 mg P.O. on Day 1, dexamethasone 8 mg P.O. daily on Day 2, and dexamethasone 8 mg b.i.d. on Day 3-4) is generally well tolerated in patients receiving highly emetogenic chemotherapy for the prevention of chemotherapy induced nausea and vomiting, with an overall pattern of clinical and laboratory adverse events similar to that of the current experience with the marketed formulations of fosaprepitant and aprepitant.

4.0 SUBGROUP ANALYSIS

4.1 Gender, Race, and Age

In order to assess the consistency of the treatment effect for the fosaprepitant regimen relative to the aprepitant regimen across subgroups (identified by gender, age group, and race group), this reviewer performs subgroup analysis applying two-sided 95% confidence interval of complete response rate in the overall phase of fosaprepitant regimen minus that of aprepitant regimen based upon FAS patient population.

Age group (age ≤ 65 versus age > 65)

Table 4.1.1 presents the results of treatment efficacy comparisons by Age group (age ≤ 65 versus age > 65).

Table 4.1.1 (Reviewer's) Efficacy comparison assessed by the complete response in the overall phase using FAS population

Age > 65

	TREATMENT GROUPS	
ENDPOINT	Fosaprepitant Regimen (F) N= 214	Aprepitant Regimen (A) N = 241
Complete Response, n (%) Difference for F - A Two-sided 95% CI of F - A	162 (76.0)	192 (80.0) -4.0% (-0.12, 0.040)

Age ≤ 65

	TREATMENT GROUPS	
ENDPOINT	Fosaprepitant Regimen (F) N= 892	Aprepitant Regimen (A) N = 893
Complete Response, n (%) Difference for F - A Two-sided 95% CI of F - A	633 (71.0)	628 (70.0) 1.0% (-0.040, 0.050)

Table 4.1.1 shows that for the patients in the Age ≤ 65, since the lower bound of the two-sided confidence interval (-4.0%) is not less than -7.0%, the proportion of the complete response in the overall phase for the fosaprepitant regimen is not inferior to that of the aprepitant regimen by more than 7% (the non-inferiority margin)

Race group (White versus Non-white)

Table 4.1.2 presents the results of treatment efficacy comparisons by Race group (White versus Non-White).

Table 4.1.2 (Reviewer's) Efficacy comparison assessed by the complete response in the overall phase using FAS population

White

	TREATMENT GROUPS	
ENDPOINT	Fosaprepitant Regimen (F) N= 622	Aprepitant Regimen (A) N = 637
Complete Response, n (%) Difference for F - A Two-sided 95% CI of F - A	470 (76.0)	473 (74.0) 2.0% (-3.5%, 6.0%)

Non- White

	TREATMENT GROUPS	
ENDPOINT	Fosaprepitant Regimen (F) N= 484	Aprepitant Regimen (A) N = 497
Complete Response, n (%) Difference for F - A Two-sided 95% CI of F - A	325 (67.0)	347 (70.0) -3.0% (-8.0%, 3.0%)

Table 4.1.2 shows that for the patients in the White group, since the lower bound of the two-sided 95% confidence interval (-3.5%) is not less than -7.0%, the proportion of the complete response in the overall phase for the fosaprepitant regimen is indicated as non-inferior to that of the aprepitant regimen by no more than 7% (the non-inferiority margin). However, as this is a subgroup analysis, a non-inferiority conclusion is not formally demonstrated.

Gender group (Male versus Female)

Table 4.1.3 presents the results of treatment efficacy comparisons by gender group (Male versus Female).

Table 4.1.3 (Reviewer's) Efficacy comparison assessed by the complete response in the overall phase using FAS population

Male

ENDPOINT	TREATMENT GROUPS	
	Fosaprepitant Regimen (F) N= 698	Aprepitant Regimen (A) N = 718
Complete Response, n (%) Difference for F - A Two-sided 95% CI of F - A	537 (77.0)	555 (77.0) 0.0% (-4.7%, 4.0%)

Female

ENDPOINT	TREATMENT GROUPS	
	Fosaprepitant Regimen (F) N= 408	Aprepitant Regimen (A) N = 416
Complete Response, n (%) Difference for F - A Two-sided 95% CI of F – A	258 (63.0)	265 (64.0) -1.0% (-7.0%, 6.0%)

Table 4.1.3 shows that since the lower bounds of the two-sided 95% confidence intervals (-4.7% and -7.0%) for both males and females are not less than -7.0%, the proportions of the complete response in the overall phase for the foaprepitant regimen are consistent with the assumption of non-inferiority to the aprepitant regimen by no more than 7% (the non-inferiority margin).

4.2 Other Special/Subgroup Populations- Not applicable

5.0 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The comments given below are based upon the primary endpoint (complete response in the overall phase).

- This reviewer's efficacy analysis by investigator-site based upon the complete response in the overall phase using the FAS population indicates that for the two sites (42205 and 44487), it seems that the complete response rates for the fosaprepitant regimen were unusually higher than that of the aprepitant regimen and for one site (41975), only one patient in fosaprepitant regimen was identified as failure in complete reponse.

  However, the sensitivity analyses by excluding data from all of the three sites do not reflect that the non-inferiority of the fosaprepitant regimen to the aprepitant regimen is dominated by these three sites. Accordingly, the non-inferiority of the fosaprepitant regimen to the aprepitant regimen is supported.

- Since a single study was submitted to support fosaprepitant regimen used for the proposed indication, this study should be of high quality with substantial demonstration of efficacy. Based upon this requirement, this study should show clear clinical benefit and efficacy

results that are internally consistent among different endpoints and subgroups as recommended in the Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998.

- The efficacy difference analysis by country shows that of the twenty-seven countries in the study, seven countries (Brazil, Canada, Guatemala, Hong Kong, Mexico, Sweden, and United States) showed complete response rates in the overall phase, for the fosaprepitant regimen, that were less than that of aprepitant regimen by more than 7% (non-inferiority margin). This indicates that the treatment effects of the fosaprepitant regimen might not be internally consistent in the sense of non-inferiority to aprepitant regimen across country. Thus, the efficacy data provided by this single study is not indicative of clear clinical benefit for the entire study population.

  In addition, for the US patients (enrolled 2.6%), the efficacy result of region analysis by US vs. Non-US indicated that the complete response rate for fosaprepitant regimen in US region was 15% less than that of aprepitant regimen (56% vs. 71%). Furthermore, it is also noted that the complete response rate for fosaprepitant regimen is more than 16% less in the North America region (US/Canada) than that in the Non-North America region (but this regional difference is not shown for the aprepitant regimen). This raises a concern that the study drug might not have sufficient treatment benefit for US patients for the proposed indication.

5.2 Conclusions and Recommendations

The purpose of this supplemental application is to support the use of a single intravenous dose of fosaprepitant 150 mg (dosed concomitantly with a 5HT3 receptor antagonist and a corticosteroid) for the prevention of acute and delayed nausea and vomiting in cancer patients undergoing (b) (4) highly emetogenic chemotherapy (HEC).

The sponsor conducted a single, multi-national trial, Study P017L1, and results of analyses of the primary endpoint (complete response in the overall phase) and secondary endpoints (complete response in the delayed phase and no vomiting in the overall phase) support the intended indication but only for cancer patients undergoing HEC, as the study enrolled patients only in that category. (b) (4)

However, based on this reviewer's treatment-by-country analysis of the primary endpoint, the study does not show convincing evidence that clinical benefit is consistent across different countries. In addition, for the findings of treatment by region analyses, US versus Non-US and US/Canada versus Non-(US/Canada), Study P017L1 does not provide clear efficacy evidence to support the use of the fosaprepitant regimen in US patients for the proposed claim. However, since only 2.6% of patients were enrolled in US sites, no formal conclusion can be made regarding the efficacy of fosaprepitant regimen in US patients.

6.0 Appendix: Tables for treatment comparisons using per protocol population

Table 6.1 (Applicant's) Proportion of patients with complete response in the overall and delayed phases using per protocol patient population

Phase	Fosaprepitant Regimen (A) n/m (%)	Aprepitant Regimen (B) n/m (%)	Difference† (A-B) %	95% CI†
Overall Phase	760/1061 (71.6)	790/1099 (71.9)	-0.3	(-4.0, 3.5)
Delayed Phase	786/1061 (74.1)	811/1098 (73.9)	0.2	(-3.5, 3.9)

† The difference and the confidence interval (CI) for the difference 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 phase = 0 to 120 hours post-initiation of cisplatin chemotherapy.
Delayed phase = 25 to 120 hours post-initiation of cisplatin chemotherapy.
n/m = Number of patients with Complete response/number of patients included in the analysis.
Note: Complete response in the overall phase is the primary endpoint;
Complete response in the delayed phase is a secondary endpoint.

Table 6.2 (Applicant's) Proportion of patients with no vomiting in the overall phase using per protocol patient population

Phase	Fosaprepitant Regimen (A) n/m (%)	Aprepitant Regimen (B) n/m (%)	Difference† (A-B) %	95% CI†
Overall Phase	771/1061 (72.7)	812/1095 (74.2)	-1.5	(-5.2, 2.2)

† The difference and the confidence interval (CI) for the difference were calculated using the method proposed by Miettinen and Nurminen and adjusted for Gender.
Overall phase = 0 to 120 hours post-initiation of cisplatin chemotherapy.
n/m = Number of patients with No Vomiting/number of patients included in the analysis.
Note: No vomiting in the overall phase is a secondary endpoint.

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/s/

WEN JEN CHEN
10/13/2010

MICHAEL E WELCH
10/14/2010

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 22023 | **Applicant: Merck** | **Stamp Date:** 10/12/09

Drug Name: EMEND (fosaprepitant dimeglumine) Injection (MK-0517)

NDA/BLA Type: SE004 efficacy supplément

Indication: Prevention for acute and delayed nausea and vomiting with (b) (4) high emetogenic chemotherapy.

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter for RTF	Yes	No	NA	Comments
1A	Paper Submission: Index is sufficient to locate necessary reports, tables, data, etc.	X			
1B	Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)			X	Single study
3	Efficacy was investigated for gender, racial, and geriatric subgroups investigated.	X			Sample size might be inadequate for gender and racial subgroup analyses
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION IS FILEABLE ? Yes

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			Only one study submitted
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	No efficacy interim analysis planned.
Appropriate references for novel statistical methodology (if present) are included.	X			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.		X		Only one study submitted
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

Background

The purpose of this supplemental application is to support the use of a single intravenous dose of fosaprepitant 150 mg (dosed concomitantly with a 5HT3 receptor antagonist and a corticosteroid) for the prevention of acute and delayed nausea and vomiting (b) (4) high emetogenic chemotherapy.

Review Issues

Since only one study is submitted for the proposed indications, the efficacy strength demonstrated by the single study will be a review concern.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

WEN JEN CHEN
12/04/2009

MICHAEL E WELCH
12/07/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022023/S-004

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

29-JUN-2010

NDA 22023/S-004

Drug Product Name

Proprietary: EMEND™ for Injection

Non-proprietary: Fosaprepitant dimeglumine

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
11-JUN-2010	11-JUN-2010	N/A	N/A
12-OCT-2009	13-OCT-2009	26-OCT-2009	26-OCT-2009

Applicant/Sponsor

Name: Merck and Co., Inc.

Address: 126 E. Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065-0900

Representative: Nicholas W. Andrew
Associate Director, Regulatory Affairs

Telephone: 732-594-5585

Name of Reviewer: Steven E. Fong, Ph.D.

Conclusion: CMC-Microbiology recommends APPROVE.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Prior approval chemistry and manufacturing controls supplement.

2. SUBMISSION PROVIDES FOR: A 150 mg dose format for EMEND™ (Fosaprepitant dimeglumine) for injection. The 150 mg format will be added to the currently approved 115 mg format. The carton labeling of the 115 mg dose will be changed to reduce confusion with the proposed 150 mg dose. (b) (4)

3. MANUFACTURING SITE: The manufacturing sites for the 150 mg dose are shown below. These sites are the same as those currently approved for the 115 dose.

Manufacturing, Primary Packaging and Sterility/Endotoxin Release Testing.

DSM Pharmaceuticals, Inc
5900 Martin Luther King Jr. Highway
Greenville, NC 27834
DER #1018495

Secondary Packaging, Release Testing (not including sterility and endotoxin testing) and Stability Testing:

Merck and Co., Inc.
770 Sumneytown Pike
West Point, PA 19486-0004
CFN/DER #2510592

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- 150 mg lyophilized powder for intravenous injection provided in a 10 mL glass vial.
- Powder is reconstituted with 5 mL sterile saline and further diluted with 145 mL sterile saline.
- Following reconstitution the drug product will be administered concomitantly with a 5HT3 receptor antagonist and a corticosteroid. This regimen would be an alternative to the currently approved three-day oral regimen with aprepitant active ingredient.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Serotonergic anti-emetic.

B. SUPPORTING/RELATED DOCUMENTS: None.

C. REMARKS:

- The submission was provided electronically in eCTD format.

- On 26-MAR-2007 a microbiology quality review was submitted for the 115 mg dose form that recommended approval. Agency approval for the 115 mg dose application was granted 03-MAY-2007.

- On 03-JUN-2010 an IR was sent to the sponsor requesting data supporting the proposed reconstitution hold period of 24 hours at room temperature. An amendment response (supporting document 85) was received 11-JUN-2010.

filename: N022023s004r1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommended for approval from a microbiology quality standpoint.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4) . The only change is that the fill volume is increased from 3.02 mL to 3.94 mL. (b) (4)

B. Brief Description of Microbiology Deficiencies – None.

C. Assessment of Risk Due to Microbiology Deficiencies – Minimal risk.

III. Administrative

A. Reviewer's Signature _____

Steven E. Fong, Ph.D.
Microbiology Reviewer

B. Endorsement Block _____

Bryan Riley, Ph.D.
Senior Microbiology Reviewer

C. CC Block: N/A

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

The application proposes a 150 mg dose format for Fosaprepitant dimeglumine for Injection. The 150 mg format will be in addition to the currently approved 115 mg format. (b) (4) The only difference is the pre-lyophilization fill volume. For the 150 mg dose the target volume is 3.94 mL; for the 115 mg dose the target volume is 3.02 mL. (b) (4) (b) (4) were assessed in a 26-MAR-2007 review and found to be acceptable. A comparison of the composition of the 115 mg and 150 mg doses is presented in Table 1 below.

TABLE 1. Composition of the 115 mg and 150 mg Dose Forms for Fosaprepitant Dimeglumine Injection[1]

			115 mg Dose		150 mg Dose	
Component	Reference	Function	mg/vial[2]	mg/dose	mg/vial[2]	mg/dose
Fosaprepitant Dimeglumine (Fosaprepitant free acid)	(b) (4)	Active	197.5[3] (120.8)	188.0[3] (115.0)[4]	257.6[5] (157.5)	245.3[5] (150.0)[6]
Edetate Disodium		(b) (4)	15.1	14.4	19.7	18.8
Polysorbate-80			60.4	57.5	78.8	75.0
Lactose Anhydrous			302.0	287.5	393.8	375.0
Sodium Hydroxide[7]		pH adjustment	(b) (4)			
Hydrochloric Acid[7]		pH adjustment				

(b) (4)

(b) (4)

(b) (4)

Comment. *The proposed* (b) (4) *procedure for the 150 mg dose format for Fosaprepitant Dimeglumine for Injection is acceptable based on the fact that* (b) (4)

Microbiology Quality Specifications and Testing Methods.

- (b) (4)
-

—Acceptable—

Stability Summary and Conclusions

The stability of the 150 mg dose format for Fosaprepitant Dimeglumine for Injection was presented as a compilation of data from formal stability studies (FSS) and representative commercial production stability data.

- **Manufacture of the FSS Batches**. The batches used for FSS were manufactured at Merck's West Point, PA facility. A comparison of the processing equipment at this facility and the facility intended for commercial production, DSM Pharmaceuticals in Greenville, NC, was presented in submission Table 3.2.P.8.1-0517-injectable150mg, and is reproduced below in Table 2. The drug substance used for the FSS batches was derived from two

(b) (4)

different full scale batches (L-000758298-003C026 and TLS004). The FSS batches were also manufactured with the same packaging components to be used for commercial production.

- **Stability Study Design**. 150 mg vials from five FSS batches (WL00025284, WL00025284, WL00031134, WL00031188, WL00031200, WL00031199) were stored under ICH long term (5°C/ambient RH) and accelerated (25°C/65% RH) conditions and sampled at the time points presented below in Table 3. Microbiology quality (sterility, endotoxin content) was only assessed for vials stored under long term conditions. (Nonmicrobiological criteria, including degradants, solution clarity, pH, and nonviable particulate matter, were assessed under both long term and accelerated storage conditions.)

TABLE 3. FSS Design for Fosaprepitant Dimeglumine for Injection 150 mg Dose*

	Months						
Storage Conditions	3	6	9	12	18	24	36
5°C/AMB	Y	Y	Y	Z	Y	Z	Z
25°C/60% RH	Y	Y					

Y Composite assay, degradates, appearance, completeness and clarity of solution, visual particulates, pH, time for reconstitution, water, and particulate matter
Z Y and sterility and bacterial endotoxins (LAL)

Note: For the first FSS batch, selected tests were also performed at 2, 4, and 8 weeks. For the remaining four FSS batches, selected tests were performed at 6 weeks as well as sterility and bacterial endotoxins (LAL) at 6 months. Data is summarized in Sec. 3.2.P.8.3-0517-injectable.

**This table is a copy of submission Table 3.2.P.8.1-0517-injectable150mg:3. Microbiology quality sampling is scheduled at release (0 months) in addition to the indicated time points.*

- **FSS Results**. Available long term storage microbiology quality stability data from the FSS were presented in submission section 3.2.P.8.3-150 mg-5CAMB and are summarized below in Table 4. Samples from batch WL00025284 met the acceptance criteria for sterility and bacterial endotoxin content at 0, 12, 24, and 36 month sampling points. Samples from the remaining four FSS batches (WL00025284, WL00031134, WL00031188, WL00031200, and WL00031199) met the microbiology quality acceptance criteria at the 0 and 6 month sampling points.

TABLE 4. FSS Microbiology Quality Data for Fosaprepitant Dimeglumine 150 mg Dose Format[1]

Batch	ICH Storage Condition	Available Stability Data	Acceptance Criteria Met?[2]
WL00025284	Long term	0, 12, 24 months	Yes-All 4 time points
WL00031134	Long term	0 and 6 months	Yes-Both time points
WL00031188	Long term	0 and 6 months	Yes-Both time points
WL00031200	Long term	0 and 6 months	Yes-Both time points
WL00031199	Long term	0 and 6 months	Yes-Both time points

[1] *Long term storage data was available for batch WL00025284 through 36 months, and for batches WL00031134, WL00031188, WL00031200, and WL00031199 through 9 months. As shown in Table 3, sampling for the latter is scheduled for 0, 6, 12, and 24 months.*

[2] *Acceptance criteria refers to tests for sterility (sterile as per USP <71>) and endotoxin specification (≤ 2.3 EU/mg).*

- **Proposed Shelf-Life and Storage Condition**. A shelf life of 24 months under refrigeration (2° – 8°C) is proposed for the 150 mg dose format based on stability data collected to date (review Table 4 above) and statistical comparison of this data to that for the 115 mg format. (b) (4) [redacted]

- **Stability Data**. As with the 115 mg dose format, sterility and endotoxin testing for the 150 mg format will be performed at release and end of shelf life.

—Acceptable—

Post-reconstitution Hold Time.

A post-dilution hold period of 24 hours at room temperature is proposed for the 150 mg dose format and was approved for the 115 mg dose. On 03-JUN-2010 an IR was sent to the sponsor requesting data in support of the 24 hour hold period. On 11-JUN-2010 an amendment response (supporting document 85) was received that provided the results of growth studies in which 196 to 292 CFU *Escherichia coli*, *Staphylococcus aureus*, or *Pseudomonas aeruginosa* were inoculated into 40 mL of 1 mg/mL Fosaprepitant dimeglumine for Injection in saline (40 mL from a solution containing 115 mg of drug product reconstituted in 115 mL of saline). These studies were reported previously to the Agency in response to discussions held at a 09-NOV-2007 teleconference. In all cases the increase in growth after 24 hours incubation at room temperature never exceeded 0.3 logs. For some samples there was no increase in growth or a microcidal effect was observed (i.e., the microorganism concentration at the end of the incubation period was less than the concentration present at inoculation). No growth or a microcidal effect was observed for samples incubated at 2° – 8°C. Uninoculated negative controls did not exhibit growth. Positive controls in which the challenge microorganisms were inoculated into tryptic soy broth or saline exhibited growth increases, respectively of 3.8 to 5.4 logs and 0 to >2.4 logs. These data satisfied the acceptance criterion that challenge microorganism growth not exceed 0.5 logs, and indicated that the drug product has bacteriostatic or bacteriocidal activity when diluted to 1 mg/mL into saline. The 150 mg dose has the same post-dilution concentration as the 115 mg dose (1.0 mg/mL). The microbial challenge data for the 115 mg dose is thus applicable to both dose formats, and provides adequate justification for the proposed post-dilution hold period of 24 hours at room temperature.

—Acceptable—

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS: None.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

STEVEN E FONG
06/29/2010
Recommended for approval from a microbiology quality standpoint.

BRYAN S RILEY
06/29/2010
I concur.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 22-023 S-004 **Applicant: Merck & Co., Inc.** **Letter Date:** 10/12/2009

Drug Name: Fosaprepitant dimeglumine **NDA Type: Original NDA** **Stamp Date:** 10/13/2009

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		Submission provided electronically in CTD format.
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		Product sterilized by (b) (4). Process description provided in section 3.2.P.3.
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		Validation studies for sterile filtration, sterilization & depyrogenation of the container-closure system, sterility testing, and endotoxin testing presented in section 3.2.P.3.5.
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	Submission provided in English.
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		Product is provided as a sterile lyophilized powder. Container-closure integrity testing presented in section 3.5.4.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Specifications provided in section 3.2.P.5.1 and Table 3.2.P.5.1-0517.
7	Has the applicant submitted the results of analytical method verification studies?	X		Sections 3.2.P.3.5, 3.2.P.5.3, and 3.2.P.5.6.
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	N/A	N/A	Pre-submission microbiology quality requests were not made.
9	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: (None)

Steven Fong, Ph.D.	15-DEC-2009
Reviewing Microbiologist	Date
Stephen Langille, Ph.D.	15-DEC-2009
Microbiology Secondary Reviewer/Senior Microbiologist	Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

STEVEN E FONG
12/18/2009
Application provided sufficient information for filing from a microbiology quality standpoint.

