CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022023Orig1s017

Trade Name:	EMEND
Generic or Proper Name:	fosaprepitant
Sponsor:	Merck Sharp & Dohme
Approval Date:	April 3, 2018
Indication:	EMEND for injection is a substance P/neurokinin-1 (NK1) receptor antagonist, indicated in adults and pediatric patients 6 months of age and older, in combination with other antiemetic agents, for the prevention of : • acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin. • delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC). Limitations of Use • EMEND has not been studied for treatment of established nausea and vomiting.

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-017

SUPPLEMENT APPROVAL

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

Dear Mr. Andrew:

Please refer to your Supplemental New Drug Application (sNDA) dated October 3, 2017, received October 3, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Emend (fosaprepitant) injection, for intravenous use.

This Prior Approval supplemental new drug application provides for the use of Emend (fosaprepitant) injection for prevention of chemotherapy-induced nausea and vomiting in patients ages 6 months of age and older.

APPROVAL & LABELING

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 the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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

The SPL will be accessible from publicly available labeling repositories.

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

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 note that you have fulfilled the pediatric study requirement under this legislation for all relevant pediatric age groups for this application.

FULFILLMENT OF POSTMARKETING REQUIREMENT(S)/COMMITMENT(S)

We have received your submission dated October 3, 2017, containing the final report(s) for the following postmarketing requirement listed in the October 13, 2016 postapproval postmarketing requirement letter.

1663-3 A PK/PD study to characterize aprepitant PK parameters following administration of a single dose of intravenous fosaprepitant, in combination with a $5HT_3$ 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.

Use modeling and simulation including the results of the above study to identify 1-Day and 3-Day intravenous fosaprepitant doses in pediatric patients 0 to 17 years of age that provide similar aprepitant PK exposures to pediatric aprepitant doses and exposures which have demonstrated acceptable safety and efficacy profiles in patients receiving single and multi-day chemotherapy regimens, respectively.

We have reviewed your submission and conclude that the above requirement was fulfilled.

This completes your postmarketing requirement acknowledged in our October 13, 2016, letter.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Emend (fosaprepitant) was approved on January 25, 2008, we have become aware of reports of hypersensitivity reactions including anaphylaxis and anaphylactic shock in pediatric patients. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the unexpected serious risk of hypersensitivity reactions including anaphylaxis and anaphylactic shock in pediatric patients.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of hypersensitivity reactions including anaphylaxis and anaphylactic shock.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3361-1 Conduct a trial to evaluate the safety of multiple cycles of intravenous administration of fosaprepitant daily for three consecutive days for the prevention of chemotherapy-induced nausea and vomiting in pediatric patients 6 months to 17 years of age.

The timetable you submitted on March 28, 2018 states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2018
Final Protocol Submission:	04/2019
Trial Completion:	03/2021
Final Report Submission:	09/2021

Submit the protocol(s) to your IND 048924, with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

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:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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

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

Sincerely,

{See appended electronic signature page}

Lisa M. Soule, M.D.
Associate Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

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

Indications and Usage (1)	04/2018
Dosage and Administration (2.2, 2.3)	04/2018
Warnings and Precautions (5.2)	08/2017
Warnings and Precautions (5.3)	03/2018

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

EMEND® for injection is a substance P/neurokinin-1 (NK_1) receptor antagonist, indicated in adults and pediatric patients 6 months of age and older, in combination with other antiemetic agents, for the prevention of (1):

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

Limitations of Use (1)

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

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

- Recommended Dosage (2.1, 2.2)
- Adults: 150 mg on Day 1.
- *Pediatrics (6 months to 17 years):* a single-day of EMEND for injection on Day 1 (for single dose chemotherapy regimens) or a 3-day EMEND regimen of EMEND for injection on Day 1 and EMEND capsules or oral suspension on Days 2 and 3 (for single or multi-day chemotherapy regimens).
- Administer EMEND for injection on Day 1 as an intravenous infusion over 20 to 30 minutes (adults), 30 minutes (12 years to 17 years) or 60 minutes (6 months to less than 12 years) completing the infusion approximately 30 minutes prior to chemotherapy.
- In pediatrics, administer EMEND through a central venous catheter.
- See Full Prescr bing Information for dosages of concomitant antiemetic(s) and pediatric dosages of EMEND. (2.1, 2.2)

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

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

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

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

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

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

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

- Most common adverse reactions in adults (≥2%) are: fatigue, diarrhea, neutropenia, asthenia, anemia, peripheral neuropathy, leukopenia, dyspepsia, urinary tract infection, pain in extremity. (6.1)
- Adverse reactions in pediatrics are similar to adults.