STEPHEN E LANGILLE
12/18/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022023/S-004

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY ADDENDUM

NDA: 22-023	Submission Date: 12 OCT 2009
Submission Type:	Efficacy Supplement; SE-004
Brand Name:	Emend
Generic Name:	Fosaprepitant
Primary Reviewer:	Kristina Estes, Pharm.D.
Secondary Reviewer:	Sue Chih Lee, Ph.D.
OCP Division:	Division of Clinical Pharmacology 3
OND Division:	Division of Gastroenterology and Inborn Errors of Metabolism
Sponsor:	Merck
Formulation, Strength:	Intravenous solution 150 mg
Proposed Indication:	Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy including high-dose cisplatin [redacted] (b) (4)
Proposed Dosage Regimen:	150 mg as a single intravenous dose infused over 20-30 minutes

Background

The purpose of this addendum is to clarify the dexamethasone exposure for the 1-day IV fosaprepitant 150 mg or 3-day oral aprepitant (125mg/80mg/80mg) regimens. Given the antiemetic effects of dexamethasone and the different dose adjustments (Table 1) depending on the aprepitant/fosaprepitant regimen, it is important to ensure similar dexamethasone exposure between groups in study P017L1, the non-inferiority study comparing the efficacy of the 1-day and 3-day Emend regimens for Highly Emetogenic Chemotherapy (HEC).

Table 1. Recommended dosing of Emend, dexamethasone, and ondansetron for the 1-day and 3-day Emend regimens.

	Day 1	Day 2	Day 3	Day 4
1-Day Regimen				
EMEND	150 mg intravenous	none	none	none
Dexamethasone	12 mg orally	8 mg orally	8 mg orally twice daily	8 mg orally twice daily
Ondansetron	32 mg intravenous	none	none	none
3-Day Regimen				
EMEND	125 mg oral **or** 115 mg intravenous	80 mg orally	80 mg orally	none
Dexamethasone	12 mg orally	8 mg orally	8 mg orally once daily	8 mg orally once daily
Ondansetron	32 mg intravenous	none	none	none

Dexamethasone doses for the single-dose fosaprepitant regimen in HEC: Dexamethasone doses on Days 1 and 2 are reduced but not on Days 3 and 4.

The results of study P018L1 show dexamethasone AUC is increased by 2.01- and 1.86-fold on Days 1 and 2, respectively, when administered with 150 mg fosaprepitant on Day 1 relative to administration of dexamethasone alone. By Day 3 following co-administration, however, dexamethasone exposure is only increased by 18% relative to administration of dexamethasone alone. Based on the results of the drug interaction study, the recommended dose for dexamethasone in the HEC regimen is 12 mg on Day 1 & 8 mg on Day 2 following a single dose of 150 mg fosaprepitant on Day 1. The standard dose of dexamethasone is administered on Days 3 & 4 (8 mg *twice* daily) to reflect the lack of a persistent significant drug interaction by Days 3 & 4.

Dexamethasone doses for the 3-day oral aprepitant regimen in HEC: Dexamethasone doses on Day 1 through Day 4 are reduced.

The multiple-dose oral aprepitant regimen shows a more persistent effect upon dexamethasone pharmacokinetics as demonstrated in study P041. In that study, 125 mg aprepitant was administered on Day 1 and 80 mg aprepitant was administered on Days 2-5. This is in contrast to the approved regimen in which aprepitant is not administered beyond Day 3. Blood samples for dexamethasone were collected on Days 1 & 5 only. Dexamethasone exposure was increased 2.18- and 2.2-fold on Days 1and 5, respectively when administered with oral aprepitant for 5 days relative to administration of dexamethasone alone. Based on the results of the drug interaction study and PK data showing plasma aprepitant concentrations to remain elevated 24 hours following the 3rd dose (see Figure 1 below), the recommended dose for dexamethasone in the HEC regimen is 12 mg on Day 1 and 8 mg once daily on Days 2-4 following the 3-day oral aprepitant regimen.

A day-by-day comparison of dexamethasone exposure as administered to HEC patients.

The following is a comparison of the dexamethasone exposure between the two HEC regimens on each of the four days in which dexamethasone is administered:

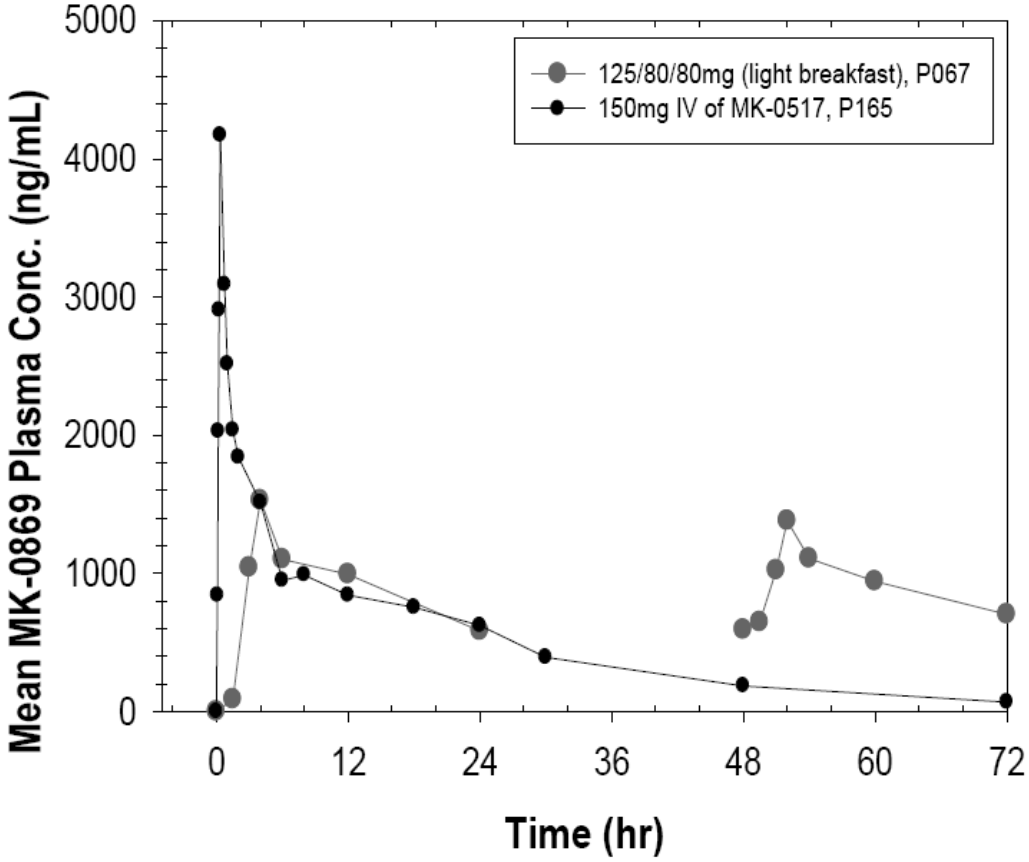
Day 1: Exposure on Day 1 is expected to be similar in both regimens based on the results of two drug interaction studies which specifically measured plasma dexamethasone concentrations on Day 1.

Day 2: Exposure on Day 2 would also be expected to be similar in both groups; however, exposure was only measured directly for the 1-day regimen. For the 3-day regimen, dexamethasone exposure on Day 2 may be inferred from the results of study P041 and are expected to be doubled relative to baseline if there is no dosage adjustment.

Day 3: By Day 3 of the 1-day regimen, the dexamethasone dose is increased to 8 mg *twice* daily (identical to standard dexamethasone dose when administered without Emend) to reflect the lack of a persistent drug interaction once aprepitant levels decline. For the 3-day regimen, dexamethasone exposure on Day 3 may be inferred from the results of study P041 and are expected to be doubled relative to baseline if there is no dosage adjustment. Therefore, when dexamethasone dose is reduced on Day 3 of the 3-day regimen, dexamethasone exposure is expected to be similar between the two groups on Day 3.

Day 4: Dexamethasone exposure on Day 4 of the 1-day regimen is expected to be similar to that observed on Day 3 given the continued decline in aprepitant plasma concentrations. Although there is no data on plasma dexamethasone exposure on Day 4 of the 3-day regimen, aprepitant concentrations remain elevated and the dexamethasone exposure is expected to remain approximately 2-fold higher than baseline without dosage adjustment. Previous PK studies showed mean aprepitant concentrations 24 hours following the 3rd oral aprepitant dose ranged from 702 to 1007 ng/mL. These levels are similar to the mean aprepitant level 24 hours following administration of the 1-day regimen, which ranged from 621 to 713 ng/mL and were associated with an approximate 2-fold increase in dexamethasone [see Figure 1 below]. Therefore, overall dexamethasone exposure is expected to be similar between the two regimens on Day 4.

Figure 1. Mean aprepitant plasma concentrations (ng/mL) versus time from single-dose intravenous 150-mg fosaprepitant administered over 20 minutes and from oral aprepitant 125/80/80-mg regimen in healthy volunteers



This figure represents data from two separate studies and shows the plasma exposure of aprepitant following the 1-day IV fosaprepitant 150 mg and 3-day oral aprepitant (125mg/80mg/80mg) regimens. Blood samples were not drawn on Day 2 of the 3-day regimen but would likely be similar to the profile shown for Day 3. Mean plasma aprepitant concentrations at 72 hours of the 3-day regimen are similar to those at 24 hours following the first dose for each regimen.

In summary, there is not expected to be an imbalance in dexamethasone exposure between the 1-day and 3-day Emend regimens in HEC patients when administered as recommended in the labeling.

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KRISTINA E ESTES
11/09/2010

SUE CHIH H LEE
11/09/2010

CLINICAL PHARMACOLOGY REVIEW

NDA: 22-023	Submission Date: 12 OCT 2009
Submission Type:	Efficacy Supplement; SE-004
Brand Name:	Emend
Generic Name:	Fosaprepitant
Primary Reviewer:	Kristina Estes, Pharm.D.
Secondary Reviewer:	Sue Chih Lee, Ph.D.
OCP Division:	Division of Clinical Pharmacology 3
OND Division:	Division of Gastroenterology and Inborn Errors of Metabolism
Sponsor:	Merck
Formulation, Strength:	Intravenous solution 150 mg
Proposed Indication:	Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy including high-dose cisplatin
	(b) (4)
Proposed Dosage Regimen:	150 mg as a single intravenous dose infused over 20-30 minutes

Table of Contents

1 Executive Summary

Intravenous Emend (fosaprepitant) was approved in 2008 in combination with other antiemetic agents (a 5 HT3 receptor antagonist and a corticosteroid) for the prevention of acute and delayed nausea and vomiting with initial and repeat courses of highly emetogenic chemotherapy and for the prevention of nausea and vomiting with initial and repeat courses of moderately emetogenic chemotherapy while oral Emend (aprepitant) was approved in 2003. The approved dosing regimen is a 3-day course in which 115 mg fosaprepitant (or 125 mg oral aprepitant) is administered on Day 1 of chemotherapy and 80 mg oral aprepitant is administered on Days 2 & 3. The current efficacy supplement is for a single dose regimen of 150 mg fosaprepitant administered intravenously on Day 1 with no subsequent doses of oral or intravenous aprepitant. In support of the application the Sponsor has submitted the results of a drug-drug interaction study and a single dose pharmacokinetic study as well as data from one safety and efficacy trial. Data from previously conducted studies were also used to support the application.

1.1 Recommendations

From a clinical pharmacology perspective, the application is acceptable provided agreement between the Agency and sponsor can be reached on label language.

1.2 Phase IV Commitments

Pediatric studies for CINV in patients 0-17 years of age will be required under PREA. The requirements will include PK characterization of aprepitant and dexamethasone and dose/exposure response with at least two dose levels of fosaprepitant in these patients.

1.3 Summary of CPB Findings

Dose Selection

The single 150 mg intravenous dose was chosen based on a combination of estimated NK_1 receptor occupancy and infusion site tolerability. Based on observed plasma aprepitant levels over several days following an infusion of fosaprepitant at different doses, CNS NK_1 receptor occupancy was predicted to remain > 90% NK_1 receptor occupancy through Day 3 and ≥ 80% through Day 4 following an infusion of 150 mg fosaprepitant over 20-30 minutes. Previous studies of aprepitant in healthy volunteers demonstrated a relationship between dose and NK_1 receptor occupancy. Furthermore, dose ranging studies of oral aprepitant in patients demonstrated a dose-response relationship up to 125 mg. However, the relationship between NK_1 receptor occupancy and the clinical efficacy of aprepitant has not been established.

Pharmacokinetics

Fosaprepitant is rapidly converted to aprepitant in vivo. This conversion is not CYP dependent and may occur in many extrahepatic tissues. Aprepitant is greater than 95% bound to plasma proteins. The mean apparent volume of distribution at steady state is approximately 70 L. Aprepitant is metabolized

primarily by CYP3A, with minor metabolism by CYP1A2 and CYP2C19. The terminal half-life of aprepitant is approximately 13 hours.

The pharmacokinetics of the 150 mg intravenous dose were not characterized in the clinical trial or in the drug interaction study. However, the sponsor has conducted a bioequivalence study in 41 healthy volunteers comparing 150 mg intravenous fosaprepitant to two oral dose levels of aprepitant. In this study, the infusion rate was 20 minutes, compared to a 30 minute infusion rate in the drug interaction study. The infusion rate specified in the clinical trial and in the proposed regimen is 20 to 30 minutes. The pharmacokinetic study showed the mean $AUC_{0-\infty}$ and C_{max} for aprepitant following a 20-minute IV infusion of 150 mg fosaprepitant were 37.34 μg*h/mL and 4.15 μg/mL, respectively. The %CV for $AUC_{0-\infty}$ and C_{max} was approximately 40% and 28%, respectively. Following a 30-minute infusion, aprepitant C_{max} would be somewhat lower relative to the 20-minute infusion. Due to nonlinear kinetics, aprepitant AUC would also be somewhat lower following a 30-minute infusion. Since the clinical trial was conducted with fosaprepitant administered over 20 to 30 minutes, the proposed infusion duration of 20 to 30 minutes is acceptable. Aprepitant metabolites do not have significant activity and were not characterized in this study.

Drug Interactions

Aprepitant, the active metabolite of fosaprepitant, is a CYP3A4 inhibitor and inducer; however, when administered as a single dose, aprepitant does not induce CYP3A4. Previous studies showed exposure of midazolam and dexamethasone, both CYP3A4 substrates, were increased up to 2.3-fold and 1.6-fold, respectively, when administered with fosaprepitant or aprepitant at doses used in the 3-day regimen. To address the potential for drug interactions with the higher dose of fosaprepitant, the Sponsor performed a drug interaction study with dexamethasone and midazolam. In each part of the study, 150 mg fosaprepitant was administered only on Day 1 while the study drugs were administered on multiple days.

> Dexamethasone: A known interaction exists between dexamethasone, a 3A4 substrate, and aprepitant when administered as a part of the 3-day dosing regimen. This study showed dexamethasone AUC was increased approximately 2-fold on Days 1 and 2 but not on Day 3 following fosaprepitant coadministration. The dexamethasone C_{max} was increased by 18 to 30% on Days 1 through 3. The increase in dexamethasone AUC is similar to that observed following administration of the 115 mg fosaprepitant dose. The primary difference is in the duration of effect; a reduction in dexamethasone dose is only necessary for the first two days with the single 150 mg fosaprepitant dose, while a reduction is necessary for four days with the 3-day regimen.
>
> Midazolam: Midazolam is a common 3A4 probe. The results of this study indicate that mean midazolam AUC is elevated by 77% and the mean C_{max}

is increased by 17% on Day 1 when 150 mg fosaprepitant is coadministered. There is no difference in midazolam exposure on Day 4. Relative to administration of midazolam alone, the increase in midazolam AUC following administration of a single 150 mg fosaprepitant dose is slightly higher (1.7-fold) than the increase observed following a 115 mg fosaprepitant dose (1.6-fold) but less than the increase in midazolam exposure following administration of the 3-day oral aprepitant regimen (up to 3.3-fold).

QT prolongation potential

The QT prolongation potential for fosaprepitant IV has been evaluated in a previous study. The results indicated that there was no QT signal for fosaprepitant 200 mg infused over 15 minutes. Therefore, the proposed dosing regimen of fosaprepitant 150mg infused over 30 minutes is not expected to prolong QT.

2 QBR

2.1 General Attributes of the Drug

2.1.1 What regulatory background or history information contributes to the assessment of the clinical pharmacology and biopharmaceutics of this drug?

Fosaprepitant was approved as a 505(b)(1) application with oral aprepitant as the reference product. A bioequivalence study was performed comparing 115 mg fosaprepitant and 125 mg oral aprepitant to bridge the two formulations. No clinical trials were conducted for the 115mg dose in support of the original application; however, additional clinical safety data was provided. For this efficacy supplement, a clinical trial was performed to assess the efficacy and safety of the single 150 mg IV dose.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

The 150 mg fosaprepitant product utilizes the [redacted] (b) (4)

Component	Function	115 mg Product (mg/dose)	150 mg Product (mg/dose)
Fosaprepitant Dimeglumine	Active	188.0	245.3
Fosaprepitant free acid	Active	115	150
EDTA	(b) (4)	14.4	18.8
Polysorbate-80		57.5	75.0
Lactose Anhydrous		287.5	375.0
NaOH	pH adjustment	(b) (4)	
HCl	pH adjustment		
			(b) (4)

2.1.3 What are the proposed dosage and route of administration?

The proposed dose is a single, 150 mg dose administered intravenously on Day 1 of chemotherapy. In contrast to the approved 3-day regimen that utilized a 115 mg IV dose, there will be no additional aprepitant doses administered on Days 2 & 3.

2.2 General Clinical Pharmacology

2.2.1 What are the design features and clinical outcomes of the pivotal clinical trial?

The clinical trial was a multicenter, randomized, double-blind, placebo-controlled, non-inferiority study comparing the single 150 mg IV dose with the three day oral aprepitant regimen in patients receiving highly emetogenic chemotherapy. Both treatment groups received IV ondansetron and oral dexamethasone; however, due to drug-drug interactions, the doses of the dexamethasone component were slightly different between the two groups.

> Fosaprepitant regimen: fosaprepitant dimeglumine 150 mg, ondansetron 32 mg IV, and dexamethasone 12 mg PO on Day 1, dexamethasone 8 mg PO on Day 2, and dexamethasone 16 mg PO on Days 3 & 4.
>
> Aprepitant regimen: aprepitant 125 mg PO, ondansetron 32 mg IV, and dexamethasone 12 mg PO on Day 1, aprepitant 80 mg PO and dexamethasone 8 mg PO on Days 2 & 3, and dexamethasone 8 mg PO on Day 4.

The aprepitant regimen is consistent with the approved 3-day oral regimen and the fosaprepitant regimen utilized in the clinical trial is consistent with

the proposed package insert and the results of the drug-drug interaction study.

The primary endpoint in this clinical trial was the proportion of patients with Complete Response (no vomiting and no use of rescue therapy) overall (in the 120 hours following initiation of cisplatin). The secondary endpoints were the proportion of patients with Complete Response in the delayed phase (25 to 120 hours following initiation of cisplatin) of treatment, and the proportion of patients with no vomiting overall.

Proportion of patients with Complete Response by phase and treatment group.

Phase	Fosaprepitant Regimen (A)		Aprepitant Regimen (B)		Difference(A-B)
	n/m	% (95% CI)	n/m	% (95% CI)	% (95% CI)[†]
Overall Phase	795/1106	71.9 (69.1, 74.5)	820/1134	72.3 (69.6, 74.9)	-0.4 (-4.1, 3.3)
Acute Phase	963/1082	89.0 (87.0, 90.8)	974/1107	88.0 (85.9, 89.8)	1.1 (-1.6, 3.8)
Delayed Phase	822/1106	74.3 (71.6, 76.9)	841/1133	74.2 (71.6, 76.8)	0.1 (-3.5, 3.7)

[†]Difference and Confidence interval (CI) for the difference 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 phase = 0 to 120 hours post-initiation of cisplatin chemotherapy.
Acute phase = 0 to 24 hours post-initiation of cisplatin chemotherapy.
Delayed phase = 25 to 120 hours post-initiation of cisplatin chemotherapy.
n/m = Number of patients with Complete response/number of patients included in the analysis.

Fosaprepitant was non-inferior to aprepitant with respect to Complete Response in the overall and delayed phases.

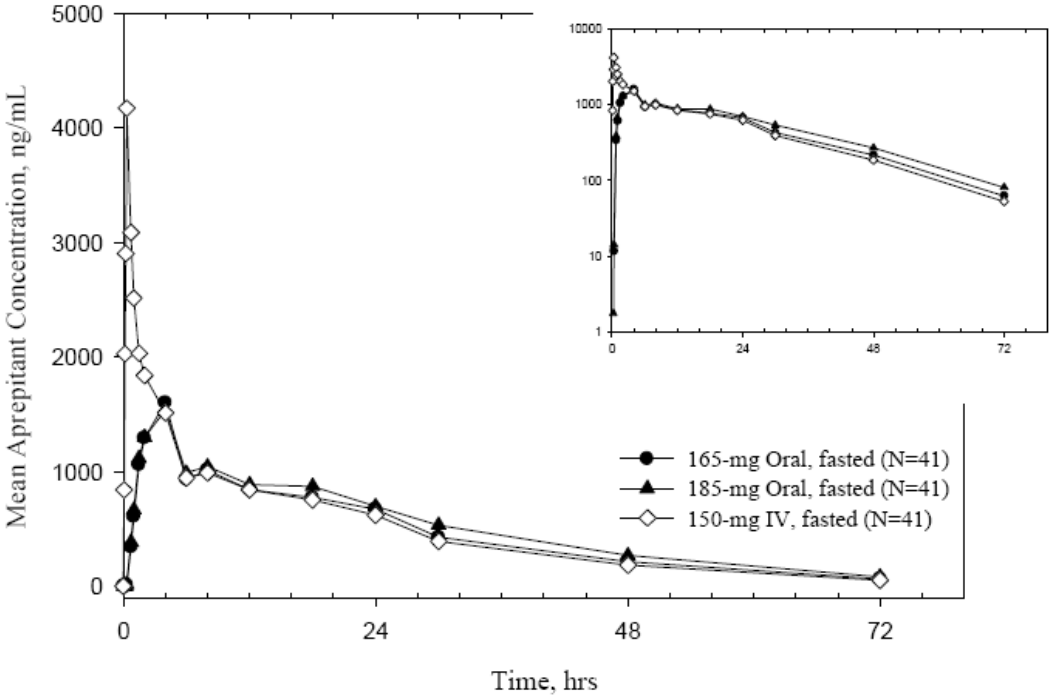
2.2.2 Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

Yes, see Section 2.6 (Analytical Section).

2.2.3 What are the single dose PK characteristics of the drug and its major metabolite?

The pharmacokinetics of the 150 mg intravenous dose were not characterized in the drug interaction study. However, the sponsor has conducted a bioequivalence study (P165) in 41 healthy volunteers comparing 150 mg intravenous fosaprepitant to two oral dose levels of aprepitant (165 mg and 185 mg). The infusion rate in Study P165 was 20 minutes, compared to a 30 minute infusion rate in the drug interaction study. The infusion rate in the clinical trials was 20 to 30 minutes.

Arithmetic mean aprepitant (ng/mL) plasma concentration following administration of a single 165 mg or 185 mg oral dose of aprepitant or 150 mg fosaprepitant IV infused over 20 minutes in healthy volunteers.



The mean $AUC_{0-\infty}$ and C_{max} for aprepitant following administration of the 150 mg IV dose of fosaprepitant were 37.34 μg*h/mL and 4.15 μg/mL, respectively. The %CV for $AUC_{0-\infty}$ and C_{max} was approximately 40% and 28%, respectively. Following single dose administration of fosaprepitant 150 mg, aprepitant 165 mg, or aprepitant 185 mg, mean aprepitant concentrations slowly decline over the 72 hour period in which subjects were followed. Mean aprepitant concentrations remain at or above 100 ng/mL during this time period for each of the three dosing regimens. Plasma concentration of the major aprepitant metabolite, an inactive compound, were not characterized in this PK study but they have previously been characterized.

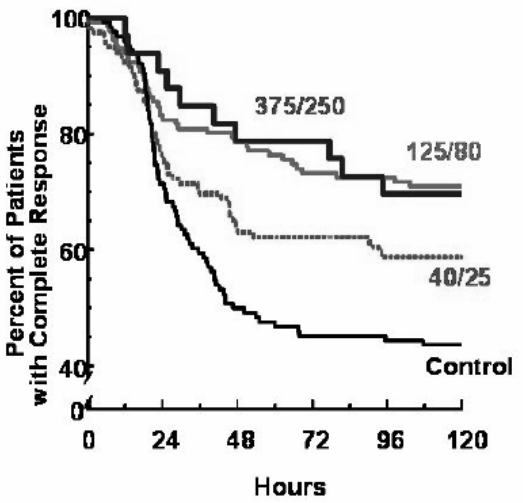
2.2.3.1 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The linearity of PK for fosaprepitant and aprepitant were not evaluated for this efficacy supplement; however, the dose-concentration relationship has previously been described. A single-dose PK study (P012L1) of fosaprepitant demonstrated that a 30% increase in dose (from 115 mg to 150 mg) corresponded to an increase in $AUC_{0-\infty}$ and C_{max} of approximately 50% and 47%, respectively, following a 15 minute infusion. Given the use of an identical infusion rate, aprepitant exposure appears to be more than dose proportional following fosapreitant administration.

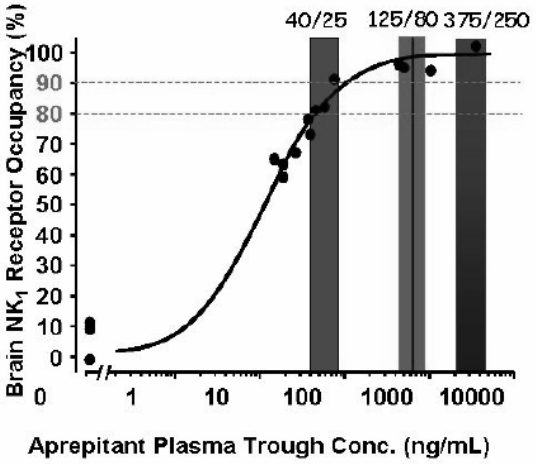
2.2.4 How was the dose selected?

The single 150 mg intravenous dose was chosen based on a combination of estimated NK_1 receptor occupancy and infusion site tolerability.

The correlation of plasma aprepitant concentrations with CNS NK1 receptor occupancy was previously assessed in two PET scanning studies in healthy volunteers. Based on these studies, concentrations of 10 and 100 ng/mL were expected to produce receptor occupancies of approximately 50 and 90%, respectively.



Dose-ranging studies of oral aprepitant showed an increase in the proportion of patients with Complete Response with increasing doses up to 125 mg on Day 1 (80 mg on Days 2 and 3). However, there was no additional benefit demonstrated with the highest dose of 375 mg on Day 1 (250 mg on Days 2 and 3).



Based on the PK/PD relationship, the sponsor concluded that 95% NK_1 receptor blockade was necessary to obtain the maximum benefit but NK_1 receptor blockade of 80 to 90% still provided significant but less than

maximal benefit. However, a definitive relationship between NK_1 receptor occupancy and the clinical efficacy of aprepitant has not been established.

Based on observed plasma aprepitant levels over several days following an infusion of fosaprepitant at different doses, CNS NK_1 receptor occupancy was predicted to remain > 90% NK_1 receptor occupancy through Day 3 and ≥ 80% through Day 4 following an infusion of 150 mg fosaprepitant over 20-30 minutes.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

Various intrinsic factors were previously studied for oral aprepitant; however, no new exploration of these factors was included in this submission.

2.3.2 *Based upon what is known about exposure-response relationships and their variability, and the groups studied; what dosage regimen adjustments, if any, are recommended for each of these subgroups?*

Increases in AUC or C_{max} were seen for several subgroups including females (C_{max} increased by 27%), elderly patients (AUC increased by 36%), Hispanics (AUC increased by 20 to 30%), or patients with moderate hepatic insufficiency (AUC increased by 20%). In addition, a 20 to 40% decrease in AUC and C_{max} was observed in patients with severe renal insufficiency. However, no dosage adjustments are recommended for any of the above mentioned subgroups.

2.4 Extrinsic Factors

2.4.1 Drug-Drug Interactions

2.4.1.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes, in vitro studies have shown aprepitant to be a substrate, inhibitor, and inducer of CYP 3A4.

2.4.1.2 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

Yes, fosaprepitant is administered in combination with a 5-HT_3 antagonist and a corticosteroid. The drug interaction potential for the 3-day aprepitant regimen was explored and the dexamethasone dose was adjusted to account for the interaction with aprepitant. The interaction

potential of the single dose IV regimen was also evaluated and the results were submitted with this efficacy supplement.

2.4.1.3 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Yes, systemic exposure of dexamethasone and midazolam, both CYP 3A4 substrates, was increased when fosaprepitant was coadministered. The Sponsor conducted a randomized, open-label, 2-part, 2-period, crossover drug interaction study. In Part 1, subjects were randomized to receive one of two different dexamethasone treatments (A or B) in each study period. In Part 2, subjects were randomized to receive one of two different midazolam treatments (C or D) in each study period. Of the 23 subjects enrolled, 11 completed Part 1 and 10 completed Part 2. Two subjects failed to complete the study; one withdrew consent and investigators withdrew one subject following a serious illness (pneumonia and a pulmonary embolus).

Treatment A: A single 8 mg daily oral dose of dexamethasone alone on Days 1, 2, & 3.

Treatment B: A single 8 mg daily oral dose of dexamethasone on Days 1, 2, & 3 co-administered with a single 150 mg IV dose of fosaprepitant infused over 30 minutes on Day 1.

Treatment C: A single 2 mg oral dose of midazolam on Days 1 & 4.

Treatment D: A single 2 mg oral dose of midazolam on Days 1 & 4 co-administered with a single 150 mg IV dose of fosaprepitant infused over 30 minutes on Day 1.

Aprepitant plasma concentrations were determined at 0, 5, 10, 15, 30, & 45 minutes and at 1, 1.5, 2, 4, 6, 8, 12, 18, & 24 hours post-dose, but only up to 45 minutes post-dose for fosaprepitant. Dexamethasone plasma concentrations were determined at 1, 2, 3, 4, 8, 12, & 24 hours post-dose. Midazolam plasma concentrations were determined at 15 & 30 minutes and 1, 2, 5, 8, 12, & 24 hours post-dose.

Part 1 Results

Demographics

Of the 11 subjects who completed Part 1, nine (82%) were male and two (18%) were female. Seven (64%) were White, two (18%) were Black, one (9%) was Asian, and one (9%) was a Native American. The mean age was 30 years of age (range: 18-45).

Dexamethasone Pharmacokinetics

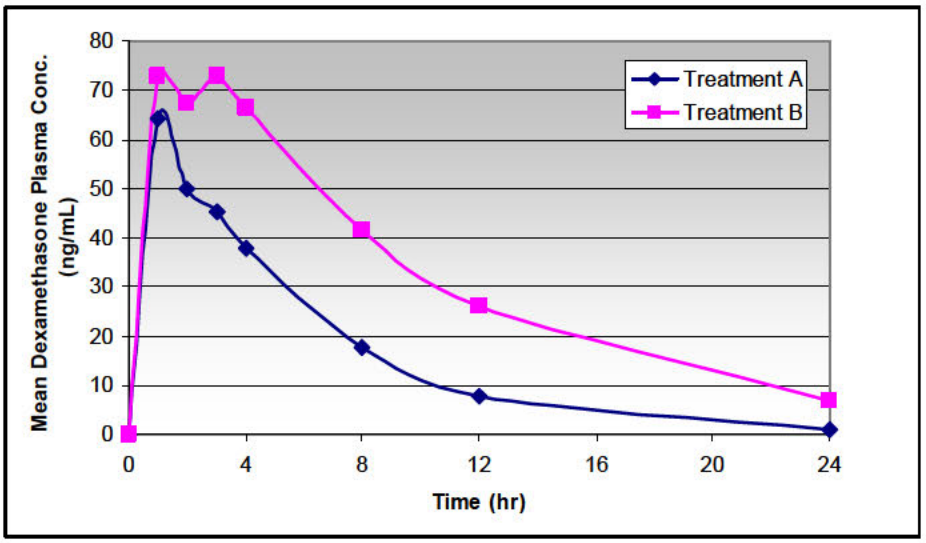
Statistical comparison of plasma PK parameters for dexamethasone (DEX) following a single 8 mg oral dose alone or in combination with a single 150 mg IV dose of fosaprepitant (FOS).

DEX PK Parameter	Day	DEX + FOS		DEX alone		DEX + FOS / DEX	
		Geo. Mean	90% CI	Geo. Mean	90% CI	GM Ratio	90% CI for GMR
AUC0-24 (ng*h/mL)	1	732.6	(620, 866)	363.8	(308, 430)	2.01	(1.84, 2.20)
	2	528.2	(447, 624)	283.3	(240, 335)	1.86	(1.71, 2.03)
	3	298.0	(252, 352)	252.5	(214, 298)	1.18	(1.08, 1.29)
Cmax (ng/mL)	1	87.53	(75, 101)	70.36	(61, 81)	1.24	(1.09, 1.42)
	2	82.28	(71, 95)	62.99	(55, 73)	1.31	(1.14, 1.49)
	3	67.11	(58, 77)	57.01	(49, 66)	1.18	(1.03, 1.34)
T½ (hr)	1	5.7	1.3	3.6	0.7	-	-
	2	4.0	0.9	3.0	0.5	-	-
	3	3.3	0.7	3.1	0.6	-	-

On Days 1 and 2, the plasma dexamethasone AUC is approximately 2-fold higher when administered with fosaprepitant (on Day 1 only) relative to administration of dexamethasone alone. The increase is dexamethasone AUC is not apparent by Day 3. In contrast, the dexamethasone C_{max} increases by only 24-31% on Days 1 and 2 when administered with fosaprepitant. The dexamethasone $t_{½}$ is prolonged by 1 to 2 hours on Days 1 and 2 but is not prolonged by Day 3 of fosaprepitant coadministration. These results are consistent with the reduction in dexamethasone dose by half on Days 1 and 2 in the clinical trials and the dosing recommendations in the labeling. There is no adjustment recommended for dexamethasone on Day 3 following the 150 mg single dose administration of fosaprepitant on Day 1.

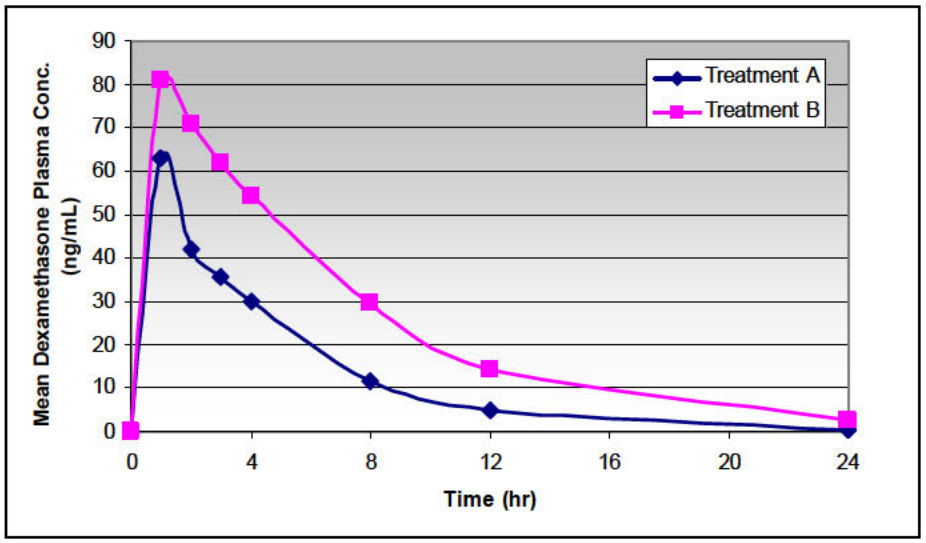
The increase in dexamethasone exposure following a single 150 mg IV dose of fosaprepitant does not exceed the increase in dexamethasone exposure observed following administration of the 3-day oral aprepitant regimen.

Mean plasma dexamethasone concentration (ng/mL) on **Day 1** following administration of a single 8mg oral dose of dexamethasone alone (Treatment A) or co-administered with 150 mg IV dose of fosaprepitant (Treatment B).



The mean dexamethasone plasma concentrations on Day 1 are clearly elevated following coadministration of 150 mg fosaprepitant on Day 1. The peak dexamethasone concentrations are also increased when administered with fosaprepitant relative to administration of dexamethasone alone on Day 1. The dexamethasone AUC was increased in all subjects while the C_{max} was elevated in 8 (73%) of subjects following fosaprepitant coadministration.

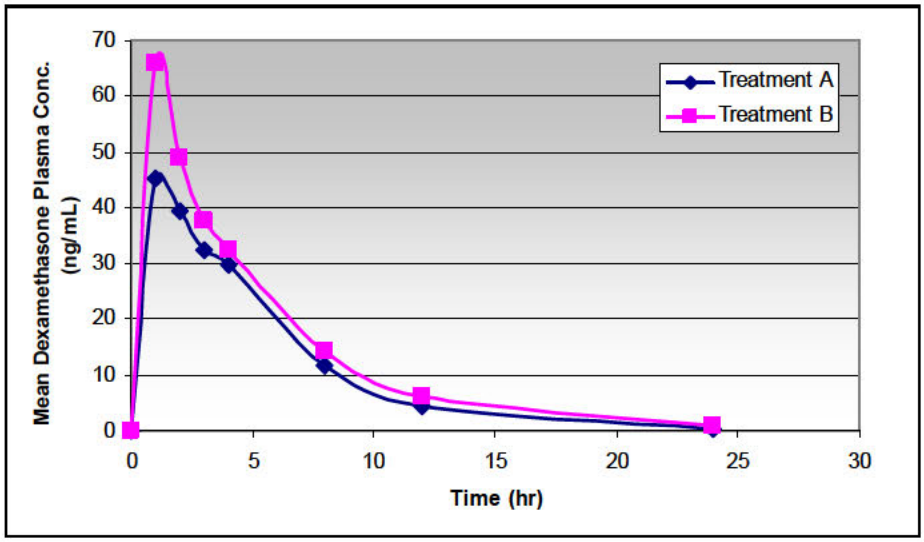
Mean plasma dexamethasone concentration (ng/mL) on **Day 2** following administration of a single 8mg oral dose of dexamethasone alone (Treatment A) or co-administered with 150 mg IV dose of fosaprepitant (Treatment B).



Similar to the effect on Day 1, mean dexamethasone concentrations continue to be elevated on Day 2 following fosaprepitant coadministration on Day 1. The peak dexamethasone concentration is

also increased on Day 2 and this increase is similar to that observed on Day 1. Also similar to Day 1, the dexamethasone AUC was increased in all subjects while the C_{max} was elevated in 8 (73%) of subjects following fosaprepitant coadministration.

Mean plasma dexamethasone concentration (ng/mL) on **Day 3** following administration of a single 8mg oral dose of dexamethasone alone (Treatment A) or co-administered with 150 mg IV dose of fosaprepitant (Treatment B).



By Day 3, the peak dexamethasone concentration following fosaprepitant coadministration remained slightly elevated; however, the mean dexamethasone concentrations over the remainder of the dosing interval did not appear to be elevated relative to administration of dexamethasone alone. Individual AUC and C_{max} values were elevated in 9 (82%) of subjects but the magnitude of these increases was small. The 18% increase in dexamethasone C_{max} would not be considered clinically meaningful. These results are consistent with the dosing recommendations for dexamethasone on Day 3, which indicate that the full dexamethasone dose should be used. This is in contrast to the 3-day aprepitant regimen in which the Day 3 dose of dexamethasone remains halved.

Part 2 Results

Demographics

Of the 10 subjects who completed Part 1, six (60%) were male and four (40%) were female. Six (60%) were Black and four (40%) were White. The mean age was 30 years of age (range: 18-44).

Midazolam Pharmacokinetics

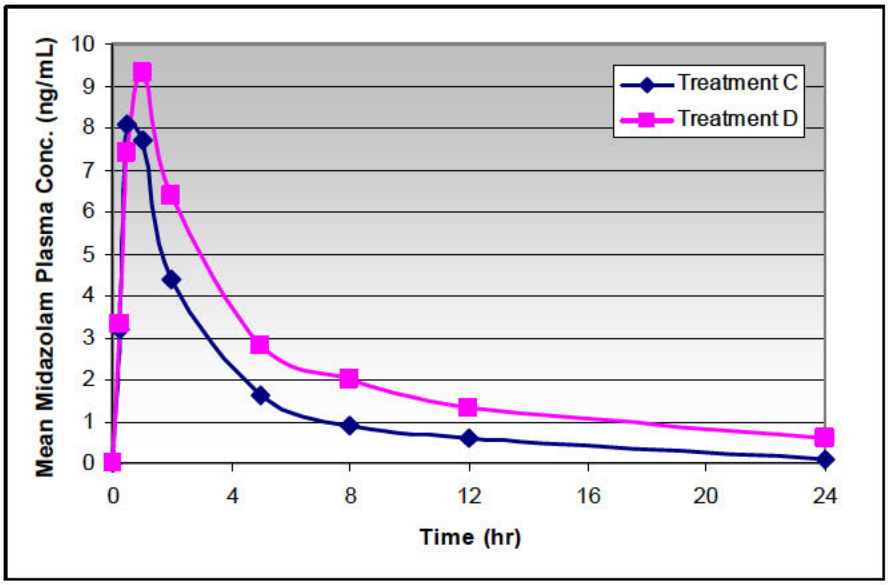
Statistical comparison of plasma PK parameters for midazolam (MDZ) following a single 2 mg oral dose alone or in combination with a single 150 mg IV dose of fosaprepitant (FOS).

MDZ PK Parameter	Day	MDZ + FOS		MDZ alone		MDZ + FOS / MDZ	
		Geo. Mean	90% CI	Geo. Mean	90% CI	GM Ratio	90% CI for GMR
AUC0-24 (ng*h/mL)	1	49.4	(33, 74)	28.0	(19, 42)	1.77	(1.52, 2.05)
	4	27.7	(18, 42)	27.2	(18, 41)	1.02	(0.88, 1.18)
Cmax (ng/mL)	1	9.8	(7.5, 12.7)	8.3	(6.4, 10.9)	1.17	(0.98, 1.38)
	4	8.4	(6.5, 11)	8.8	(6.8, 11.5)	0.96	(0.81, 1.13)
T½ (hr)	1	6.2	3.4	4.6	2.0	-	-
	4	3.7	2.2	3.8	2.3	-	-

On Day 1, the plasma midazolam AUC is increased by approximately 77% when administered with fosaprepitant (on Day 1 only) relative to administration of midazolam alone. The increase is dexamethasone AUC is not apparent on Day 4, the next day for which data is available. There is a 17% increase in midazolam C_{max} on Day 1 that is not apparent by Day 4 following fosaprepitant coadministration on Day 1. The midazolam $t_{½}$ is prolonged by approximately 1.5 hours on Days 1 but is not prolonged by Day 4. These results suggest the sedative effects of midazolam may be prolonged on Day 1 but are not likely to be prolonged on subsequent days.

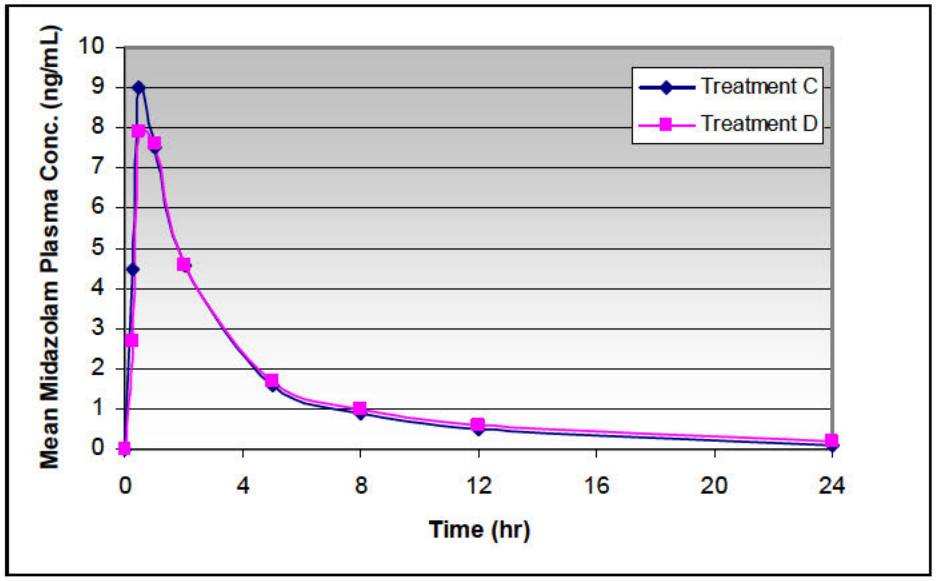
The increase in midazolam exposure following administration of a single 150 mg IV dose of fosaprepitant is less than the increase in midazolam exposure observed following administration of the 3-day oral aprepitant regimen but slightly higher than midazolam exposure following a 115 mg dose of fosaprepitant.

Mean plasma midazolam concentration (ng/mL) on **Day 1** following administration of a single 2 mg oral dose of midazolam alone (Treatment C) or co-administered with 150 mg IV dose of fosaprepitant (Treatment D)



Both the mean midazolam AUC and C_{max} were increased when administered with fosaprepitant on Day 1 relative to administration of midazolam alone. The AUC was increased in all subjects; however, C_{max} was increased in only 6 (60%) of subjects following fosaprepitant coadministration. There are no recommended dosage adjustments for midazolam; however, there may be a prolonged sedative effect when midazolam and fosaprepitant are coadministered.