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

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

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

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

Revised: 04/2018

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, in combination with other antiemetic agents, is indicated in adults and pediatric patients 6 months of age and older for the prevention of:

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

Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Prevention of Nausea and Vomiting Associated with HEC and MEC in Adult Patients

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

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

	Day 1	Day 2	Day 3	Day 4
EMEND for injection	150 mg intravenously over 20 to 30 minutes approximately 30 minutes prior to chemotherapy	none	none	none
Dexamethasone*	12 mg orally	8 mg orally	8 mg orally twice daily	8 mg orally twice daily
5-HT_3 antagonist	See selected 5-HT_3 antagonist prescribing information for the recommended dosage	none	none	none

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

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

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

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

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

The recommended pediatric dose regimens of EMEND, to be administered with a 5-HT_3 antagonist, with or without a corticosteroid, for the prevention of nausea and vomiting associated with administration of single or multi-day chemotherapy regimens of HEC or MEC, are shown in Tables 3 and 4. Single-day chemotherapy regimens include those regimens in which HEC or MEC is administered for a single day

only. Multi-day chemotherapy regimens include chemotherapy regimens in which HEC or MEC is administered for 2 or more days.

EMEND Dosage Regimens for Use with Single-Day Chemotherapy Regimens

For pediatric patients weighing at least 6 kg receiving single-day HEC or MEC, EMEND may be administered as:

- a single dose regimen of EMEND for injection infused through a central venous catheter on Day 1, as shown in Table 3; or
- as a 3-day EMEND regimen consisting of EMEND for injection as an intravenous infusion through a central venous catheter on Day 1 and EMEND capsules or EMEND for oral suspension on Days 2 and 3, as shown in Table 4.

Administer EMEND for injection on Day 1 over 30 minutes (12 years to 17 years) or 60 minutes (6 months to less than 12 years), completing the infusion approximately 30 minutes prior to chemotherapy.

Table 3
Single Dose Regimen of EMEND for injection for Pediatric Patients 6 Months* to 17 Years for the Prevention of Nausea and Vomiting Associated with Single-Day Regimens of HEC or MEC

Drug	Age	Regimen
EMEND for injection	12 Years to 17 Years	150 mg intravenously over 30 minutes
	2 Years to less than 12 Years	4 mg/kg (maximum dose 150 mg) intravenously over 60 minutes
	6 Months to less than 2 Years	5 mg/kg (maximum dose 150 mg) intravenously over 60 minutes
Dexamethasone†	6 Months to 17 Years	If a corticosteroid, such as dexamethasone, is co-administered, administer 50% of the recommended corticosteroid dose on Days 1 and 2.
5-HT_3 antagonist	6 Months to 17 Years	See selected 5-HT_3 antagonist prescribing information for the recommended dosage

* Dosing in pediatric patients less than 6 kg is not recommended
†Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1

EMEND Dosage Regimen for Use with Multi-Day Chemotherapy Regimens

For pediatric patients weighing at least 6 kg receiving multi-day regimens of HEC or MEC, administer EMEND on Days 1, 2, and 3. Administer EMEND for injection as an intravenous infusion through a central venous catheter on Day 1 and EMEND capsules or EMEND for oral suspension on Days 2 and 3, as shown in Table 4.

Administer EMEND for injection on Day 1 over 30 minutes (12 years to 17 years) or 60 minutes (6 months to less than 12 years), completing the infusion approximately 30 minutes prior to chemotherapy.