Mean plasma midazolam concentration (ng/mL) on **Day 4** following administration of a single 2 mg oral dose of midazolam alone (Treatment C) or co-administered with 150 mg IV dose of fosaprepitant (Treatment D)



By Day 4, there is no apparent difference in midazolam exposure when midazolam is administered with or without fosaprepitant on Day 1.

2.4.2 ***What issues related to dose, dosing regimens or administration are unresolved, and represent significant omissions?***

There are no significant issues that remain unresolved.

2.5 General Biopharmaceutics

(b) (4) Therefore, there are no new biopharmaceutical issues related to this application.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

For Study P018L1, dexamethasone and midazolam were measured by LC/MS/MS. The Sponsor did not analyze metabolite concentrations in either Part 1 or Part 2 of the drug interaction study. For Study 165, aprepitant concentrations were measured by LC/MS/MS. Fosaprepitant concentrations and aprepitant metabolite concentrations were not measured in either study.

2.6.1.1 What are the lower and upper limits of quantification (LLOQ/ ULOQ)?

The LLOQ was (b) (4) for dexamethasone and midazolam, respectively. The ULOQ was (b) (4) for dexamethasone and midazolam, respectively. For aprepitant (MK-0869), the LLOQ was (b) (4) and the ULOQ was (b) (4). The ranges for dexamethasone and midazolam were appropriate for the concentrations achieved in Protocol 018.

2.6.1.2 What is the accuracy and precision at these limits? What is the range of the standard curve?

Study	Analytes	Range of Standard Curve (ng/mL)	Precision (%)	Accuracy (%)	Dilution Variation
Protocol 018	Dexamethasone	0.500 - 500 r^2 ≥0.9976	(b) (4)		CV: ≤ 2.73%
	Midazolam	0.100 -100 r^2 ≥0.9970			Not performed
Protocol 165	Aprepitant	10.0 - 5000 r^2 ≥0.9967			Not performed

2.6.1.3 What is the sample stability under the conditions used in the study?

Dexamethasone samples were found to be stable for 307 days at -20°C. Midazolam and aprepitant samples were stable for one year at -20°C. The maximum time samples were stored from collection to analysis was 90 days.

2.6.1.4 What is the QC sample plan?

For dexamethasone, the QC concentrations were (b) (4). For midazolam, the QC concentrations were (b) (4). For aprepitant, the QC concentrations were (b) (4). See table above (under Section 2.6.1.2) for the assessment of precision and accuracy.

3 Detailed Labeling Recommendations

(b) (4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

KRISTINA E ESTES
07/22/2010

SUE CHIH H LEE
07/22/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022023/S-004

OTHER REVIEW(S)

SEALD LABELING: FINAL SIGN-OFF REVIEW

APPLICATION NUMBER	NDA 22-023/004
APPLICANT	Merck
DRUG NAME	EMEND (fosaprepitant dimeglumine)
SUBMISSION DATE	October 13, 2009
PDUFA DATE	November 13, 2010
SEALD REVIEW DATE	November 12, 2010
OND ASSOCIATE DIRECTOR FOR LABELING	Laurie Burke

This review confirms that the final draft prescribing information (PI) corrects the regulatory deficiencies defined in 21 CFR 201.56 and 201.57 and noted in the SEALD labeling review filed on October 20, 2010. SEALD agrees with the Division that the PI is ready for approval at this time.

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/s/

LAURIE B BURKE
11/12/2010

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Gastroenterology Products

Application Number: NDA 022023/S-004

Name of Drug: EMEND (fosaprepitant dimeglumine) for Injection

Applicant: Merck Sharpe & Dohme Corp.

Material Reviewed:

Submitted Date	Received Date	SPL Submitted Date	Type of Labeling Submitted
October 12, 2010	October 13, 2009	October 12, 2010	PDF PI and PPI WORD PI and PPI SPL
April 8, 2010	April 8, 2010	April 8, 2010	PDF PI and PPI WORD PI and PPI SPL

Note: This labeling review was completed on April 29, 2010. Upon further evaluation, it was noticed that the review was not submitted into DARRTS. Therefore, the labeling review is being submitted into DARRTS on November 12, 2010 for the administrative record.

Background and Summary

EMEND (fosaprepitant dimeglumine) received initial approval on January 25, 2008 for:

- the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy (CINV-HEC)
- the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (CINV-MEC)

NDA 0022023/S-004 was submitted on October 12, 2009. This supplement proposes a new dosing regimen of a single 150 mg dose of I.V. fosaprepitant for prevention of chemotherapy induced nausea and vomiting. The sponsor's proposed PI label was not submitted in PLR format with the supplemental application. The sponsor was requested to submit PI labeling in PLR format in the filing communication correspondence (74-day letter) dated December 18, 2009.

In their response date January 27, 2010, Merck noted that prior approval labeling supplement S-002 was still pending and in final stages of agreement. This labeling supplement provided for a PLR conversion of the EMEND for Injection label. Merck proposed to submit their proposed PI label for S-004 in PLR format after agreement of labeling for S-002. FDA agreed with Merck's proposal.

On April 8, 2010, Merck submitted their updated, proposed PI and PPI label for S-004. The PI label included revision in PLR format.

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

Highlights

1. The Product Title should include the route of administration (for intravenous use).
2. The PI label should be revised to include the RECENT MAJOR CHANGES section. The sponsor's proposed PI label omits this section.
3. The INDICATIONS AND USAGE section should be revised to include the established pharmacologic class [substance P/neurokinin-1 (NK1) receptor antagonist].
4. The ADVERSE REACTIONS section should only include adverse reactions as defined in 21 CFR 201.57(a)(11), not (b) (4).

Table of Contents

1. The (b) (4) should be removed.

Full Prescribing Information (FPI)

1. Bold font should be used sparingly throughout the FPI. Other font such as underline or italics should be used.
2. In association with the "Highlights-Recent Major Changes" section, the corresponding new or revised text in the FPI should be marked with a vertical like on the left edge.
3. The following required statement should be moved to after subsection 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."
4. Only adverse reactions as defined in 21 CFR 201.57(a)(11) should be included in section 6 ADVERSE REACTIONS. The terms (b) (4) should be removed from this section and included subsection.
5. The subsection heading (b) (4) should be removed.

Recommendations

Further content review will be performed by each discipline and combined with the above revisions which have been made to the label. Upon discipline agreement, the changes to the label will be shared with the sponsor for further negotiation. The approval letter will remind the sponsor to submit final SPL that is identical to the approved labeling.

Jagjit Grewal, M.P.H.
Regulatory Project Manger

Drafted: JSG/4-19-10
Revised/Initialed: JSG/4-29-10
Finalized: JSG/11-11-10
Filename: N022023-S004 RPM Label Review.doc
CSO LABELING REVIEW OF PLR FORMAT

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JAGJIT S GREWAL
11/12/2010

SEALD LABELING REVIEW

This review identifies aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA 22-023/004
APPLICANT	Merck and Company, Inc.
DRUG NAME	EMEND (fosaprepitant dimeglumine)
SUBMISSION DATE	October 13, 2009
PDUFA DATE	November 13, 2010
SEALD REVIEW DATE	October 20, 2010
SEALD LABELING REVIEWER(S)	Jeanne M. Delasko, RN, MS

Outlined below are the following outstanding labeling issues that must be corrected before the final draft labeling is approved. Issues are listed in the order mandated by the regulations or guidance.

If there are no issues for a particular heading in highlights (HL) or for sections in the full prescribing information (FPI), "none" is stated. If clearly inapplicable sections are omitted from the FPI, "not applicable" is stated. In addition, "not applicable" is stated if optional headings (i.e., Drug Interactions or Use in Specific Populations) are omitted from HL.

The following comments delineate major deficiencies noted in the label. Please note that all reviewers' comments are noted in *italics*.

Highlights (HL):

- **Highlights Limitation Statement:** *EMEND not* (b) (4) *should appear in the HL limitation statement since EMEND is the trade name.*
- **Product Title Line:** *None*
- **Initial U.S. Approval:** *None*
- **Boxed Warning:** *Not applicable*
- **Recent Major Changes:** *None*
- **Indications and Usage:** *None*
- **Dosage and Administration:** *None*
- **Dosage Forms and Strengths:** *None*

- **Contraindications:** *None*
- **Warnings and Precautions:** *None*
- **Adverse Reactions:** *None*
- **Drug Interactions:** *Not applicable*
- **Use in Specific Populations:** *None*
- **Patient Counseling Information Statement:** *None*
- **Revision Date:** *Enter revision date in month/year (i.e., November/2010) format. Remember to update at time of approval.*

Table of Contents (TOC):

None

Full Prescribing Information:

Boxed Warning: *Not applicable*

1 Indications and Usage: *None*

2 Dosage and Administration: *None*

3 Dosage Forms and Strengths: *None*

4 Contraindications: *None*

5 Warnings and Precautions: *None*

6 Adverse Reactions: *None*

7 Drug Interactions: *None*

8 Use in Specific Populations: *None*

9 Drug Abuse and Dependence: *Not applicable*

10 Overdosage: *None*

11 Description: *None*

12 Clinical Pharmacology: *None*

13 Nonclinical Toxicology: *None*

14 Clinical Studies: *None*

15 References: *None*

16 How Supplied/Storage and Handling: *None*

17 Patient Counseling Information: *None*

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/s/

JEANNE M DELASKO
10/21/2010

ANN M TRENTACOSTI
10/21/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 31, 2010
Application Type/Number:	NDA 022023 SLR-004
To:	Donna Griebel, MD, Director Division of Gastroenterology Products
Through:	Todd Bridges, RPh, Team Leader Kellie Taylor, PharmD, MPH, Associate Director Division of Medication Error Prevention and Analysis
From:	Jibril Abdus-Samad, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Emend (Fosaprepitant Dimeglumine) for Injection 150 mg
Applicant:	Merck and Co., Inc.
OSE RCM #:	2009-2359

1 BACKGROUND

1.1 INTRODUCTION

This review responds to a request from Division of Gastroenterology Products (DGP) to review of the proposed labels and labeling for Emend for Injection 150 mg. DGP requests DMEPA's assessment of the proposed labels and labeling for Emend for Injection for their vulnerability to medication errors. On October 12, 2009, the Applicant submitted a prior approval supplement SLR-004 supplement that introduces a 150 mg single intravenous dose of Emend for Injection as an alternative to the currently marketed dosing regimens of Emend (fosaprepitant dimeglumine) for Injection and Emend (aprepitant) capsules.

(b) (4)

The proposed 150 mg strength vial will provide for two (b) (4) dosing regimens for prevention of Chemotherapy Induced Nausea and Vomiting (CINV) associated with Highly Emetogenic Chemotherapy (HEC) (b) (4)

Prevention of CINV associated with HEC

150 mg Dose Regimen

	Day 1	Day 2	Day 3	Day 4
EMEND	150 mg intravenous	none	none	none
Dexamethasone**	12 mg orally	8 mg orally	8 mg orally twice daily	8 mg orally twice daily
Ondansetron†	32 mg intravenous	none	none	none

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

†Ondansetron should be administered 30 minutes prior to chemotherapy treatment on Day 1.

115 mg Dose Regimen

	Day 1	Day 2	Day 3	Day 4
EMEND	115 mg intravenous	80 mg orally	80 mg orally	none
Dexamethasone**	12 mg orally	8 mg orally	8 mg orally	8 mg orally
Ondansetron†	32 mg intravenous	none	none	none

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

†Ondansetron should be administered 30 minutes prior to chemotherapy treatment on Day 1.

(b) (4)

115 mg Dose Regimen

	Day 1	Day 2	Day 3
EMEND	115 mg intravenous	80 mg orally	80 mg orally
Dexamethasone**	12 mg orally	none	none
Ondansetron†	8 mg orally twice daily	none	none

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

†Ondansetron 8-mg capsule should be administered 30 to 60 minutes prior to chemotherapy treatment and one 8-mg capsule should be administered 8 hours after the first dose on Day 1.

1.2 REGULATORY HISTORY

Emend (aprepitant) capsules was originally approved on March 27, 2003, as 40 mg and 80 mg capsules. Emend (fosaprepitant dimeglumine) for Injection 115 mg, was originally approved on January 25, 2008.

DMEPA participated in the labeling meeting with DGP's review team on July 14, 2010. During this meeting, DMEPA presented our recommendations for the insert labeling (see Appendix A). DGP incorporated our recommendations into the insert labeling prior to sending it to the Applicant on July 14, 2010.

2 METHODS AND MATERIALS

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) AND QUANTROS MEDMARX *** DATABASES

Since Emend for Injection is currently marketed, the Division of Medication Error Prevention and Analysis searched the Adverse Events Reporting System (AERS) database for any medication errors involving Emend. For this review, DMEPA performed an AERS search on July 9, 2010, for medication errors submitted for this product. The following criteria was used: active ingredient *Fosaprepitant* and *Aprepitant*, trade name *Emend*, and the verbatim terms *Fosap%*, *Aprep%*, and *Emen%*; and the MedDRA reactions *Medication Errors* (HLGT) and *Product Quality Issue* (PT) to identify medication errors that would be relevant to this review.

*** **This document contains proprietary data from the Institute for Safe Medication Practices (ISMP) and Quantros which cannot be shared outside of the FDA. Users wanting this information must contact Matthew Grissinger, RPh, FISMP, FASCP, Director, Error Reporting Programs at (215) 947-7797*****

Additionally, DMEPA requested search of the Quantros MEDMARX*** database to identify medication errors involving Emend (fosaprepitant) for Injection and Emend (aprepitant) capsules.

2.2 LABELS AND LABELING

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis[1] (FMEA) to evaluate the labels and labeling that were submitted on October 12, 2009 (Appendices B through F; no image of insert labeling).

3 RESULTS AND DISCUSSION

3.1 AERS AND QUANTROS MEDMARX*** RESULTS

The AERS search retrieved a total of 33 reports. Of these cases, 10 were excluded from further analysis because they were determined to adverse reactions not related to the product labeling issues or occurred in foreign countries. All of the remaining 23 reports involved errors with the use of Emend (aprepitant) capsules. However, one of these reports involved an extra dose error involving Emend for injection. A patient was dispensed Emend Tripack (125 mg, 80 mg, 80 mg capsules) and also received an unspecified dose of Emend intravenously before chemotherapy. This was the only medication error retrieved from AERS database that involved Emend (fosaprepitant) for Injection.

The Quantros MEDMARX*** database search retrieved a total of (b) (4) medication error reports. Of these cases, (b) (4) were removed because they were errors involving deteriorated drug, monitoring errors, patient non-compliance or medication administered to the wrong patient. All of the remaining (b) (4) involved Emend (aprepitant) capsules. (b) (4)

The 23 reports from AERS and (b) (4) from Quantros MEDMARX*** of medication errors involving Emend (aprepitant) capsules that are relevant to this review were attributed to the complex dosing for the Emend product line. Although the Emend 150 mg for Injection dosing regimen eliminates the need for Emend capsules, we are concerned patients may not receive the appropriate dose or duration of therapy for Emend, ondansetron, and dexamethasone due to the complexity of the four available dosing regimens. Organizing the insert labeling in a fashion that clearly delineates the different dosing regimens for prevention of CINV associated with HEC and MEC may help minimize confusion and errors.

*** **This document contains proprietary data from the Institute for Safe Medication Practices (ISMP) and Quantros which cannot be shared outside of the FDA. Users wanting this information must contact Matthew Grissinger, RPh, FISMP, FASCP, Director, Error Reporting Programs at (215) 947-7797*****

[1] Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

3.2 INTRODUCTION OF NEW STRENGTH

3.2.1 Dosage and Administration

The introduction of a 150 mg strength of Emend for Injection eliminates the need for additional Emend 80 mg capsules on Days 2 and 3 of chemotherapy. Despite this elimination of Emend 80 mg capsules for patients receiving Emend 150 mg for Injection, patients will still require concomitant ondansetron and dexamethasone therapy. More importantly each regimen for prevention of CINV associated with HEC and MEC requires different dosing instructions for ondansetron and dexamethasone. Thus, we anticipate health care providers and patients may be confused about these specific dose instructions. Organization of the insert labeling that allows for easy location and comparison of the dosing regimens for the specific indications may help minimize confusion and errors.

3.2.2 Differentiation of Strength

The currently marketed container label and carton labeling for the 115 mg vial employ green colored font which is identical to the color on the proposed container label and carton labeling for the proposed 150 mg vial. During the introduction into the market, there will be a time period at which the currently marketed green 115 mg vial will be on the pharmacy shelf next to the new green 150 mg vial. (b) (4) .

3.2.3 Utilization of 150 mg vial

There is a risk of pharmacies utilizing the 150 mg vial to prepare the 115 mg infusion due to a combination of health care provider familiarity with the 115 mg vial and regimen, the likelihood of health care institution use of pre-printed order sets detailing the Emend 115 mg dosing regimen, and its lack of availability during removal from the market. Utilization of the 150 mg vial to prepare a 115 mg infusion may lead to both overdosing, resulting in patient experiencing increased adverse reactions, and also under dosing, resulting in patients experiencing nausea and vomiting. Educating health care practitioners about the proposed 150 mg strength and the removal of the 115 mg strength may help mitigate these risks.

Additionally, there is also a risk of pharmacies saving the remaining reconstituted solution in the 150 mg vial for utilization in another future infusion. This may lead to use of deteriorated drug product. Revising the container label and carton labeling to include statements such as Single-Use vial and Discard Unused Portion may mitigate these risks.

3.3 INSERT LABELING

The presentation of the Dosage and Administration is organized based on the available strengths of Emend for Injection (115 mg and 150 mg) with the listed of possible dosing regimens for the respective strengths. This presentation makes it difficult to compare the available regimens for specific indications (CINV associated with HEC or MEC). (b) (4) We anticipate health care providers may be confused about the dosing regimens with respect to the total duration of therapy for Emend, ondansetron and dexamethasone. Reorganizing the Dosage and Administration section of the insert labeling improve allows for easier location of the available dosing regimens for the specific indications.

4 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation noted areas where information on the labels and labeling can be clarified and improved on to minimize the potential for medication errors. Section 4.1 (*Comments to the Applicant)* contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 4.1 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have any questions or need clarification, contact Nitin Patel, OSE project manager, at 301-796-5412.

4.1 COMMENTS TO THE APPLICANT

The proposed labels and labeling for Emend (fosaprepitant) for injection can be improved on to minimize the potential for medication errors. Additionally, at the time of product launch, we recommend that you inform healthcare practitioners about the differences between the proposed 150 mg and currently marketed 115 mg vials and regimens and your plans to remove the 115 mg vial from the market.

A. Container Label and Carton Labeling (115 mg and 150 mg)

1. Revise the colors schemes for the Emend for Injection product line to minimize the likelihood of product selection errors. (b) (4)

2. Revise the expression of the strength of the product to read as follows:

150 mg/vial and 115 mg/vial
or
150 mg per vial and 115 mg per vial

B. Container Label (115 mg and 150 mg)

Revise the statement *Single-Dose Vial* on the principal display panel to read *Single-Dose Vial - Discard Unused Portion*.

There is a risk of pharmacies utilizing the 150 mg vial to prepare the 115 mg infusion due to a combination of health care provider familiarity with the 115 mg vial and regimen, the likelihood of health care institution use of pre-printed order sets detailing the Emend 115 mg dosing regimen, and its lack of availability during removal from the market. Additionally, there is also a risk of pharmacies saving the remaining reconstituted solution in the 150 mg vial for utilization in subsequent infusion preparation resulting in use of deteriorated drug product.

C. Carton Labeling (115 mg and 150 mg)

1. Replace the term *saline* with *0.9% Sodium Chloride injection* on the principal display panel. Additionally, on the side panel, replace the term *saline* with *normal saline* to more accurately describe 0.9% Sodium Chloride injection.

2. Add the statement *Vial for single use only. Discard unused portion* to the side panel after the stability statement. There is a risk of pharmacies utilizing the 150 mg vial to prepare the 115 mg infusion due to a combination of health care provider familiarity with the 115 mg vial and regimen, the likelihood of health care institution use of pre-printed order sets detailing the Emend 115 mg dosing regimen, and its lack of availability during removal from the market. Additionally, there is also a risk of pharmacies saving the remaining reconstituted solution in the 150 mg vial for utilization in subsequent infusion preparation resulting in use of deteriorated drug product.

D. Container Label and Carton Labeling (150 mg)

(b) (4) For treatment of CINV associated with HEC, the 150 mg (1-Day Regimen) recommends a treatment regimen of 4 days when considering the duration of dexamethasone treatment. This descriptor is misleading (b) (4)

REFERENCES

1. Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

2. MEDMARX

MEDMARX is a national, Internet-accessible database that hospitals and health care systems use to track and trend adverse drug reactions and medication errors. Hospitals and health care systems participate in MEDMARX voluntarily and subscribe to it on an annual basis. MEDMARX is a quality improvement tool, which facilitates productive and efficient documentation, reporting, analysis, tracking, trending, and prevention of adverse drug events.

APPENDICES

Appendix A: DMEPA Insert Labeling recommendation presented at July 14, 2010, labeling meeting

1. **Section 2 - Dosage and Administration**

   Revise the Dosage and Administration section of the Full Prescribing Information by placing the proposed indications as the header statements. The subsections should read as follows:

   2 Dosage and Administration

   2.1 Prevention of Nausea and Vomiting Associated with Highly Emetogenic Chemotherapy

   2.2 Prevention of Nausea and Vomiting Associated with Moderately Emetogenic Chemotherapy

   2.3 Preparation of Emend for Injection

   Additionally, clearly delineate the available dosing regimens under each indication sub-section. This revision reorganizes the insert labeling to a format that allows for easier location of the available dosing regimens for the specific indications. This is important because Emend for Injection has four different dosing regimens.

2. **Section 2 - Dosage and Administration**

   Revise the descriptive titles for the product strengths to more accurately reflect both the course of Emend, dexamethasone, and ondansetron. (b) (4)

3. **Section 2.3 - Preparation of Emend**

   Replace the term *saline* with *normal saline* to more accurately describe 0.9% Sodium Chloride injection.