Table 4
Pediatric Patients 6 Months* to 17 Years Recommended 3-Day EMEND Dosage Regimen for Prevention of Nausea and Vomiting Associated with Single or Multi-day Regimens of HEC or MEC

Age Group	Drug	Day 1	Day 2	Day 3
12 Years to 17 Years	EMEND for injection	115 mg intravenously over 30 minutes	--	--
	EMEND capsules†	--	80 mg orally	80 mg orally
6 Months to Less than 12 Years	EMEND for injection	3 mg/kg (maximum dose 115 mg) intravenously over 60 minutes	--	--
	EMEND for oral suspension	--	2 mg/kg orally (maximum 80 mg)	2 mg/kg orally (maximum 80 mg)
6 Months to 17 Years	Dexamethasone‡	If a corticosteroid, such as dexamethasone, is co-administered, administer 50% of the recommended corticosteroid dose on Days 1 through 4		
6 Months to 17 Years	5-HT_3 antagonist	See selected 5-HT_3 antagonist prescr bing information for the recommended dosage		

* Dosing in pediatric patients less than 6 kg is not recommended
† For patients 12 years to 17 years who cannot swallow oral capsules, EMEND for oral suspension can be used instead.
‡ Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1

2.3 Preparation of EMEND for injection

Table 5
Preparation Instructions for EMEND for injection (150 mg)

Step 1	Aseptically inject 5 mL 0.9% Sodium Chloride Injection, USP into the vial. Assure that 0.9% Sodium Chloride Injection, USP is added to the vial along the vial wall in order to prevent foaming. Swirl the vial gently. Avoid shaking and jetting 0.9% Sodium Chloride Injection, USP into the vial.
Step 2	Aseptically prepare an infusion bag filled with 145 mL of 0.9% Sodium Chloride Injection, USP.
Step 3	Aseptically withdraw the entire volume from the vial and transfer it into the infusion bag containing 145 mL of 0.9% Sodium Chloride Injection, USP to yield a **total** volume of 150 mL and a final concentration of 1 mg/mL**.**
Step 4	Gently invert the bag 2 to 3 times.
Step 5	Determine the volume to be administered from this prepared infusion bag, based on the recommended dose *[see Dosage and Administration (2.1, 2.2)]*. <u>Adults</u> The entire volume of the prepared infusion bag (150 mL) should be administered. <u>Pediatrics</u> In patients 12 years and older, the volume to be administered is calculated as follows: • Volume to administer (mL) equals the recommended dose (mg) In patients 6 months to less than 12 years, the volume to be administered is calculated as follows: • Volume to administer (mL) = recommended dose (mg/kg) x weight (kg) o *<u>Note: Do not exceed the maximum dose</u> [see Dosage and Administration (2.2)]* In pediatric patients, the entire volume in the infusion bag may not be required.
Step 6	If necessary, for volumes less than 150 mL, the calculated volume can be transferred to an appropriate size bag or syringe prior to administration by infusion.
Step 7	Before administration, inspect the bag for particulate matter and discoloration. Discard the bag if particulate and/or discoloration are observed.

The recommended dose of EMEND for injection is based on the patient's age and weight.

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

Storage

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

EMEND is contraindicated in patients:

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Clinically Significant CYP3A4 Drug Interactions

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

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

See Table 7 and Table 8 for a listing of potentially significant drug interactions *[see Drug Interactions (7.1, 7.2)].*

5.2 Hypersensitivity Reactions

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

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

5.3 Infusion Site Reactions

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

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

5.4 Decrease in INR with Concomitant Warfarin

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

5.5 Risk of Reduced Efficacy of Hormonal Contraceptives

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

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity Reactions *[see Warnings and Precautions (5.2)]*
- Infusion Site Reactions *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

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

The overall safety of EMEND for injection was evaluated in approximately 1800 adult and pediatric patients.

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

In an active-controlled clinical trial in patients receiving MEC, safety was evaluated in 504 patients receiving a single dose of EMEND for injection in combination with ondansetron and dexamethasone (EMEND regimen) compared to 497 patients receiving ondansetron and dexamethasone alone (standard therapy). The most common adverse reactions are listed in Table 6.

Table 6
Most Common Adverse Reactions in Patients Receiving MEC*

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

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

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

infusion-site thrombophlebitis (0.6%, 0.0%), reported in the EMEND regimen compared to standard therapy, respectively.

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

In an active-controlled clinical study in patients receiving HEC, safety was evaluated for 1143 patients receiving a single dose of EMEND for injection compared to 1169 patients receiving the 3-day regimen of oral EMEND (aprepitant) *[see Clinical Studies (14.1)]*. The safety profile was generally similar to that seen in the MEC study with fosaprepitant and prior HEC studies with aprepitant. However, infusion-site reactions occurred at a higher incidence in patients in the fosaprepitant group (3.0%) compared to those in the aprepitant group (0.5%). The following additional infusion-site reactions occurred in the HEC study and were not reported in the MEC study described above: infusion-site erythema (0.5%, 0.1%), infusion-site pruritus (0.3%, 0.0%), and infusion-site induration (0.2%, 0.1%), reported in the fosaprepitant group compared to the aprepitant group, respectively.

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

Single-Dose EMEND for Injection Regimen

The safety of a single dose of EMEND for injection in pediatric patients (6 months to 17 years) was evaluated in two active-controlled and a single-arm clinical study in patients who received either HEC or MEC. Patients also received ondansetron with or without dexamethasone. The adverse reaction profile was similar to adults. The safety analysis included 69 pediatric patients who received the recommended dose. An additional 70 patients received a single, higher-than-recommended dose. The most common adverse reactions that occurred in >15% of patients who received the recommended dose were anemia, neutropenia, thrombocytopenia, and febrile neutropenia.

3-Day IV/Oral/Oral EMEND Regimen

In pediatric patients (12 to 17 years), the safety of the 3-day IV/oral/oral EMEND regimen was evaluated in a single-arm clinical study including 12 patients who received a regimen of either HEC or MEC. In pediatric patients 6 months to 12 years of age, the safety of the 3-day IV/oral/oral EMEND regimen was not directly evaluated. The safety of a single-dose of EMEND for injection (3 mg/kg) administered on day 1 of the 3-day IV/oral/oral regimen was evaluated in one active-controlled and one single-arm study including 48 patients who received a regimen of either HEC or MEC. Patients also received ondansetron with or without dexamethasone. The adverse reaction profile was similar to adults and pediatric patients receiving a single dose of EMEND for injection.

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

6.2 Postmarketing Experience

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

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

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

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

7 DRUG INTERACTIONS

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

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

Fosaprepitant, given as a single 150-mg dose, is a weak inhibitor of CYP3A4, and the weak inhibition of CYP3A4 continues for 2 days after single dose administration. Single dose fosaprepitant does

not induce CYP3A4. Aprepitant is a substrate, an inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9 *[see Clinical Pharmacology (12.3)]*.

Some substrates of CYP3A4 are contraindicated with EMEND *[see Contraindications (4)]*. Dosage adjustment of some CYP3A4 and CYP2C9 substrates may be warranted, as shown in Table 7.

Table 7
Effects of Fosaprepitant/Aprepitant on the Pharmacokinetics of Other Drugs

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

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

Aprepitant is a CYP3A4 substrate *[see Clinical Pharmacology (12.3)]*. Co-administration of EMEND with drugs that are inhibitors or inducers of CYP3A4 may result in increased or decreased plasma concentrations of aprepitant, respectively, as shown in Table 8.

Table 8
Effects of Other Drugs on Pharmacokinetics of Fosaprepitant/Aprepitant

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Contraception

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

8.4 Pediatric Use

The safety and effectiveness of a single dose regimen of EMEND for injection and a 3-day IV/oral/oral EMEND regimen have been established in pediatric patients 6 months to 17 years for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC and MEC.

Use of EMEND in this age group is supported by evidence from adequate and well-controlled studies of EMEND for injection in adults, with additional safety, efficacy and pharmacokinetic data in pediatric patients 6 months to 17 years. Efficacy was also supported by data from an adequate and well-controlled study of a 3-day oral aprepitant regimen in pediatric patients 6 months to 17 years. See the full prescribing information for EMEND capsules for complete clinical information regarding studies performed with oral aprepitant. Adverse reactions were similar to those reported in adult patients. *[See Dosage and Administration (2.2), Adverse Reactions (6.1), Clinical Pharmacology (12.3)].*

The safety of EMEND for injection administered on consecutive days has not been established in pediatric patients 6 months to 17 years for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC and MEC.