4. **Section 3 - Dosage Forms and Strengths**
   Section 16 - How Supplied/Storage and Handling

   (b) (4)

5. Patient Package Insert

(b) (4)

(b) (4)

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

Appendix G: AERS ISR numbers

4106160	4	4649868	4	4948051	2
4106596	1	4649871	4	4954684	X
4110599	0	4649872	6	4954695	4
4110601	6	4661292	7	4984886	8
4148917	X	4661313	1	5081900	9
4232676	6	4683321	7	5295915	9
4289087	7	4741744	1	5441400	0
4437269	3	4741767	2	5764874	4
4601720	6	4820037	8	5838664	8
4601721	8	4869936	1	6652437	8
4601722	X	4887947	7	6671403	X

*****This document contains proprietary data from the Institute for Safe Medication Practices (ISMP) and Quantros which cannot be shared outside of the FDA. Users wanting this information must contact Matthew Grissinger, RPh, FISMP, FASCP, Director, Error Reporting Programs at (215) 947-7797.*****

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

JIBRIL ABDUS-SAMAD
08/31/2010

TODD D BRIDGES
08/31/2010

KELLIE A TAYLOR
08/31/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	July 6, 2010
To:	Donna Griebel, M.D., Director **Division of Gastroenterology Products (DGP)**
Through:	Mary Willy, PhD, Deputy Director **Division of Risk Management (DRISK)** Sharon Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer, Acting Team Leader **Division of Risk Management**
From:	John Hubbard, MPAS, PA-C Patient Labeling Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Patient Package Insert)
Drug Name(s):	EMEND (fosaprepitant dimeglumine) Injection
Application Type/Number:	NDA 22-023
Submission Number:	S-004
Applicant/sponsor:	Merck & Co., Inc.
OSE RCM #:	2009-2359

1 INTRODUCTION

On October 12, 2009, Merck & Co., Inc. submitted a Prior Approval Supplement, sNDA 22-023/004, for EMEND (fosaprepitant dimeglumine) for injection. The Applicant proposes a single intravenous dose of EMEND (fosaprepitant dimeglumine) for injection, dosed concomitantly with a 5HT3 receptor antagonist and a corticosteroid, as an alternative for the approved 3-day oral aprepitant regimen. The Applicant also submitted a proposed EU Risk Management Plan with this supplement. Additionally, the PI has also been converted to Physician's Labeling Rule (PLR) format with this supplement.

This review is written in response to a request by the Division of Gastroenterology Products (DGP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for EMEND (fosaprepitant dimeglumine) for Injection.

Please let us know if DGP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIAL REVIEWED

- Draft EMEND (fosaprepitant dimeglumine) for Injection Prescribing Information (PI) submitted December 7, 2009, revised by the Review Division throughout the review cycle and provided to DRISK on June 21, 2010.
- Draft EMEND (fosaprepitant dimeglumine) for Injection Patient Package Insert (PPI) submitted on December 7, 2009.

3 RESULTS OF REVIEW

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- rearranged information due to conversion of the PI to PLR format
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

This DRISK reviewer did not review the EU Risk Management Plan submitted by the Applicant. Please contact DRISK if DGP feels that there are serious or significant risks associated with EMEND for injection that may require a Risk Evaluation and Mitigation Strategy.

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

Please let us know if you have any questions.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

JOHN C HUBBARD
07/06/2010
N22-023/S-004 Emend for Injection

MARY E WILLY
07/06/2010
I concur

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****Pre-decisional Agency Information****

Memorandum

Date: June 30, 2010

To: Jagjit Grewal, Regulatory Health Project Manager,
Division of Gastroenterology Products (DGP)

From: Kathleen Klemm, Regulatory Review Officer
Sheetal Patel, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Lisa Hubbard, Professional Group Leader, DDMAC
Aline Moukhtara, Acting DTC Group Leader, DDMAC
Wayne Amchin, Regulatory Health Project Manager, DDMAC

Subject: NDA 022023/S-004

DDMAC labeling comments for EMEND (fosaprepitant dimeglumine) for Injection

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In response to DGP's December 7, 2009, consult request, DDMAC has reviewed the draft product labeling (PI), Patient Package Insert (PPI), and carton/container labeling for EMEND (fosaprepitant dimeglumine) for Injection (Emend). DDMAC's comments on the PI are based on the proposed draft marked-up labeling titled, "Sponsor Proposed PI – DGP EDITS.doc" that was modified in the e-room on June 23, 2010, at 11:00am. DDMAC's comments on the PPI are based on the proposed draft marked-up labeling titled, "Sponsor Proposed PPI – DGP EDITS.doc" that was modified in the e-room on June 2, 2010, at 11:57am.

DDMAC's comments on the PI and PPI are provided directly in the marked-up document attached (see below). DDMAC's comments on the carton/container labeling follow.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions regarding the PI or carton/container labels, please contact Kathleen Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov. If you have any questions regarding the PPI, please contact Sheetal Patel at 301.796.5167 or Sheetal.Patel@fda.hhs.gov.

Carton/Container Labeling

DDMAC has reviewed the following carton/container labeling pieces, modified in the e-room on March 22, 2010, and has no comments at this time.

- Proposed Trade Carton 115mg – 1 single dose vial 10.12.09.pdf
- Proposed Trade Carton 115mg – 10 single dose vials 10.12.09.pdf
- Proposed Trade Carton 150mg – 1 single dose vial 10.12.09.pdf
- Proposed Trade Container 115mg 10.12.09.pdf
- Proposed Trade Container 150mg 10.12.09.pdf

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

KATHLEEN KLEMM
06/30/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 022023 BLA# N/A	NDA Supplement #:S- 004 BLA STN # N/A	Efficacy Supplement Type SE- 2
Proprietary Name: EMEND for Injection Established/Proper Name: fosaprepitant dimeglumine Dosage Form: intravenous injection Strengths: 150 mg		
Applicant: Merck & Co., Inc. Agent for Applicant (if applicable): N/A		
Date of Application: October 12, 2009 Date of Receipt: October 13, 2009 Date clock started after UN: N/A		
PDUFA Goal Date: August 13, 2010	Action Goal Date (if different): N/A	
Filing Date: December 12, 2009	Date of Filing Meeting: November 30, 2009	
Chemical Classification: (1,2,3 etc.) (original NDAs only) N/A		
Proposed indication(s)/Proposed change(s): New dosing regimen for a single 150 mg I.V. dose of fosaprepitant dimeglumine for the prevention of chemotherapy-induced nausea and vomiting.		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2) ☒ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*): N/A	
List referenced IND Number(s): 048924, 050283	

Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status	Payment for this application:
If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).			X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*			X	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:			X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		X		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: N/A ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	N/A			
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	X			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:* N/A		X		EMEND (fosaprepitant dimeglumine) I.V. has not been classified as a controlled substance.
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			X	

Forms and Certifications				
***Electronic** forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, **paper** forms and certifications with hand-written signatures must be included. **Forms** include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:** Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:** Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	This is an electronic submission.

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	X			(b) (4) [redacted]
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***		X		(b) (4) [redacted]
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***		X		

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***			X	The proprietary name was found acceptable with initial approval of NDA 022023.
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?		X		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***		X		PLR format for the PI will be requested.
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
REMS consulted to OSE/DRISK?			X	- The sponsor has submitted a Risk Management Plan, but proposes no additional risk management actions be undertaken other than routine pharmacovigilance.
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL)			

	☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***			X	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		X		

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** N/A ***If yes, distribute minutes before filing meeting***		X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** N/A ***If yes, distribute minutes before filing meeting***		X		No pre-NDA meeting was held, but type C meetings were held on 1/11/07 and 4/19/07 to discuss study design, dose selection, non-inferiority margin, and the adequacy of a single phase 3 study to support the new dosing regimen. Additionally, a telecon was held on 6/17/09 to discuss the sponsor's proposed statistical methods.
Any Special Protocol Assessments (SPAs)? **Date(s):** 11/29/07 - No Agreement ***If yes, distribute letter and/or relevant minutes before filing meeting***	X			SPA (clinical protocol) response sent on 11/29/07.

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 30, 2009

BLA/NDA/Supp #: NDA 022023/S-004

PROPRIETARY NAME: EMEND for Injection

ESTABLISHED/PROPER NAME: fosaprepitant dimeglumine

DOSAGE FORM/STRENGTH: intravenous injection, 150 mg

APPLICANT: Merck & Co., Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): New Dosing Regimen - A single intravenous dose of fosaprepitant dimeglumine 150 mg, dosed concomitantly with a 5HT-3 receptor antagonist and a corticosteroid, for the prevention of chemotherapy induced nausea and vomiting (CINV).

BACKGROUND:
NDA 022023 EMEND (fosaprepitant dimeglumine) for Injection, 115 mg was granted initial approval on January 25, 2008. EMEND for Injection is a NK-1 receptor antagonist approved for the following indications:

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

The currently approved dosing regimen for EMEND for Injection for both CINV-HEC and CINV-MEC is:

Day 1: fosaprepitant I.V. 115 mg + corticosteroid + 5HT3 antagonist

Days 2 & 3: aprepitant oral capsule 80 mg + corticosteroid

NDA 022023/S-004 was submitted on October 12, 2009. This supplement proposes a new dosing regimen for a <u>single</u> 150 mg dose of EMEND (fosaprepitant dimeglumine) for Injection, dosed concomitantly with a 5HT3 receptor antagonist and a corticosteroid, for the prevention of CINV (b) (4) CINV-HEC (b) (4) The sponsor has proposed this new dosing regimen as an alternative to the currently approved 3-day oral EMEND (aprepitant) capsule regimen.

The primary evidence of efficacy and safety to support the new dosing regimen is P017L1, which was a non-inferiority trial comparing the single dose of 150 mg I.V. fosaprepitant to the currently approved 3-day oral aprepitant regimen. (<u>P017L1</u>: a multicenter, randomized, double-blind, parallel-group trial with in-house blinding to assess the safety, tolerability, and efficacy of a single dose of I.V. fosaprepitant for the prevention of CINV in patients receiving cisplatin chemotherapy).

The sponsor has noted that demonstration of safety, tolerability and efficacy for the single dose 150 mg fosaprepitant I.V. regimen in patients receiving cisplatin-based HEC, combined with the extensive clinical experience with the currently approved aprepitant and fosaprepitant based 3-day regimens in HEC and MEC, would serve as an adequate test of the hypothesis that a single dose fosaprepitant regimen would be an appropriate alternative to the approved 3-day regimens for patients receiving HEC (b) (4)

The sponsor has also submitted study P018L1 which is an open label 2-part, randomized, 2-period, crossover, single-center study to evaluate the effect of a single 150 mg dose of fosaprepitant dimeglumine on the pharmacokinetics of oral dexamethasone (Part 1) and on oral midazolam (Part 2) in healthy young adult subjects.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jagjit Grewal	Y
	CPMS/TL:	Brian Strongin	N
Cross-Discipline Team Leader (CDTL)	Nancy Snow		Y
Clinical	Reviewer:	Tamara Johnson	Y
	TL:	Nancy Snow	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Kristina Estes	Y
	TL:	Sue Chih Lee	Y
Biostatistics	Reviewer:	Wen Jen Chen	Y
	TL:	Michael Welch	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:		

	TL:	Sushanta Chakder	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	David Lewis	Y
	TL:	Hasmukh Patel	N
Quality Microbiology *(for sterile products)*	Reviewer:	Steven Fong	Y
	TL:	James McVey	N
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	TBD	N
	TL:	TBD	N
OSE/DRISK (REMS)	Reviewer:	Mary Dempsey	Y
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	TBD	N
	TL:	TBD	N
Other reviewers			
Other attendees	Donna Griebel, DGP Director Ruyi He, DGP Acting Deputy Director Nitin Patel, OSE RPM Ann Mackey, OSE/DPV Safety Evaluator		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues?	☒ Not Applicable

If yes, list issues:	☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: N/A	☐ Not Applicable
CLINICAL **Comments**: Review issue to note is the acceptability of a single phase 3 trial to support the new dosing regimen. The clinical reviewer also has information requests to include in the 74-day letter.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO

CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**: Review issue to note is the acceptability of a single phase 3 trial to support the new dosing regimen. The statistical reviewer also has information requests to include in the 74-day letter.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted?	☐ Not Applicable ☒ YES ☐ NO ☐ YES

If EA submitted, consulted to EA officer (OPS)? **Comments**:	☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**: Per the CMC reviewer EER is not needed as there are no new facilities. Additionally, (b) (4) is referenced.	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☒ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs/BLA supplements only) **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Donna Griebel, M.D. Director, Division of Gastroenterology Products **21st Century Review Milestones (see attached)** (optional): Filing Date: 12/12/09; Day 74 Letter: 12/26/09; Midcycle Meeting: 3/22/10; Wrap Up Meeting: 6/23/10; Target Date to Communicate Labeling/PMCs/PMRs to sponsor: 7/2/10

Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): 1. The acceptability of a single phase 3 trial to support approval of the proposed new dosing regimen. Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☐	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Other: Include in the 74-day letter requests for additional information from the clinical and statistical reviewers. Also include requests to submit PI labeling in PLR format, certification for sponsor's request of partial waiver, and expand upon the sponsor's proposed pediatric plan.

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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

/s/

JAGJIT S GREWAL
12/16/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022023/S-004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022023 SUPPL # 004 HFD # 180

Trade Name EMEND

Generic Name fosaprepitant dimeglumine

Applicant Name Merck Sharpe & Dohme Corp.

Approval Date, If Known November 12, 2010

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1) - SE2 New Dosing Regimen: Single 150mg dose of I.V. fosaprepitant for prevention of acute and delayed nausea and vomiting associated with highly emetogenic cancer chemotherapy.

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

N/A

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 022023 EMEND (fosaprepitant dimeglumine) for Injection

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

N/A

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

N/A

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

N/A

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Protocol 017L1 - A Phase III, Randomized, Double-Blind, Active-Controlled, Parallel-Group Study, Conducted Under In-House Blinding Conditions, to Examine the Safety, Tolerability, and Efficacy of a Single Dose of Intravenous MK-0517 for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) Associated with Cisplatin Chemotherapy

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

N/A

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

N/A

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Protocol 017L1 - A Phase III, Randomized, Double-Blind, Active-Controlled, Parallel-Group Study, Conducted Under In-House Blinding Conditions, to Examine the Safety, Tolerability, and Efficacy of a Single Dose of Intravenous MK-0517 for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) Associated with Cisplatin Chemotherapy

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 048924	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Jagjit Grewal, M.P.H
Title: Senior Regulatory Health Project Manager
Date: November 10, 2010

Name of Office/Division Director signing form: Donna Griebel, M.D.
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

JAGJIT S GREWAL
11/10/2010

DONNA J GRIEBEL
11/10/2010

Organization: DGP **Product Name:** EMEND FOR INJECTION
Appl Type No: NDA 22023 **Applicant:** MERCK AND CO INC
Submission Type #: SUPPL - 4 **Submission Status:** PENDING

FDA Received Date	Dosage Form	Orphan	Subm Status Date	Goal Due Date	Submission Classification/ Supplement Category Level Two	Submission Indication
10/13/2009	POWDER, FOR INJECTION SOLUTION, LYOPHILIZED	N	10/13/2009	8/13/2010	DOSING	
10/13/2009	POWDER, FOR INJECTION SOLUTION, LYOPHILIZED	N	10/13/2009	11/13/2010	DOSING	

Pediatric Record ID	PREA Study Status	Pediatric Category	Min Value	Max Value	Waiver/ Deferral Reason	Waiver/ Deferral Reason Explanation	Study Due Date
767	DEFERRED	FULL	0	16	PRODUCT IS READY FOR APPROVAL IN ADULTS	PREVENTION OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING (HEC)	1/30/2014

Orga	Product I	Appl Typ	Subm Ty	Applic	Subm	FDA Rec	Dosag	Orph	Subm S	Goal Du	Submi	Su	Pe	PREA S	Pediat	Min Va	Max V	Waive	Waive	Study
DG	EMEND	NDA	SUPPL	MER	PEN	10/13/2	PO	N	10/13	8/13/2	DOS		7	DEFE	FUL	0	16	PRO	PRE	1/30/
DG	EMEND	NDA	SUPPL	MER	PEN	10/13/2	PO	N	10/13	11/13/	DOS		7	DEFE	FUL	0	16	PRO	PRE	1/30/

Debarment Certification

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck & Co., Inc did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

Nicholas Andrew, M.S.
Associate Director
Regulatory Affairs

01 october 2009
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 022023 BLA #	NDA Supplement # 004 BLA STN #	If NDA, Efficacy Supplement Type: SE2
Proprietary Name: EMEND Established/Proper Name: fosaprepitant dimeglumine Dosage Form: intravenous injection		Applicant: Merck Sharp & Dohme Corp. Agent for Applicant (if applicable):
RPM: Jagjit Grewal		Division: Division of Gastroenterology Products (HFD-180)

NDAs:
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 11/13/10	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics [2]

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	11/18/10
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval 11/12/10
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Sponsor submitted 11/12/10
• Original applicant-proposed labeling	Received 10/13/09
• Example of class labeling, if applicable	EMEND (aprepitant) capsules 3/19/10

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Sponsor submitted 11/9/10
• Original applicant-proposed labeling	Received 10/13/09
• Example of class labeling, if applicable	EMEND (aprepitant) capsules 3/19/10
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	Sponsor proposed: 115 mg - 10 vial carton 10/27/10 115 mg - 1 vial carton 9/7/10 115 mg container 9/7/10 150 mg carton 8/30/10 150 mg container 8/30/10
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	 N/A N/A
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 11/12/10 ☒ DMEPA 8/31/10 ☒ DRISK 7/6/10 ☒ DDMAC 6/30/10 ☐ CSS ☒ Other reviews SEALD 11/12/10; 10/21/10
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	12/6/09 ☒ Not a (b)(2) ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 7/7/10 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	 ☒ Included

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	PI revision email 11/10/10 PI revision email 11/9/10 PI-PREA PMR email 11/4/10 PPI revision email 10/28/10 PI revision email 10/27/10 Carton-Container email 10/18/10 Clinical IR 8/20/10 PDUFA Extension 8/6/10 PI revision email 8/2/10 PPI-Cart/Cont-PREA email7/23/10 PI revision email 7/14/10 Clinical-CMC IR 6/3/10 Safety update advice ltr 2/9/10 Filing Communication 12/18/09 Clinical IR 12/15/09 Acknowledgement ltr 11/10/09
❖ Internal memoranda, telecons, etc.	(b) (4) Memo (sNDA type): 11/10/09
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	Tcon (stats methods) 6/24/09 Type C (stats & clinical) 5/10/07 Type C (stats & clinical) 2/7/07
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	N/A
• 48-hour alert or minutes, if available *(do not include transcript)*	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 11/12/10
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 11/10/10; 10/19/10
PMR/PMC Development Templates *(indicate total number)*	☐ None 2 PREA PMRs: 11/10/10
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	see CDTL reviews co-signed primary reviews:

[5] Filing reviews should be filed with the discipline reviews.

	10/17/10, 1/25/10, 12/9/09
• Clinical review(s) *(indicate date for each review)*	10/15/10; 1/25/10; 12/9/09
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Clinical review 10/15/10 (p.17)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	N/A N/A ☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None co-signed primary reviews 10/14/10, 12/7/09
Statistical Review(s) *(indicate date for each review)*	☐ None 10/13/10; 12/4/09
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None co-signed primary reviews 11/9/10, 7/22/10
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 11/9/10; 7/22/10
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None 7/1/10; 11/30/09
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☒ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None co-signed primary reviews 7/12/10, 11/30/09
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 7/12/10; 11/30/09
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 6/29/10
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	CMC review 7/12/10 (p. 3)
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: see CMC review 7/12/10 (p. 8) ☐ Acceptable ☐ Withhold recommendation ☒ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

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/s/

JAGJIT S GREWAL
11/18/2010

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	November 9, 2010
TIME:	1:30PM – 2:00PM EST
APPLICATION:	NDA 022023/S-004/ (b) (4)
DRUG NAME:	EMEND (fosaprepitant dimeglumine) for Injection, 150 mg
TYPE OF MEETING:	Teleconference (732-594-5585)
MEETING RECORDER:	Jagjit Grewal

FDA ATTENDEES:

Division of Gastroenterology Products

Jagjit Grewal, M.P.H.	Senior Regulatory Health Project Manager

Office of Regulatory Policy

Michael Jones	Senior Program Management Officer

EXTERNAL CONSTITUENT ATTENDEES:

Merck Sharpe & Dohme Corp.

Nicholas Andrew, M.S.	Associate Director, Worldwide Regulatory Affairs
Georgianna Harris, Ph.D	Senior Director, Worldwide Regulatory Affairs

BACKGROUND:

Reference is made to NDA 022023/S-004 EMEND (fosaprepitant dimeglumine) for Injection 150 mg, dated October 12, 2009. This supplemental application proposes a new single 150 mg dose of fosaprepitant I.V. for the prevention of chemotherapy induced nausea and vomiting.

Upon further review, it was determined that Merck proposed multiple claims with this application which require separate clinical data to support approval. Therefore, the application was split into two separate supplemental applications. The supplemental applications were separated as follows:

- S-004: Proposes a single 150 mg dose of I.V. fosaprepitant for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy (CINV-HEC).
- (b) (4)

MEETING OBJECTIVES:

(b) (4)

DISCUSSION POINTS:

FDA explained that Merck's application was divided into two separate supplemental applications, S-004 (b) (4). FDA stated that separate clinical data was needed to support the single dose I.V. regimen for each claim of prevention of CINV-HEC and (b) (4)

FDA informed Merck not to withdraw the supplemental applications. (b) (4) A user fee payment will be required if the sponsor withdraws the sNDA prior to notifying FDA of their decision.

Merck asked why two separate user fees were required. FDA replied that the statute indicates that a user fee is required per each change. Furthermore, the clinical evidence needed to support the dosing regimen for prevention of CINV-HEC is different than that needed for (b) (4)

Merck asked by when they needed to notify FDA of their decision. FDA agreed that Merck could provide their notification by Tuesday, November 16, 2010. FDA noted that it may take longer to have the user fee processed, but a notification of intent should be submitted by the indicated date. Merck agreed.

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JAGJIT S GREWAL
11/12/2010

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	September 24, 2010
TIME:	12:45PM – 1:15PM EST
APPLICATION:	NDA 022023/S-004/ (b) (4)
DRUG NAME:	EMEND (fosaprepitant dimeglumine) for Injection, 150 mg
TYPE OF MEETING:	Teleconference (877-423-2663)
MEETING RECORDER:	Jagjit Grewal

FDA ATTENDEES:

Division of Gastroenterology Products

Donna Griebel, M.D.	Director
Nancy Snow, D.O., M.P.A.	Acting Medical Team Leader
Tamara Johnson, M.D.	Medical Reviewer
Sushanta Chakder, Ph.D.	Pharmacology Team Leader
Jagjit Grewal, M.P.H.	Regulatory Project Manager

Office of Clinical Pharmacology

Kristina Estes, Pharm.D.	Reviewer

Division of Biometrics III

Wen Jen Chen, Ph.D.	Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Merck Sharpe & Dohme Corp.