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

Juvenile Animal Toxicity Data

In juvenile dogs treated with fosaprepitant, changes in reproductive organs were observed. In juvenile rats treated with aprepitant, slight changes in sexual maturation were observed without an effect on reproduction. No effects on neurobehavior, sensory and motor function, or learning and memory were observed in rats.

In a toxicity study in juvenile dogs treated with fosaprepitant from postnatal day 14 (equivalent to a newborn human) to day 42 (approximately equivalent to a 2 year old human), decreased testicular weight and Leydig cell size were seen in the males at 6 mg/kg/day and increased uterine weight, hypertrophy of the uterus and cervix, and edema of vaginal tissues were seen in females from 4 mg/kg/day. A study was also conducted in young rats to evaluate the effects of aprepitant on growth and on neurobehavioral and sexual development. Rats were treated at oral doses up to the maximum feasible dose of 1000 mg/kg twice daily (providing exposure in male and female rats lower than the exposure at the recommended pediatric human dose) from the early postnatal period (Postnatal Day 10 (equivalent to a newborn human) through Postnatal Day 58 (approximately equivalent to a 15 year old human)). Slight changes in the onset of sexual maturation were observed in female and male rats; however, there were no effects on mating, fertility, embryonic-fetal survival, or histomorphology of the reproductive organs. There were no effects in neurobehavioral tests of sensory function, motor function, and learning and memory.

8.5 Geriatric Use

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

8.6 Patients with Hepatic Impairment

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

10 OVERDOSAGE

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

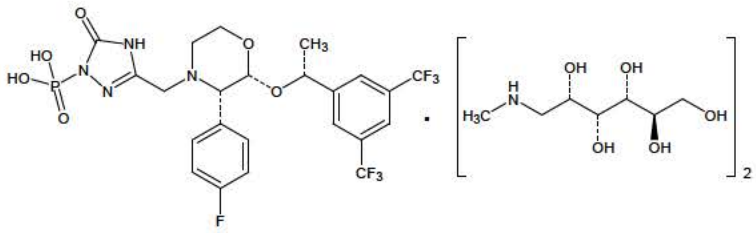
In the event of overdose, EMEND should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of EMEND, drug-induced emesis may not be effective in cases of EMEND overdosage.

Aprepitant is not removed by hemodialysis.

11 DESCRIPTION

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

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



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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK_1) receptors. Aprepitant has little or no affinity for serotonin ($5\text{-}HT_3$), dopamine, and corticosteroid receptors, the targets of existing therapies for chemotherapy-induced nausea and vomiting (CINV). Aprepitant has been shown in animal models to inhibit emesis induced by cytotoxic chemotherapeutic agents, such as 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 have shown that aprepitant augments the antiemetic activity of the $5\text{-}HT_3$-receptor antagonist ondansetron and the corticosteroid dexamethasone and inhibits both the acute and delayed phases of cisplatin-induced emesis.

12.2 Pharmacodynamics

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

Aprepitant after Fosaprepitant Administration

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

Distribution

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

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

Elimination

Metabolism

Fosaprepitant is converted to aprepitant in *in vitro* incubations with human liver preparations and in S9 preparations from multiple other human tissues including kidney, lung and ileum. Thus, it appears that the conversion of fosaprepitant to aprepitant can occur in multiple extrahepatic tissues in addition to the liver.

Aprepitant undergoes extensive metabolism. *In vitro* studies using human liver microsomes indicate that aprepitant is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19. Metabolism is largely via oxidation at the morpholine ring and its side chains. No metabolism by CYP2D6, CYP2C9, or CYP2E1 was detected.

In healthy young adults, aprepitant accounts for approximately 24% of the radioactivity in plasma over 72 hours following a single oral 300-mg dose of [^{14}C]-aprepitant, indicating a substantial presence of metabolites in the plasma. Seven metabolites of aprepitant, which are only weakly active, have been identified in human plasma.