Nicholas Andrew, M.S.	Associate Director, Worldwide Regulatory Affairs
Georgianna Harris, Ph.D	Senior Director, Worldwide Regulatory Affairs
Juan Camilo Arjona Ferreira, M.D.	Director, Clinical Research
Susan Loftus, B.S.	Senior Clinical Research Specialist, Clinical Research
Craig Shadle, M.S.	Senior Clinical Associate, Clinical Pharmacology
Marian Iwamoto, Ph.D.	Senior Director, Clinical Pharmacology
Dan Tatosian, Ph.D.	Senior Pharmacokineticist, Clinical Pharmacology
Susie Li, Ph.D.	Research Fellow, Drug Metabolism
Alexandra Carides, Ph.D.	Associate Director, Clinical Biostatistics
Janet Vessotskie	Director, Global Medical Policy

BACKGROUND:

Reference is made to NDA 022023/S-004 (b) (4) EMEND (fosaprepitant dimeglumine) for Injection 150 mg, dated October 12, 2009. These supplemental applications proposes a new single 150 mg dose of fosaprepitant I.V. for the prevention of nausea and vomiting associated for highly emetogenic chemotherapy (HEC) (b) (4)
Reference is also made to FDA's request for additional information to support (b) (4) dated August 20, 2010, and Merck's response dated August 30, 3010.

MEETING OBJECTIVES:

The purpose of this teleconference was to inform the sponsor of FDA's continued concerns regarding (b) (4)

DISCUSSION POINTS:

FDA explained that substantial evidence was not provided with non-inferiority trial P017 to support the (b) (4) FDA stated that Merck's response dated August 30, 2010 did not sufficiently address these issues.

(b) (4)

Merck explained that in previous HEC trials, the 3-day aprepitant regimen provided substantial therapy versus standard of care. Merck argued that efficacy shown in the delayed phase was derived from the effect of aprepitant. (b) (4) Dexamethasone dosing was adjusted in these prior HEC (b) (4) studies to ensure that exposures were consistent between the treatment and comparator arms. In trial P017, the single dose I.V. regimen demonstrated non-inferiority to the 3-day aprepitant regimen during the acute, delayed, and overall phases. This supports that the single dose I.V. regimen would likely show the same superiority versus standard therapy as previously demonstrated in the 3-day aprepitant trials. (b) (4)

FDA asked about the possible additional effect of dexamethasone dosing after Day 1. Merck replied that in looking at the original HEC data with dexamethasone given on Days 2 and 3, aprepitant provided efficacy over standard of care with dexamethasone. Therefore, the additional benefit can be attributed entirely to aprepitant.

FDA asked what the capability was of dexamethasone dosed after Day 1 to compensate for the decline in aprepitant receptor occupancy over time. (b) (4) . Also with the approved 3-day regimen, aprepitant is given on Days 2 and 3.

Merck replied that trial P017 was conducted in the HEC setting with the gold standard for chemotherapy, cisplatin. The single dose I.V. regimen demonstrated non-inferiority to the 3-day aprepitant regimen in the delayed phase using very tight margins. If dexamethasone is providing

substantial effect, you would not expect to see a difference in efficacy between the arms in previous HEC trials.

FDA asked if aprepitant concentrations and receptor occupancy levels are both decreasing over time, how far do these levels need to fall before dexamethasone is no longer capable of making up for the difference in effect. Merck could not provide a response.

FDA asked if Merck has looked at receptor occupancy for aprepitant and potential variability across populations. (b) (4) Merck will look further at the available receptor occupancy data and provide justification for FDA review.

Merck asked if there was additional data, other than receptor occupancy, that FDA would need. FDA asked if Merck had demographic data with respect to receptor occupancy such as gender, age, etc. Merck was not certain if this data was available, but would look further. FDA also recommended that Merck consider receptor occupancy as a function of time (i.e. is there sufficient receptor occupancy on Day 3).

ACTION ITEMS:

1. Merck will provide receptor occupancy data and additional information to support the (b) (4)

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/s/

JAGJIT S GREWAL
11/12/2010

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Wednesday, November 10, 2010 3:06 PM
To: 'Andrew, Nicholas W.'
Cc: Grewal, Jagjit
Subject: FW: NDA 022023/S-004 EMEND - FDA comment to Merck proposed PI label change 11/10/10
Attachments: N022023-S004 EMEND (fosaprepitant) FDA revised PI label 11.10.10.doc

Hello Nick,

FDA agrees with Merck's proposed change to the Highlights-"Dosage and Administration" section. FDA proposes one additional revision, adding "capsules" after "EMEND" in Highlights as indicated in the attached annotated package insert label.

Please review and provide your concurrence. Thank you.

Jagjit Grewal, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846
Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

From: Andrew, Nicholas W. [mailto:nicholas_andrew@merck.com]
Sent: Wednesday, November 10, 2010 12:21 PM
To: Grewal, Jagjit
Subject: RE: NDA 022023/S-004 EMEND - Commenst to FDA proposed changes to the label.

Jagjit,
We will send this information formally today, however, I wanted to send to you by email in advance.

We agree with FDA revision with to the highlight section, however, propose one revision for (b) (4)

I have attached above the annotated, clean and clean versions with revision marks. In the annotated version, the Merck proposed text submitted as an amendment to PAS S004 on 08 Nov are shown in clean text with proposed changes from today's submission shown with revision marks.

Pleas let me know if I can provide any additional information at this time.

Kind Regards,
Nick

From: Grewal, Jagjit
Sent: Tuesday, November 09, 2010 1:24 PM
To: 'Andrew, Nicholas W.'
Cc: Grewal, Jagjit
Subject: RE: N022023/S-004 EMEND (fosaprepitant dimeglumine) for Injection - FDA revised PI label
Importance: High

Hello Nick,

Reference is made to you supplemental application dated October 12, 2009 for NDA 022023/S-004 EMEND (fosaprepitant dimeglumine) for Injection. We also refer to the FDA email correspondence dated November 4, 2010 (below), containing edits to the proposed package insert (PI) label.

Upon further review, FDA has included additional edits to the Highlights-"Dosage And Administration" section of the PI label. Please review the attached annotated WORD document of the PI label and provide your response by Wednesday, November 10, 2010.

I can be reached through email or at the below phone number with any questions.

Jagjit Grewal, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846
Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

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/s/

JAGJIT S GREWAL
11/10/2010

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Title: A PK/PD study to characterize aprepitant PK parameters following administration of a single dose of intravenous fosaprepitant, in combination with a 5HT3 antagonist and dexamethasone, in pediatric cancer patients ages 0 to 17 years undergoing treatment with highly emetogenic chemotherapy.

PMR/PMC Schedule Milestones:

Protocol Submission Date:	02/01/2011
Study Completion Date:	02/01/2014
Final Study Report Submission Date:	05/01/2014

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

(b) (4)

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 4***.

   - **Which regulation?**

     ☐ Accelerated approval
     ☐ Animal efficacy confirmatory studies
     ☒ Pediatric requirement
     ☐ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

     The drug and the specific dosage regimen proposed with this supplemental NDA has not been studied in the pediatric population.

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

NA

- **If the PMR is a FDAAA safety study/clinical trial, does it:**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

NA

4. If not required by regulation, characterize the review issue leading to this **PMC**

NA

5. What type of study or clinical trial is required or agreed upon (describe)?

A PK/PD study to characterize aprepitant PK parameters following administration of a single dose of intravenous fosaprepitant, in combination with a 5HT3 antagonist and dexamethasone, in pediatric cancer patients ages 0 to 17 years undergoing treatment with highly emetogenic chemotherapy.

Required

☐ Pharmacoepidemiologic study (list risk to be evaluated)

☐ Registry studies
☐ Primary safety study or clinical trial (list risk to be evaluated)

☒ Subpopulation (list type)
Pediatric patients 0-17 years
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☒ Dosing studies
☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
PREA PMR

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
☐ Dose-response study performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

6. Is the PMR/PMC clear and feasible?

   ☒ Are the schedule milestones and objectives clear?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:
This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality. ☒

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Title: An adequate, placebo-controlled, double-blind, randomized, add-on design, superiority study to evaluate the safety and efficacy of a single dose of intravenous fosaprepitant, in combination with a 5HT3 antagonist, as compared to standard therapy (a 5HT3 antagonist) in pediatric cancer patients ages 0 to 17 years undergoing treatment with highly emetogenic chemotherapy.

PMR/PMC Schedule Milestones:

Protocol Submission Date:	08/01/2014
Study Completion Date:	08/01/2017
Final Study Report Submission Date:	12/01/2017

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

(b) (4)

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 4***.

   - **Which regulation?**

     ☐ Accelerated approval
     ☐ Animal efficacy confirmatory studies
     ☒ Pediatric requirement
     ☐ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

     The drug and the specific dosage regimen proposed with this supplemental NDA has not been studied in the pediatric population.

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

NA

- **If the PMR is a FDAAA safety study/clinical trial, does it:**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

NA

4. If not required by regulation, characterize the review issue leading to this **PMC**

NA

5. What type of study or clinical trial is required or agreed upon (describe)?

An adequate, placebo-controlled, double-blind, randomized, add-on design, superiority study to evaluate the safety and efficacy of a single dose of intravenous fosaprepitant, in combination with a 5HT3 antagonist, as compared to standard therapy (a 5HT3 antagonist) in pediatric cancer patients ages 0 to 17 years undergoing treatment with highly emetogenic chemotherapy.

Required

☐ Pharmacoepidemiologic study (list risk to be evaluated)

☐ Registry studies
☒ Primary safety study or clinical trial (list risk to be evaluated)

☒ Subpopulation (list type)
Pediatric patients 0-17 years
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing studies
☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
PREA PMR

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
☐ Dose-response study performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

6. Is the PMR/PMC clear and feasible?

   ☒ Are the schedule milestones and objectives clear?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:
This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality. ☒

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/s/

JAGJIT S GREWAL
11/09/2010

NANCY C SNOW
11/10/2010

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Tuesday, November 09, 2010 1:24 PM
To: 'Andrew, Nicholas W.'
Cc: Grewal, Jagjit
Subject: RE: N022023/S-004 EMEND (fosaprepitant dimeglumine) for Injection - FDA revised PI label
Importance: High
Attachments: N022023-S004 EMEND (fosaprepitant) - FDA PI revisions 11.9.10.doc

Hello Nick,

Reference is made to you supplemental application dated October 12, 2009 for NDA 022023/S-004 EMEND (fosaprepitant dimeglumine) for Injection. We also refer to the FDA email correspondence dated November 4, 2010 (below), containing edits to the proposed package insert (PI) label.

Upon further review, FDA has included additional edits to the Highlights-"Dosage And Administration" section of the PI label. Please review the attached annotated WORD document of the PI label and provide your response by Wednesday, November 10, 2010.

I can be reached through email or at the below phone number with any questions.

Jagjit Grewal, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846
Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

From: Grewal, Jagjit
Sent: Thursday, November 04, 2010 12:56 PM
To: 'Andrew, Nicholas W.'
Cc: Grewal, Jagjit
Subject: N022023/S-004 EMEND (fosaprepitant dimeglumine) for Injection - FDA revised PI label & PREA PMRs

Hello Nick,

Reference is made to you supplemental application dated October 12, 2009 for NDA 022023/S-004 EMEND (fosaprepitant dimeglumine) for Injection. We also refer to your submission dated November 2, 2010 containing edits to the proposed package insert label (PI) and patient package insert label (PPI).

Attached is an annotated WORD document containing FDA's most recent revisions to your proposed PI label. We have no further comments on the PPI label. Please review the PI label revisions and provide your acceptance and/or proposed edits by close of business Monday, November 8, 2010.

Additional reference is made to your submissions dated July 27, 2010 and November 2, 2010 confirming your

agreement with the required postmarketing pediatric studies under PREA and providing a revised final protocol submission date for the PK/PD study PREA requirement #1. Upon further review, FDA has revised the required pediatric studies as follows (deleted text shown as strikethrough). The milestone timelines listed in your November 2, 2010 submission will remain unchanged.

1. A PK/PD study to characterize aprepitant PK parameters following administration of a single dose of intravenous fosaprepitant, in combination with a 5HT3 antagonist and dexamethasone, in pediatric cancer patients ages 0 to 17 years undergoing treatment with highly (b) (4) -emetogenic chemotherapy.
2. An adequate, placebo-controlled, double-blind, randomized, add-on design, superiority study to evaluate the safety and efficacy of a single dose of intravenous fosaprepitant, in combination with a 5HT3 antagonist, as compared to standard therapy (a 5HT3 antagonist) in pediatric cancer patients ages 0 to 17 years undergoing treatment with highly (b) (4) -emetogenic chemotherapy.

I can be reached through email or at the below phone number with any questions. Thank you.

Jagjit Grewal, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846
Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

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/s/

JAGJIT S GREWAL
11/09/2010

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Thursday, November 04, 2010 12:56 PM
To: 'Andrew, Nicholas W.'
Cc: Grewal, Jagjit
Subject: N022023/S-004 EMEND (fosaprepitant dimeglumine) for Injection - FDA revised PI label & PREA PMRs
Attachments: N022023-S004 EMEND (fosaprepitant) - FDA PI revisions 11.4.10.doc

Hello Nick,

Reference is made to you supplemental application dated October 12, 2009 for NDA 022023/S-004 EMEND (fosaprepitant dimeglumine) for Injection. We also refer to your submission dated November 2, 2010 containing edits to the proposed package insert label (PI) and patient package insert label (PPI).

Attached is an annotated WORD document containing FDA's most recent revisions to your proposed PI label. We have no further comments on the PPI label. Please review the PI label revisions and provide your acceptance and/or proposed edits by close of business Monday, November 8, 2010.

Additional reference is made to your submissions dated July 27, 2010 and November 2, 2010 confirming your agreement with the required postmarketing pediatric studies under PREA and providing a revised final protocol submission date for the PK/PD study PREA requirement #1. Upon further review, FDA has revised the required pediatric studies as follows (deleted text shown as strikethrough). The milestone timelines listed in your November 2, 2010 submission will remain unchanged.

1. A PK/PD study to characterize aprepitant PK parameters following administration of a single dose of intravenous fosaprepitant, in combination with a 5HT3 antagonist and dexamethasone, in pediatric cancer patients ages 0 to 17 years undergoing treatment with highly (b) (4) -emetogenic chemotherapy.
2. An adequate, placebo-controlled, double-blind, randomized, add-on design, superiority study to evaluate the safety and efficacy of a single dose of intravenous fosaprepitant, in combination with a 5HT3 antagonist, as compared to standard therapy (a 5HT3 antagonist) in pediatric cancer patients ages 0 to 17 years undergoing treatment with highly (b) (4) -emetogenic chemotherapy.

I can be reached through email or at the below phone number with any questions. Thank you.

Jagjit Grewal, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846
Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

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/s/

JAGJIT S GREWAL
11/04/2010

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Thursday, October 28, 2010 10:37 PM
To: 'Andrew, Nicholas W.'
Cc: Harris, Georgianna; Grewal, Jagjit
Subject: N022023/S-004 EMEND (fosaprepitant dimeglumine) for Injection - FDA revised PPI label
Attachments: FDA Revised PPI Label 10.28.10.doc

Hello Nick,

Reference is made to you supplemental application dated October 12, 2009 for NDA 022023/S-004 EMEND (fosaprepitant dimeglumine) for Injection. We also refer to Merck's email correspondence dated July 27, 2010 containing edits to the proposed patient package insert (PPI) label.

Attached is an annotated WORD document containing the FDA's most recent revisions to your proposed patient package insert label. Please review the PPI label revisions and provide your acceptance and/or proposed edits by close of business Tuesday, November 2, 2010.

I can be reached through email or at the below phone number with any questions.

Jagjit Grewal, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846
Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

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/s/

JAGJIT S GREWAL
10/28/2010

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Wednesday, October 27, 2010 6:07 PM
To: 'Andrew, Nicholas W.'
Cc: Harris, Georgianna; Grewal, Jagjit
Subject: N022023/S-004 EMEND (fosaprepitant dimeglumine) for Injection - FDA revised PI label
Importance: High
Attachments: N022023-S004 EMEND (fosaprepitant) - FDA PI revisions 10.27.10.doc

Hello Nick,

Reference is made to you supplemental application dated October 12, 2009 for NDA 022023/S-004 EMEND (fosaprepitant dimeglumine) for Injection. We also refer to Merck's email correspondence dated August 5, 2010 containing edits to the proposed package label insert label.

Attached is an annotated WORD document containing the FDA's most recent revisions to your proposed package insert label. Please review the PI label revisions and provide your acceptance and/or proposed edits by close of business Tuesday, November 2, 2010.

I can be reached through email or at the below phone number with any questions.

Jagjit Grewal, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846
Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

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/s/

JAGJIT S GREWAL
10/27/2010

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Monday, October 18, 2010 1:54 PM
To: 'Andrew, Nicholas W.'
Cc: Grewal, Jagjit
Subject: N022023/S-004 EMEND (fosaprepitant dimeglumine) for Injection - FDA carton labeling revision
Attachments: proposed-trade-carton-115-mg-10x-pas-07sep2010-iv_09072010.pdf

Hello Nick,

Reference is made to you supplemental application dated October 12, 2009 for NDA 022023/S-004 EMEND (fosaprepitant dimeglumine) for Injection. Further reference is made to your submissions dated August 30, 2010 and September 7, 2010 containing annotated and clean versions of your proposed carton and container labeling.

We have the following comments regarding your proposed container and carton labeling:

1. With regards to the attached 115 mg Carton Labeling (10 vials), separate the statement "Single-Dose Vials - Discard Unused Portion" from the net quantity statement "10 vials" on the principal display panel, top tuck flap panel, and back panel.
2. All other proposed carton and container labeling revisions are acceptable.

Please review the comments and respond with your acceptance and/or proposed changes. Include clean and annotated versions of any additional labeling changes made.

I can be reached at the below phone number or through email with any questions. Thank you.

Jagjit Grewal, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846
Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

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/s/

JAGJIT S GREWAL
10/18/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022023/S-004

INFORMATION REQUEST

Merck Sharp & Dohme Corp.
Attention: Nicholas Andrew
Associate Director, Regulatory Affairs
126 East Lincoln Avenue
P.O. Box 2000, RY 33-200
Rahway, NJ 07065-0900

Dear Mr. Andrew:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EMEND (fosaprepitant dimeglumine) for Injection, 150 mg.

We also refer to your email correspondence dated August 3, 2010 responding to the July 22, 2010 FDA carton and container labeling comments.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental application.

Efficacy of the Single Dose Fosaprepitant Regimen

The phase 3 trial for the single dose regimen of fosaprepitant in patients receiving highly emetogenic chemotherapy (HEC) involved multiple days of dosing with dexamethasone (Days 1-4). The pharmacokinetic information presented for the single dose fosaprepitant regimen and for the 3-day oral aprepitant regimen (e.g., Figure 2.5:2, p.13 of 2.5 Clinical Overview), shows that the aprepitant exposure differs between the two regimens after the first 24-48 hours. (b) (4)

Carton and Container Labeling Comments

1. *Carton and Container Label (150 mg and 115 mg)*: There is potential for pharmacies to utilize the 150 mg vial to prepare the 115 mg infusion. In this scenario, there is a risk of pharmacies saving the remaining reconstituted solution in the 150 mg vial for utilization in subsequent infusion preparation.

   Thus, we still recommend you revise the statement "Single-Dose Vial" on the principal display panel of the container label to read "Single-Dose Vial - Discard Unused Portion." We also recommend you add the statement "Vial for single use only. Discard unused portion" to the side panel of the carton label after the stability statement.

2. *Carton and Container Labels (150 mg)*: Delete the statement [redacted] (b) (4)

3. Your responses regarding the FDA comments on color differentiation, expression of strength, and description of saline are acceptable.

[redacted] (b) (4)

If you have questions, call Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

DONNA J GRIEBEL
08/20/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022023/S-004

REVIEW EXTENSION – EFFICACY SUPPLEMENT

Merck Sharp & Dohme Corp.
Attention: Nicholas Andrew
Associate Director, Regulatory Affairs
126 East Lincoln Avenue
P.O. Box 2000, RY 33-200
Rahway, NJ 07065-0900

Dear Mr. Andrew:

Please refer to your October 12, 2009 Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EMEND (fosaprepitant dimeglumine) for Injection, 150 mg.

On June 11, 2010, we received your June 11, 2010, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is November 13, 2010.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by October 8, 2010.

If you have questions, call Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

BRIAN K STRONGIN
08/06/2010

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Monday, August 02, 2010 4:54 PM
To: 'Andrew, Nicholas W.'
Cc: Grewal, Jagjit
Subject: NDA 022023/S-004 EMEND (fosaprepitant) for Injection - FDA revised PI label
Attachments: N22023-S004 EMEND (fosaprepitant) FDA PI revision 8.2.10.doc

Hello Nick,

Reference is made to you supplemental application dated October 12, 2009 for NDA 022023/S-004 EMEND (fosaprepitant dimeglumine) for Injection. Further reference is made to the July 14, 2010 FDA correspondence containing revisions to the package insert (PI) label, and Merck's email response dated July 22, 2010.

Attached is an annotated WORD document containing the FDA's most recent revisions to your proposed package insert label.

Please review the noted changes and respond with your acceptance and/or proposed changes. I can be reached at the below phone number or through email with any questions. Thank you.

Jagjit Grewal, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846
Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

JAGJIT S GREWAL
08/02/2010

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Thursday, July 22, 2010 5:35 PM
To: 'Andrew, Nicholas W.'
Cc: Grewal, Jagjit
Subject: N022023/S-004 EMEND (fosaprepitant dimeglumine) for Injection - FDA labeling revisions and PREA commitments
Attachments: N022023-S004 EMEND (fosaprepitant) - FDA PPI revisions 7.22.10.doc

Hello Nick,

Reference is made to you supplemental application dated October 12, 2009 for NDA 022023/S-004 EMEND (fosaprepitant dimeglumine) for Injection. Please find attached an annotated WORD document containing FDA's revisions to your proposed patient package insert label.

We also have the following comments regarding your proposed container and carton labeling:

Container Label and Carton Labeling (150 mg and 115 mg)

1. Color differentiation - Revise the colors schemes for the Emend for injection product line to minimize the likelihood of product selection errors. (b) (4) [redacted]

2. Expression of strength – Revise the expression of the strength of the product to read as follows: 150 mg/vial and 115 mg/vial or 150 mg per vial and 115 mg per vial

Container Label (150 mg and 115 mg)

1. Revise the statement "Single-Dose Vial" on the principal display panel to read "Single-Dose Vial - Discard Unused Portion".

Carton Labeling (150 mg and 115 mg)

1. Replace the term "saline" with "0.9% Sodium Chloride injection" on the principal display panel. Additionally, on the side panel, replace the term "saline" with "normal saline" to more accurately describe 0.9% Sodium Chloride injection.

2. Add the statement "Vial for single use only. Discard unused portion" to the side panel after the stability statement.

Container Label and Carton Labeling (150 mg)

1. Delete the descriptive title (b) (4) [redacted] because it is misleading. (b) (4) [redacted]

Please review the PPI changes and container/carton labeling comments. Provide a response with your acceptance and/or proposed revisions by close of business Tuesday, July 28, 2010.

Additionally, you will be responsible for the following required postmarketing studies under the Pediatric Research Equity Act (PREA). Upon review of the required pediatric studies, submit to your supplemental NDA a timetable identifying the following milestone dates for each study: **Final Protocol Submission Date, Study Completion**

Date, and the Final Study Report Submission Date.

1. A PK/PD study to characterize aprepitant PK parameters following administration of a single dose of intravenous fosaprepitant, in combination with a 5HT3 antagonist and dexamethasone, in pediatric cancer patients ages 0 to 17 years undergoing treatment with highly and moderately emetogenic chemotherapy.
2. An adequate, placebo-controlled, double-blind, randomized, add-on design, superiority study to evaluate the safety and efficacy of a single dose of intravenous fosaprepitant, in combination with a 5HT3 antagonist, as compared to standard therapy (a 5HT3 antagonist) in pediatric cancer patients ages 0 to 17 years undergoing treatment with highly and moderately emetogenic chemotherapy.

I can be reached through email or at the below phone number with any questions. Thank you.

Jagjit Grewal, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846
Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

JAGJIT S GREWAL
07/23/2010

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Wednesday, July 14, 2010 4:51 PM
To: 'Andrew, Nicholas W.'
Cc: Grewal, Jagjit
Subject: NDA 022023/S-004 EMEND (fosaprepitant) for Injection - FDA proposed PI revisions
Importance: High
Attachments: N022023-S004 EMEND (fosaprepitant) - FDA revisions 7.14.10.doc

Hello Nick,

Reference is made to you supplemental application dated October 12, 2009 for NDA 022023/S-004 EMEND (fosaprepitant dimeglumine) for Injection. Please find attached an annotated WORD document containing the FDA's revisions to your proposed package insert label.

Please review the noted changes and respond with your acceptance and/or proposed changes. Additionally, please acknowledge receipt of this correspondence.

I can be reached at the below phone number or through email with any questions. Thank you.

Jagjit Grewal, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846
Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

JAGJIT S GREWAL
07/14/2010

MEMORANDUM OF TELECON

DATE: June 17, 2009; 11:15AM EST

APPLICATION NUMBER: IND 48,924 EMEND (fosaprepitant dimeglumine) for Injection

BETWEEN:

Name:	Nick Andrew	Associate Director, Regulatory Affairs
	Charlotte Merritt	Senior Director, Regulatory Affairs
	Alexandra Carides	Associate Director, BioStatistics
	Dr. Ivan Chan	Senior Director, BioStatistics
	Dr. Stuart Green	Senior Director, Clinical Research

Phone: (877) 423-2663
Representing: Merck & Company, Inc.

AND

Name: Donna Griebel, M.D., Director
Anne Pariser, M.D., Acting Deputy Director
Nancy Snow, D.O., Medical Team Leader
John Troiani, M.D., Ph.D., Medical Reviewer
Michael Welch, Ph.D., Statistical Team Leader
Wen Jen Chen, Ph.D., Statistical Reviewer
Jagjit Grewal, M.P.H., Regulatory Project Manager
Division of Gastroenterology Products, HFD-180

SUBJECT: Discussion on sponsor's proposed Statistical Methods in support of Protocol 017

Reference is made to Merck's protocol amendment to Protocol 017 "*A Phase III, Randomized, Double-Blind, Active-Controlled, Parallel-Group Study, Conducted Under In-House Blinding Conditions, to Examine the Safety, Tolerability, and Efficacy of a Single Dose of Intravenous MK-0517 for the Prevention of CINV Associated With Cisplatin Chemotherapy*," dated November 18, 2008. On March 2, 2009, FDA provided comments and requests for additional information on the sponsor's proposed statistical analysis plan. Additional reference is made to Merck's response dated April 10, 2009 and the FDA letter dated May 28, 2009 providing additional comments on the sponsor's statistical methods.

On June 3, 2009, Merck requested a teleconference to obtain clarification on the FDA comments regarding the sponsor's statistical methods for P017. Merck noted that the study has completed and they plan to unblind the study by the end of June 2009. P017 is a non-inferiority study comparing the currently approved 3 day oral aprepitant regimen to a single I.V. dose of fosaprepitant.

Merck provided the meeting background package on June 12, 2009. In an email dated June 16, 2009, Merck noted that they were changing the number of strata in the M-N calculation of the

95% confidence interval to include only 1 stratified factor (gender) rather than the 3 initially proposed (see attached email dated 6/16/09).

6/17/09 Teleconference Discussion

Question #1a & 1b:

FDA began the teleconference by noting that agreements cannot be made regarding the sponsor's proposed statistical methods at this time as it is a review issue. Additionally, FDA stated that the sponsor's proposed methods are unconventional and have not been established. The simulation results presented in the referenced article from Merck's background package does not provide theoretical proof of the proposed methodology. FDA indicated that simulations cannot cover every situation, but rather look at a specific configuration. FDA also expressed concern that the sample size needed for Z_w to be standard normal distribution is not known.

FDA recommended the sponsor use a more conventional approach, referenced in an article by Koch et al., to compute the two-sided 95% confidence intervals for the primary efficacy analysis. FDA agreed to provide Merck with the referenced article by Koch et al.

Merck stated that they have used the same proposed methodology with their vaccine products. Prior to the teleconference, FDA discussed this with the statistical reviewers from the Division of Anti-Viral Products, and their comments are consistent with the Division of Gastroenterology Product's advice. FDA indicated that Merck may use their proposed statistical methodology, but the methodology referenced by FDA is preferred.

Merck proposed to use the FDA recommended methodology as a secondary analysis and retain their proposed method as the primary analysis. FDA did not agree. FDA also expressed that in order for the proposed indication to be supported by substantial evidence, both Merck's proposed methods and FDA recommended methods should demonstrate positive results in favor of the study drug (a single I.V. dose of fosaprepitant).

FDA acknowledged Merck's plan to decrease the number of stratification levels and informed Merck that the change should be incorporated in the clinical study report. Merck agreed and noted that the primary analysis will only be adjusted for gender.

Question #2:

FDA clarified that if any one stratum has a proportion less than -0.07 then Merck must conduct a qualitative interaction test. Merck agreed.

FDA also noted that since there is only a single study, strong study results for the primary and secondary endpoints are needed.

Merck expects to submit the supplemental NDA by mid-October 2009.

Post-Teleconference Action

In an email correspondence to Merck dated 6/19/09 (see attached), FDA provided the recommended formulae to compute the two-sided 95% confidence interval and the referenced article by Koch et al.

Jagjit Grewal
Regulatory Project Manager

Grewal, Jagjit

From: Andrew, Nicholas W. [nicholas_andrew@merck.com]
Sent: Tuesday, June 16, 2009 10:15 AM
To: Grewal, Jagjit
Subject: IND 48,924

Jagjit,
As referenced in my MVX, we have reviewed the blinded data through medical monitoring during the course of the study. At this point the blinded data is complete and undergoing cleaning in preparation for the unblinding. We have reviewed the completed data in the last couple of days and it revealed that we have very few patients in one of the levels of the region stratum and also in one level of the additional chemotherapy stratum. In light of this blinded review we are changing the number of relevant strata in the M-N calculation of the 95% CI to include only 1 stratum: gender rather than the 3 stratum proposed in the background package. We are providing this information to assist FDA in preparing for tomorrows meeting and look forward to a dialog on the statistical methods Merck plans on employing in this study.

Please let me know if any additional information is needed at this time.

Kind Regards,
Nick

Worldwide Regulatory Affairs
Merck Research Laboratories
Phone 732-594-5585
Fax 908-594-4980

Grewal, Jagjit

From: Grewal, Jagjit
Sent: Friday, June 19, 2009 12:23 PM
To: 'Andrew, Nicholas W.'
Cc: Grewal, Jagjit
Subject: IND 48,924 Emend (fosaprepitant) I.V. - follow up to 6/17/09 tcon
Attachments: I48,924 - CMHWeightAnalysis.doc

Hello Nick,

Per discussion at the 6/17/09 teleconference, please see the attached document containing information on FDA's recommended statistical analysis and the reference that FDA agreed to provide. I can be reached through email or at the below phone number with any questions. Thank you.

Jagjit Grewal, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODE III
Food & Drug Administration

Phone: (301) 796-0846
Fax: (301) 796-9905
Email: Jagjit.Grewal@fda.hhs.gov

Reference for Merck

The division would use different formulae to compute two-sided 95% confidence intervals for the primary efficacy analysis. The calculation of the difference of proportions and its confidence intervals is based on stratum-adjusted Mantel-Haenszel (CMH) proportions. This difference is weighted by the harmonic mean of sample size per arm for each stratum. Mathematically, if n_{1h} and n_{2h} are the sample sizes of the two comparison arms 1 and 2 in stratum h, then the weight

$$w_h = \frac{n_{1h} n_{2h}}{n_{1h} + n_{2h}}$$

is used for stratum h in calculating the overall difference.

Let $d_h = p_{1h} - p_{2h}$ be the difference in the proportion of complete response in the overall phase (CR) of arm 1 (Fosaprepitant) and arm 2 (Active control) in stratum h, then the stratum-adjusted CMH proportion is

$$d = \frac{\sum w_h d_h}{\sum w_h}.$$

Its continuity-corrected variance Var(d) can be estimated by

$$\frac{\sum w_h^2 \left(\frac{p^*_{1h}(1-p^*_{1h})}{n_{1h}-1} + \frac{p^*_{2h}(1-p^*_{2h})}{n_{2h}-1}\right)}{(\sum w_h)^2}$$

where $p^*_{1h} = \frac{m_{1h}+0.5}{n_{1h}+1}$ and $p^*_{2h} = \frac{m_{2h}+0.5}{n_{2h}+1}$ and m_{1h} and m_{2h} are the number of CR in treatment groups 1 and 2.

Note: In Koch et al, the variance, Var(d), is estimated to be

$$\frac{\sum w_h^2 \left(\frac{p_{1h}(1-p_{1h})}{n_{1h}-1} + \frac{p_{2h}(1-p_{2h})}{n_{2h}-1}\right)}{(\sum w_h)^2}$$

where $p_{1h} = \frac{m_{1h}}{n_{1h}}$ and $p_{2h} = \frac{m_{2h}}{n_{2h}}$.

Then, use $\mathbf{Z = (d - \delta) / (\sqrt{Var(d)})}$ to calculate the two-sided 95% CI; here, $\boldsymbol{\delta = E(d)}$.

Reference:

Koch, G.G., Carr, G.J., Amara, I.A., Stokes, M.E.. and Uryniak, T.J. (1989). Categorical Data Analysis. Chapter 13 in Berry, D.A. (ed.), Statistical Methodology in the Pharmaceutical Sciences, Marcel Dekker, New York, pp. 414-421.

Linked Applications	Sponsor Name	Drug Name / Subject
IND 48924	MERCK AND CO INC	FOSAPREPITANT DIMEGLUMINE

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/s/

JAGJIT S GREWAL
06/24/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022023/S-004 **INFORMATION REQUEST**

Merck Sharp & Dohme Corp.
Attention: Nicholas Andrew
Associate Director, Regulatory Affairs
126 East Lincoln Avenue
P.O. Box 2000, RY 33-200
Rahway, NJ 07065-0900

Dear Mr. Andrew:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EMEND (fosaprepitant dimeglumine) for Injection, 150 mg.

We are reviewing the Clinical and Chemistry sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental application.

1. As noted in your Protocol 017L1 study report, severe infusion-site reactions and infusion site related thrombophlebitis were classified as events of clinical interest and their incidences demonstrated in Table 12-17, page 160 of the study report. Please provide an additional incidence table similar to Table 12-17 which includes all infusion site related adverse events regardless of severity.

2. The proposed 24 hour post-dilution hold period at room temperature for the 150 mg and 115 mg dose forms of fosaprepitant dimeglumine injection poses a risk to microbiology quality. Please provide a justification for the proposed hold time or indicate a post constitution hold time of 4 hours at room temperature. If available include data from microbiology stability studies.

If you have questions, call Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

BRIAN K STRONGIN
06/03/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022023/S-004

GENERAL ADVICE

Merck Sharp & Dohme Corp.
Attention: Nicholas Andrew
Associate Director, Regulatory Affairs
126 East Lincoln Avenue
P.O. Box 2000, RY 33-200
Rahway, NJ 07065-0900

Dear Mr. Andrew:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EMEND (fosaprepitant dimeglumine) for Injection, 150 mg.

We also refer to your January 8, 2010 submission, requesting a waiver of the 4-month safety update as there are no additional non-clinical or clinical studies information that would impact the safety data provided with this supplemental application.

We have reviewed the referenced material and have the following comment.

1. We agree with your request and waive the requirement to submit a 4-month safety update for this supplemental application.

If you have questions, call Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

JOYCE A KORVICK
02/09/2010

DSI CONSULT: Request for Clinical Inspections

Date: December 24, 2009

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Tamara Johnson, M.D./Clinical Reviewer/HFD-180
Nancy Snow, M.D./Clinical Team Leader/HFD-180
Donna Griebel, M.D./Division Director/HFD-180
Division of Gastroenterology Products HFD-180

From: Jagjit Grewal, Regulatory Project Manager/DGP/HFD-180

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 022023/S-004
Applicant/Applicant contact information (to include phone/email):

Merck Sharp & Dohme Corp.
Nicholas Andrew
Associate Director, Regulatory Affairs
126 East Lincoln Avenue
P.O. Box 2000, RY 33-200
Rahway, NJ 07065-0900
Email: nicholas_andrew@merck.com
Phone: 732-594-5585
Fax: 732-594-4980

Drug Proprietary Name: EMEND (fosaprepitant dimeglumine) for Injection, 150 mg
NME or Original BLA (Yes/No): No
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Dosing Regimen: A single intravenous dose of EMEND (fosaprepitant dimeglumine) for Injection 150 mg, dosed concomitantly with a 5HT-3 receptor antagonist and a corticosteroid, for the prevention of chemotherapy-induced nausea and vomiting (CINV).

PDUFA: August 13, 2010
Action Goal Date: August 13, 2010
Inspection Summary Goal Date: July 1, 2010

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
(b) (4)			

III. Site Selection/Rationale

The sites were selected on the basis that the Complete Response rate (primary endpoint) for the study regimen appears to be unusually high or much higher than that of the control regimen.

Domestic Inspections:

Reasons for inspections (please check all that apply):

____ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
__X__ Other (specify): These three sites are selected for inspection because the primary endpoint, proportion of patients with complete response, for the treatment group was unusually high (site (b) (4) or much higher when compared to the control group. The site numbers and associated complete response rates are listed below:

Site number	Complete Response rate	
	Fosaprepitant	Aprepitant (Control)
(b) (4)		

Enrollment at domestic sites was much lower in numbers, making the much lower response rate at domestic sites difficult to interpret relative to these specific foreign sites.

IV. Tables of Specific Data to be Verified (if applicable)

N/A

Should you require any additional information, please contact *Jagjit Grewal (RPM)* at *301-796-0846* or *Dr. Tamara Johnson (MO)* at *301-796-1522*.

Concurrence: (as needed)

_Dr. Nancy Snow 12-18-09___ Medical Team Leader
_Dr. Tamara Johnson 12-18-09 Medical Reviewer
_Dr. Donna Griebel 12-24-09 _ Division Director (for foreign inspection requests or requests for 5 or more sites only)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

JAGJIT S GREWAL
12/25/2009

DONNA J GRIEBEL
12/28/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022023/S-004 **FILING COMMUNICATION**

Merck Sharp & Dohme Corp.
Attention: Nicholas Andrew
Associate Director, Regulatory Affairs
126 East Lincoln Avenue
P.O. Box 2000, RY 33-200
Rahway, NJ 07065-0900

Dear Mr. Andrew:

Please refer to your October 12, 2009 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EMEND (fosaprepitant dimeglumine) for Injection, 150 mg.

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Standard**. Therefore, the user fee goal date is August 13, 2010.

We are reviewing your supplemental application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by July 2, 2010.

During our filing review of your supplemental application, we identified the following potential review issue:

1. You have submitted one pivotal trial in support of your supplemental application, although the Agency generally prefers two adequate and well-controlled trials. The results of your single pivotal trial must be robust to support the proposed new dosing regimen.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the supplemental application.

We also request that you submit the following information:

Clinical:

1. Submit a rationale for assuming the applicability of foreign data to the U.S. population and U.S. practice of medicine. You must address the potential effects of regional differences (e.g. medical practice, follow-up of patients, incidence of adverse events, coding and verbatim practices in reporting of adverse events) that may influence the drug's efficacy and safety. Supportive evidence (i.e. tables, figures) should be included. Please see ICH guidance "*E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data*" and the related "*Guidance for Industry: E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data – Questions and Answers*."
2. If you are referencing the original approval of NDA 022023 for additional safety patient exposures to doses ≥ 150 mg in phase 1, safety data from phase 1 subjects should be summarized in a Clinical Summary or Integrated Summary of Safety.
3. We are unable to locate the coding dictionary. Please submit or clarify the location.

Statistical:

4. The SAS program m0resp0exp.sas was not found in the datasets for the non-inferiority study PN 017 located within module 5.3.5.1 under study P017L1. Please provide the dataset in electronic format consistent with "*Guidance for Industry: Providing Regulatory Submissions in Electronic Format – General Considerations*." It is suggested that the following variables be included:
   a. Study number
   b. Investigator or Site Number
   c. Country Name
   d. Region
   e. Unique Subject Identifier (USUBJID in your submitted data sets)
   f. Subject Identifier for the study (SUBJID in your submitted data sets)
   g. Actual Treatment Group (TRTA in your submitted data sets)
   h. Planned Treatment Group (TRTP in your submitted data sets)
   i. Treated population (Y for yes; N for no)
   j. Full analysis set population (Y for yes; N for no)
   k. Per-protocol populations (Y for yes; N for no)
   l. Use of concomitant chemotherapy (Y for yes; N for no)
   m. Missing indicator (Y for missing data; N for data not missing)
   n. Gender
   o. Age
   p. Race

q. Phase
r. Complete Response in overall phase (success or failure)
s. Complete Response in acute phase (success or failure)
t. Complete Response in delayed phase (success or failure)
u. No Vomiting in overall phase (success or failure)
v. No Vomiting in acute phase (success or failure)
w. No Vomiting in delayed phase (success or failure)
x. No use of Rescue Therapy in overall phase (success or failure)
y. No use of Rescue Therapy in acute phase (success or failure)
z. No use of Rescue Therapy in delayed phase (success or failure)
aa. No Impact of CINV on Daily Life assessed by total score/average item score (yes or no)
bb. No Significant Nausea in overall phase (success or failure)
cc. No Significant Nausea in acute phase (success or failure)
dd. No Significant Nausea in delayed phase (success or failure)
ee. No Nausea in overall phase (success or failure)
ff. No Nausea in acute phase (success or failure)
gg. No Nausea in delayed phase (success or failure)
hh. Time to first vomiting episode in the overall phase
ii. Complete Protection in overall phase (success or failure)
jj. Complete Protection in acute phase (success or failure)
kk. Complete Protection in delayed phase (success or failure)

5. Modify your submitted program s11t3.sas (used to create Table 11-3) to include m0resp0exp.sas as one SAS program and to allow the input of data from the dataset described above in #4. If necessary, add additional variables to the dataset described by #4 so that the modified SAS program can create Table 11-3.

6. Submit the program utilizing the statistical methodology recommended by the Agency for the primary endpoint analysis.

Pediatrics:

7. Please revise your proposed pediatric plan to address the following:
    a. Population in which the study will be performed
    b. Number of patients to be studied or power of study to be achieved
    c. Entry criteria
    d. Clinical endpoints
    e. Timing of assessments
    f. Statistical analysis of the data to be performed

8. Per 21 CFR 314.55(c)(3), provide a justification for your request to waive pediatric studies for ages birth to < 6 months.

Labeling:

9. Submit your proposed labeling in Physician Labeling Rule (PLR) format.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff Division of
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

BRIAN K STRONGIN
12/18/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022023/S-004 **INFORMATION REQUEST**

Merck Sharp & Dohme Corp.
Attention: Nicholas Andrew
Associate Director, Regulatory Affairs
126 East Lincoln Avenue
P.O. Box 2000, RY 33-200
Rahway, NJ 07065-0900

Dear Mr. Andrew:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EMEND (fosaprepitant dimeglumine) for Injection, 150 mg.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental application.

For study P017L1, provide a table of all study centers with site ID numbers as referenced in your statistical datasets, number of patients enrolled at each study site, and associated investigator information for each study site to include:

a. investigator name
b. site address
c. phone number
d. fax number
e. email address

If you have questions, call Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

BRIAN K STRONGIN
12/15/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Division of Drug Marketing, Advertising, & Communications (DDMAC)
Attn: Wayne Amchin
6-0421

FROM:
Jagjit Grewal, RPM 6-0846
WO22, RM 5109
Division of Gastroenterology Products (DGP); HFD-180

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
December 7, 2009		N022023/S-004	supplemental NDA – SE2	October 12, 2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
EMEND (fosaprepitant dimeglumine) for Injection	moderate	Antiemetic	June 14, 2010

NAME OF FIRM: Merck Sharp & 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 II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☒ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

- ☐ PHASE IV 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
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

DGP has received an efficacy supplement for **NDA 022023/S-004 EMEND (fosaprepitant dimeglumine) for Injection, 150 mg**. With this supplement, Merck is proposing a new dosing regimen (SE2) for a single intravenous dose of fosaprepitant 150 mg, dosed concomitantly with a 5HT3 receptor antagonist and corticosteroid, for the prevention of chemotherapy-induced nausea and vomiting (CINV). Merck is proposing this new single day dosing regimen as an alternative to the currently approved 3-day oral aprepitant capsule regimen (Day 1: 125 mg capsule; Days 2 & 3: 80 mg capsule).

EMEND (fosaprepitant dimeglumine) for Injection was originally approved on 1/25/08 for the prevention of CINV [highly emetogenic (CINV-HEC) & moderately emetogenic chemotherapies (CINV-MEC)]. The currently approved I.V dosing regimen for both CINV-HEC & CINV-MEC is:

Day 1: fosaprepitant I.V 115 mg
Days 2 & 3: aprepitant capsule 80 mg

This sNDA proposes changes to both the PI and PPI labeling for EMEND (fosaprepitant dimeglumine) for Injection. The sponsor has also proposed new carton/container labeling for the fosaprepitant I.V. 150 mg product and changes to the approved carton/container labeling for the fosaprepitant I.V. 115 mg product to differentiate between the two dosage strengths.

Please note that the sponsor's proposed PI labeling is not in PLR format. They will be requested to resubmit their proposed labeling in PLR format with the 74-day filing communication letter.

The submission is in eCTD format and can be found at the following link.
Global Submit Review (sequence #0044; dated 10/12/09): \\CDSESUB1\EVSPROD\NDA022023\022023.enx

DGP requests that DDMAC's assistance in review of the sponsor's proposed labeling. The goal date for communicating labeling revisions to the sponsor is July 2, 2010. The PDUFA date for this application is **AUGUST 13, 2010**.

Medical Officer: Tamara Johnson
Medical Team Leader: Nancy Snow

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Jagjit Grewal; 6-0846	☐ MAIL ☐ HAND ☒ DARRTS ☒ EMAIL
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER
	N/A

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

JAGJIT S GREWAL
12/07/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE
Nitin Patel; 6-5412
Project Manager

FROM:
Jagjit Grewal, RPM 6-0846
WO22, RM 5109
Division of Gastroenterology Products (DGP); HFD-180

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
December 7, 2009		N022023/S-004	supplemental NDA – SE2	October 12, 2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
EMEND (fosaprepitant dimeglumine) for Injection	moderate	Antiemetic	June 14, 2010

NAME OF FIRM: Merck Sharp & 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 II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
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- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☒ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

- ☐ PHASE IV 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
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

DGP has received an efficacy supplement for **NDA 022023/S-004 EMEND (fosaprepitant dimeglumine) for Injection, 150 mg**. With this supplement, Merck is proposing a new dosing regimen (SE2) for a single intravenous dose of fosaprepitant 150 mg, dosed concomitantly with a 5HT3 receptor antagonist and corticosteroid, for the prevention of chemotherapy-induced nausea and vomiting (CINV). Merck is proposing this new single day dosing regimen as an alternative to the currently approved 3-day oral aprepitant capsule regimen (Day 1: 125 mg capsule; Days 2 & 3: 80 mg capsule).

EMEND (fosaprepitant dimeglumine) for Injection was originally approved on 1/25/08 for the prevention of CINV [highly emetogenic (CINV-HEC) & moderately emetogenic chemotherapies (CINV-MEC)]. The currently approved I.V dosing regimen for both CINV-HEC & CINV-MEC is:

Day 1: fosaprepitant I.V 115 mg
Days 2 & 3: aprepitant capsule 80 mg

This sNDA proposes changes to both the PI and PPI labeling for EMEND (fosaprepitant dimeglumine) for Injection. The sponsor has also proposed new carton/container labeling for the fosaprepitant I.V. 150 mg product and changes to the approved carton/container labeling for the fosaprepitant I.V. 115 mg product to differentiate between the two dosage strengths. Additionally, the sponsor has submitted a Risk Management Plan (eCTD module 1.16).

Please note that the sponsor's proposed PI labeling is not in PLR format. They will be requested to resubmit their proposed labeling in PLR format with the 74-day filing communication letter.

The submission is in eCTD format and can be found at the following link.
Global Submit Review (sequence #0044; dated 10/12/09): \\CDSESUB1\EVSPROD\NDA022023\022023.enx

DGP requests that OSE's assistance in review of the sponsor's proposed labeling. The goal date for communicating labeling revisions to the sponsor is July 2, 2010. The PDUFA date for this application is **AUGUST 13, 2010**.

Medical Officer: Tamara Johnson
Medical Team Leader: Nancy Snow

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Jagjit Grewal; 6-0846	☐ MAIL ☐ HAND ☒ DARRTS ☒ EMAIL
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER
	N/A

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

JAGJIT S GREWAL
12/07/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022023/S-004 **PRIOR APPROVAL SUPPLEMENT**

Merck & Co., Inc.
Attention: Nicholas Andrew
Associate Director, Regulatory Affairs
126 East Lincoln Avenue
P.O. Box 2000, RY 33-200
Rahway, NJ 07065-0900

Dear Mr. Andrew:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	EMEND (fosaprepitant dimeglumine) for Injection
NDA Number:	022023
Supplement number:	004
Review Priority Classification:	Standard (S)
Date of supplement:	October 12, 2009
Date of receipt:	October 13, 2009

This supplemental application proposes the following change:

- A new dosing regimen for the use of a single intravenous dose of fosaprepitant 150 mg, dosed concomitantly with a 5HT3 receptor antagonist and a corticosteroid, for the prevention of chemotherapy induced nausea and vomiting.

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 December 12, 2009 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 13, 2010.

Please 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 Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have questions, call me at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Jagjit Grewal, M.P.H.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

JAGJIT S GREWAL
11/10/2009

The Division of Gastroenterology Products has determined that NDA 22-023/S-004 is a prior approval efficacy supplement.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22023	SUPPL-4	MERCK AND CO INC	EMEND FOR INJECTION

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/s/

JAGJIT S GREWAL
11/10/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND #48,924

Merck & Co., Inc.
Attn: Vijay K. Tammara, Ph.D.
Director, Regulatory Affairs
P.O. Box 1000, UG2CD-48
North Wales, PA 19454-1099

Dear Vijay Tammara:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-0517.

We also refer to the meeting between representatives of your firm and the FDA on April 19, 2007. The purpose of this meeting was to provide feedback regarding unresolved issues following our January 11, 2007 meeting. Specifically, an approach to selection of the non-inferiority margin based on confidence interval, adjustment of the dexamethasone dose on days 2 ad 3 of the study, and the adequacy of a single study to support registration of MK-0517 (fosaprepitant) single-dose I.V. regimen as an alternative to the 3-day regimen of EMEND.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0980.

Sincerely,

{See appended electronic signature page}

Giuseppe Randazzo
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

...minutes of the meeting are enclosed. You are responsible for notifying...

Enclosure

FOOD AND DRUG ADMINISTRATION

Meeting Date and Time:	April 19, 2007
Meeting Type:	C – Face-to-Face
Meeting Category:	Other
Meeting Location:	FDA/CDER White Oak Building #22 10903 New Hampshire Ave. Silver Spring, MD 20993
Application Number:	I 48,924
Product Name:	MK-0517 (Emend)
Received Briefing Package	March 19, 2007
Sponsor Name:	Merck & Co., Inc.
Meeting Requestor:	Vijay Tammara
Meeting Chair:	Dr. Hugo Gallo-Torres
Meeting Recorder:	Giuseppe Randazzo

Meeting Attendees:

FDA Attendees:

Joyce Korvick, M.D. M.P.H., Division of Gastroenterology Products (DGP)
Hugo Gallo-Torres, M.D., Ph.D., P.N.S., Gastrointestinal Medical Team Leader (DGP)
Wen-Yi Gao, M.D., Ph.D. Medical Reviewer (DGP)
Sue-Chih Lee, Ph.D., Clinical Biopharm Reviewer
Sushanta Chakder, Ph.D., Pharmacologist Reviewer (DGP)
Wen-Jen Chen, Ph.D., Statistical Reviewer
Mike Welch, Ph.D., Acting Statistical Team Leader
Giuseppe Randazzo, Regulatory Project Manager (DGP)

External Attendees

Joe Arena, Ph.D.	Executive Director, Regulatory Affairs
Alexandria Carides, Ph.D.,	Associate Director, Clinical Biostatistics
Betsy Fallen	Senior Regulatory Manager, Regulatory Affairs
Stuart Green, M.D.,	Senior Director, Clinical Research
Robert Lupinacci, Ph.D.,	Associate Director, Clinical Biostatistics
Gail Murphy, M.D.,	Executive Director, Clinical Pharmacology
Craig Shadle,	Senior Associate, Clinical Pharmacology
Vijay Tammara, Ph.D.,	Director, Regulatory Affairs
Robert Tipping, Ph.D.,	Senior Director, Clinical Biostatistics
Jack Valentine, Ph.D.,	Research Fellow, Drug Metabolism and PK

1.0 BACKGROUND

On October 30, 2007 we received a meeting request from Merck and Co. asking for FDA guidance on a proposal to conduct a study to support a single dose of MK-0517 as an alternative to the approved oral 3-day regimen of Emend™. On January 11, 2007 a meeting was held to discuss if one single dose I.V study is adequate to support an I.V. formulation as an alternative to EMEND 3-day regimen, as well as discuss the proposed study design, dose, and non-inferiority margin. At this meeting it was agreed the sponsor would submit additional rationale with a data analysis plan to justify the non-inferiority margin and the single study.

This meeting was a follow up to the January 11, 2007 meeting to discus an approach to selection of the non-inferiority margin based on confidence interval, adjustment of the dexamethasone dose on days 2 ad 3 of the study, and the adequacy of a single study.

2.0 DISCUSSION

Proposed questions:
MR is planning to conduct a single, randomized, non-inferiority clinical study to demonstrate that the safety and efficacy of MK-0517 (fosaprepitant 150 mg) as a single dose IV regimen given on day 1 is equivalent to the safety and efficacy of the approved regimen of EMEND (a 3-day regimen with a single 125-mg oral dose given on day 1 followed by 80-mg dose each on days 2 and 3) for the prevention of chemotherapy induced nausea and vomiting (CINV). Both the single-dose IV regimen of MK0517 and 3-day oral regimen of EMEND would include concomitant administration of a 5HT3 antagonist and dexamethasone. Based on this information, in conjunction with the safety and efficacy data derived from Phase II clinical trials of MK-0517 (incorporated in the original NDA for EMEND for Injection [22,023]), and the efficacy and safety data from the pivotal studies in CINV patients using the approved EMEND oral capsule, MRL believes there will be adequate evidence for the efficacy and safety of MK-0517 to support registration of the single-dose IV fosaprepitant 150 mg regimen as an alternative to the approved 3-day oral regimen of EMEND in CINV patients.

1. Does the Agency concur with the concept and that one single dose IV study is adequate to support the registration of an IV formulation as an alterative to EMEND 3-day regimen and the proposed study design, and non-inferiority margin?

Response: **No. We do not agree with the proposal to use one single intravenous dose study to support the registration as an alternative to the 3-day regimen for the following reasons:**

1. **Fosaprepitant (100 mg) alone was significantly less effective (35.1% vs. 82.8%) than the standard therapy of ondansetron (32 mg, I.V.) in preventing acute phase emesis post-cisplatin (≥70 mg/m^2) administration (Study P007L1).**

2. **In the same study, the single dose fosaprepitant regimen was numerically but not statistically more effective in the treatment of delayed phase emesis than the standard therapy (44.6% vs. 37.9%).**

3. **The single dose regimen was significantly less effective (44.6% vs. 59.3%) than the combination regimen of fosaprepitant (Day 1) and aprepitant (Days 2 to 5) in the treatment of delayed emesis.**

4. **Increasing the fosaprepitant dose level from 115 mg to 150 mg may not improve the efficacy against CINV. This is because previous Phase II studies showed a plateau of efficacy of 125 mg aprepitant in the treatment of CINV. The dose level of 125 mg aprepitant is equivalent to 115 mg fosaprepitant.**

   In addition, Study P041 concluded that no additional efficacy was expected from a higher C_{max} with fosaprepitant.

5. **Because the safety of 150 mg fosaprepitant of the proposed market formulation has only been evaluated in 10 healthy adults to date, it is not known if increasing fosaprepitant dose level to 150 mg may bring about potential safety issues. The plasma level at the end of a 15-min infusion of 115 mg fosaprepitant was significantly higher than the oral aprepitant 125 mg (5800 ng/mL vs. 3095 ng/mL). We believe that the safety of 150 mg fosaprepitant should be evaluated prior and during the Phase III trial.**

We recommend that the effect of single-dose (150 mg) I.V. fosaprepitant plus dexamethasone plus a 5-HT3 antagonist (the proposed fosaprepitant regimen) be evaluated in comparison with the approved 3-day oral aprepitant regimen (Emend™) to show equivalence between these two regimens so that one can substitute for the other.

Because the safety information with fosaprepitant is limited, we recommend you conduct 2 adequate and well controlled Phase 3 trials. [See also the statistical recommendations under 2.2) Single Study, below].

Additional discussion questions:

2. Selection of the non-inferiority margin based on the confidence interval approach and adequacy of a single study.

Response: **Based upon your proposed study design and non-inferiority margin, we have the following comments regarding 1) non-inferiority margin, 2) single study, and 3) multiplicity adjustment:**

1) Non-Inferiority Margin

You propose a non-inferiority (NI) margin of 0.08 derived by preserving 50% of the lower bound of the 80% confidence interval (CI) for the true difference between the two treatment regimens (aprepitant regimen and standard therapy). Your assumed efficacy of the active control is based on a pooled analysis of Studies 052 and 054.

We recommend your NI calculation account for study-to-study variability with a meta-analytic method employing a random effects model and preserve 50% of the lower bound of the 95% CI. This would yield of NI margin of 0.07.

2) Single Study

Data regarding the efficacy of your proposed fosaprepitant I.V. regimen versus that of standard therapy or versus that of the aprepitant regimen proposed in the IND submission can not be found in the NDA 22023 submission. Accordingly, that submission would not provide supportive efficacy data for the fosaprepitant I.V. regimen planned in this IND submission.

As stated in our January 11, 2007 meeting minutes, we recommend you conduct two, well-controlled Phase 3 trials in order to provide substantial evidence to support the study drug fosaprepitant I.V. regimen for use in the proposed indication.

3) Multiplicity Adjustment

As commented at the January 11, 2007 meeting, if you intend to claim effectiveness of the study drug fosaprepitant I.V. regimen for both acute and delayed phases, you should propose a suitable Type I error adjustment method for these multiple endpoints.

If your proposed secondary and exploratory endpoints are to be included in your labeling, we also recommend that you address multiplicity adjustment methods for these additional endpoints. The adjustment techniques should control for Type I error in the strong sense.

3. Selection of the dexamethasone dose on Days 2, 3 and 4 based on modeling and Drug Interaction Information.

Response: **Your modeling and simulation (M/S) appears to be a reasonable first step for determining the dexamethasone dose when fosaprepitant is coadministered.**

However, M/S involves assumptions and can lead to deviations from the true value. As such, we recommend you conduct a study to demonstrate that the predicted dose for patients taking concomitant fosaprepitant will result in similar dexamethasone concentrations compared to those observed in patients who are not on concomitant fosaprepitant.

Additional comments: In your background package you submitted a "Core Protocol." We recommend you submit a complete protocol with detailed statistical and analytical plans for review.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

N/A

4.0 ACTION ITEMS

Please read dialogue above in the **DISCUSSION** section.

5.0 ATTACHMENTS AND HANDOUTS

N/A

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

/s/

Hugo Gallo Torres
5/10/2007 10:48:44 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND #48,924

Merck & Co., Inc.
Attn: Vijay K. Tammara, Ph.D.
Director, Regulatory Affairs
P.O. Box 1000, UG2CD-48
North Wales, PA 19454-1099

Dear Vijay Tammara:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-0517.

We also refer to the meeting between representatives of your firm and the FDA on January 11, 2007. The purpose of this meeting was to provide feedback regarding study design, dose selection, non-inferiority margin, and adequacy of single study to register MK-0517 as an alternative to the 3-day oral regimen of Emend.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0980.

Sincerely,

{See appended electronic signature page}

Giuseppe Randazzo
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

FOOD AND DRUG ADMINISTRATION

Meeting Date and Time:	January 11, 2007
Meeting Type:	C – Face-to-Face
Meeting Category:	Other
Meeting Location:	FDA/CDER White Oak Building #22 10903 New Hampshire Ave. Silver Spring, MD 20993
Application Number:	I 48,924
Product Name:	MK-0517 (Emend)
Received Briefing Package	December 19, 2006
Sponsor Name:	Merck & Co., Inc.
Meeting Requestor:	Vijay Tammara
Meeting Chair:	Dr. Hugo Gallo-Torres
Meeting Recorder:	Giuseppe Randazzo

Meeting Attendees:

FDA Attendees:

Joyce Korvick, M.D. M.P.H., Division of Gastroenterology Products (DGP)
Hugo Gallo-Torres, M.D., Ph.D., P.N.S., Gastrointestinal Medical Team Leader (DGP)
Wen-Yi Gao, M.D., Ph.D. Medical Reviewer (DGP)
Tapash Ghosh, Ph.D., Clinical Biopharm Active Team Leader
Sue-Chih Lee, Ph.D., Clinical Biopharm Reviewer
Sushanta Chakder, Ph.D., Pharmacologist Reviewer (DGP)
Wen-Jen Chen, Ph.D., Statistical Reviewer
Mike Welch, Ph.D., Acting Statistical Team Leader
Giuseppe Randazzo, Regulatory Project Manager (DGP)

External Attendees

Murray Abramson	Senior Director, Clinical Research
Joe Arena	Senior Director, Regulatory Affairs
Alexandria Carides	Associate Director, Clinical Biostatistics
Stuart Green	Senior Director, Clinical Research
James Kocsis	Senior Regulatory Coordinator Regulatory Affairs
Gail Murphy	Executive Director, Clinical Pharmacology
Craig Shadle	Senior Associate, Clinical Pharmacology
Vijay Tammara	Director, Regulatory Affairs
Robert Tipping	Director, Clinical Biostatistics
Yasrnine Wasfi	Associate Director, Clinical Research

1.0 BACKGROUND

On October 30, 2007 we received a meeting request from Merck and Co. asking for FDA guidance on a proposal to conduct a study to support a single dose of MK-0517 as an alternative to the approved oral 3-day regimen of Emend™.

2.0 DISCUSSION

Question 1: MRL is planning to conduct a single randomized, non-inferiority clinical study to demonstrate that the safety and efficacy of a single dose IV (150 mg) given on day 1 would be equivalent to the safety and efficacy of approved Emend regimen (a three day regimen with a single 125 mg oral dose given on day 1 followed by 80 mg dose each on days 2 and 3). Based on this information, in conjunction with the safety and efficacy data derived from Phase II clinical trials of MK-0517 (incorporated in the original NDA for EMEND for Injection [22,023], and the efficacy and safety data from the pivotal studies in CINV patients using the approved EMEND™ oral capsule, MRL believes there will be adequate evidence for the efficacy and safety of MK-0517 to support registration of a 150 mg IV dose of MK-0517 as an alternative to the EMEND 3-day regimen in CINV patients. Does the Agency concur with the concept and that one single dose IV study is adequate to support the registration of an IV formulation as an alternative to EMEND 3-day regimen, with the supporting data from MK-0517 Phase II studies and data from Pivotal studies with approved EMEND?

Does the Agency concur with the concept and that one single dose IV study is adequate to support the registration of an IV formulation as an alternative to EMEND 3-day regimen and the proposed study design, dose, and non-inferiority margin?

FDA Response for 01/11/2007 meeting:

Based upon the study design presented in the core protocol (protocol 017-00), the following three issues require comment: 1) non-inferiority margin selection, 2) multiplicity adjustment, and 3) single study.

1) Non-inferiority selection

In protocol 017-00, you did not provide the algorithm and data used to generate the non-inferiority margin of 0.66 for the odds ratio of standard therapy versus aprepitant regimen. In addition, from the supporting documents submitted and mentioned in Question 1 for the selected non-inferiority margin, it appears that only one historical NDA study (NDA 21-549/SE1-008) had a treatment arm similar to the active controlled arm (aprepitant regimen) proposed by protocol 017-00. In order to better understand the non-inferiority margin of 0.66 selected for the odds ratio of standard therapy versus aprepitant regimen, we request you provide the algorithm and data used to generate the non-inferiority margin of 0.66. Please follow guidance provided by ICH E10, *"Guidance for Industry, Choice of Control Group and Related Issues in Clinical Trials"*, to collect data from the historical studies used for the selection of the non-inferiority margin.

Following the guidance provided by ICH E10 regarding the selection of the non-inferiority margin, in order to address the issues of assay sensitivity and assay constancy, a conservative approach is recommended to generate the non-inferiority margin. The 97.5% upper confidence limit for the odds ratio of standard therapy versus active-controlled arm on the log scale is recommended to estimate the effectiveness of the active controlled arm (aprepitant regimen). Then, the non-inferiority margin is the anti-log value of half of the estimated effectiveness on the log scale. In addition, if you intend to claim effectiveness of the study drug fosaprepitant regimen for both acute and delayed phases, then the non-inferiority margins for both acute and delayed phases are required.

As an alternative to a non-inferiority approach, consider assessing the effectiveness of the fosaprepitant regimen using a superiority analysis to directly compare the efficacy of the fosaprepitant regimen versus the standard regimen.

> **Additional Discussion on 01/11/2007: The sponsor agreed to submit additional rational with a data analysis plan to justify the non-inferiority margin and the single study.**

2) Multiplicity adjustment

It is noted that only one primary efficacy analysis with respect to the proportion of patients with Complete Response in the 120 hours following initiation of chemotherapy is proposed in protocol 017-00. However, if you intend to claim effectiveness of the study drug fosaprepitant regimen for both acute and delayed phases, in order to control the overall Type I error rate, it is recommended you propose a multiplicity adjustment method to adjust for the multiple comparisons for the acute and delayed phases.

In addition, if more than one secondary endpoint is planned for the proposed phase III trial and you intend to include the results of the secondary endpoints to the

labeling package, it is recommended you propose a multiplicity adjustment method to control the Type I error rate for the secondary endpoints.

Additional Discussion on 01/11/2007: The sponsor proposes to detail their multiplicity adjustment in the protocol.

3) Single study

Typically, applicants need to conduct two adequate and well controlled phase III trials to demonstrate confirmation of positive trial results, in the sense that one study shows a significant efficacy result and the other study confirms the significant result. Accordingly, in order to provide substantial evidence to support the study drug (fosaprepitant regimen) for use in this indication, two well-controlled trials are recommended.

Please consider the following:

You stated that receptor occupancy of 80 % – 90 % is needed to demonstrate the antiemetic effect. However, the approved dosing regimen for oral aprepitant has trough concentrations much higher than (~ 7 times) the concentration needed for 90% receptor occupancy.

Compared to the approved oral regimen, the proposed single I.V. administration of fosaprepitant 150 mg over 15 minutes is associated with lower concentrations from approximately 30 hours onwards. It is unclear how this may affect the efficacy at your proposed dose.

Additional Discussion on 01/11/2007: The sponsor agreed to submit additional rational with a data analysis plan to justify the non-inferiority margin and the single study.

Question 2: An interaction study with Midazolam at the proposed dose of MK-0517 (150 mg) will be conducted to assess the potential for drug-drug interaction with CYP3A4 inhibitors. Does the Agency concur?

FDA Response for 01/11/2007 meeting:

The interaction study appears to be designed for evaluation of the degree of CYP3A4 inhibition by fosaprepitant at the proposed dose. For this purpose, the proposed fosaprepitant dose (150 mg) is acceptable if the final dose for the NDA submission does not go any higher than that. Additionally, if dexamethasone is to be coadministered, a drug interaction study with dexamethasone should also be conducted.

Additional Discussion on 01/11/2007: The sponsor agreed to submit the Midazolam drug-drug interaction data.

Regarding the dexamethasone dosing, the sponsor will provide rational including data or modeling to support their dose selection in days 2-4.

Additional comments for 01/11/2007 meeting:

Please clarify your proposed indication.

Additional Discussion on 01/11/2007: The sponsor clarified that the indication would remain the same as the original.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

N/A

4.0 ACTION ITEMS

Please read dialogue above in the **DISCUSSION** section.

5.0 ATTACHMENTS AND HANDOUTS

N/A

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

/s/

Hugo Gallo Torres
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