Excretion

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

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

Specific Populations

Age: Geriatric Population

Following oral administration of a single 125-mg dose of aprepitant on Day 1 and 80 mg once daily on Days 2 through 5, the $AUC_{0\text{-}24hr}$ of aprepitant was 21% higher on Day 1 and 36% higher on Day 5 in elderly (65 years and older) relative to younger adults. The C_{max} was 10% higher on Day 1 and 24% higher on Day 5 in elderly relative to younger adults. These differences are not considered clinically meaningful *[see Use in Specific Populations (8.5)]*.

Age: Pediatric Population

Single-Dose EMEND for Injection Regimen: Simulated systemic exposures of aprepitant in patients 2 years to less than 12 years and observed systemic exposures in patients 6 months to less than 2 years and 12 to 17 years are shown in Table 9, including $AUC_{0\text{-}24hr}$, peak plasma concentration (C_{max}) on Day 1 and concentrations at the end of Day 1 (C_{24}), Day 2 (C_{48}) and Day 3 (C_{72}).

Table 9
Systemic Exposures of Aprepitant for Single-Dose EMEND for Injection Regimen in Pediatric Patients

Population	Single-Dose of EMEND for Injection Regimen	Geometric Mean				
		$AUC_{0\text{-}24hr.}$ (mcg*hr/mL)	C_{max} (mcg/mL)	C_{24} (mcg/mL)	C_{48} (mcg/mL)	C_{72} (mcg/mL)
12 Years to 17 Years	150 mg	29.4	3.4	0.7	ND*	ND*
6 Years to less than 12 Years	4 mg/kg	35.2	3.6	0.7	0.2	0.05
2 Years to less than 6 Years		28.2	3.1	0.4	0.1	0.02
6 Months to less than 2 Years	5 mg/kg	32.7	3.3	0.4	NE†	ND*

*ND = Not Determined. Pharmacokinetic samples were not collected to support the parameter value of interest.
†NE = Not Estimated. The geometric mean could not be estimated due to values being below the limitation of quantification.

3-Day IV/Oral/Oral EMEND Regimen: Simulated aprepitant systemic exposures in patients 6 months to less than 12 years and observed systemic exposures in patients 12 to 17 years are shown in Table 10, including $AUC_{0\text{-}24hr}$, peak plasma concentration (C_{max}) on Day 1 and concentrations at the end of Day 1 (C_{24}), Day 2 (C_{48}) and Day 3 (C_{72}).

Table 10
Systemic Exposures of Aprepitant for 3-Day IV/Oral/Oral Regimen in Pediatric Patients

Population	3-Day Dose of EMEND (IV/Oral/Oral*)	Geometric Mean				
		$AUC_{0\text{-}24hr.}$ (mcg*hr/mL)	C_{max} (mcg/mL)	C_{24} (mcg/mL)	C_{48} (mcg/mL)	C_{72} (mcg/mL)
12 Years to 17 Years	115/80/80 mg	18.0	3.0	0.4	0.2	NE[†]
6 Years to less than 12 Years	3/2/2 mg/kg	25.7	2.7	0.5	0.3	0.3
2 Years to less than 6 Years		20.2	2.3	0.3	0.2	0.2
6 Months to less than 2 Years		16.6	1.9	0.2	0.1	0.1

*IV on Day 1, Oral on Day 2, and Oral on Day 3
[†]NE = Not Estimated. The geometric mean could not be estimated due to values being below the limitation of quantification.

Plasma concentrations of fosaprepitant are negligible within 15 – 30 minutes after the completion of the infusion in pediatric patients.

Sex

Following oral administration of a single dose of aprepitant, ranging from 40 mg to 375 mg, the $AUC_{0\text{-}24hr}$ and C_{max} are 9% and 17% higher in females as compared with males. The half-life of aprepitant is approximately 25% lower in females as compared with males and T_{max} occurs at approximately the same time. These differences are not considered clinically meaningful. A population pharmacokinetic analysis of aprepitant in pediatric patients (6 months to 17 years) suggests that sex has no clinically meaningful effect on the pharmacokinetics of aprepitant.

Race/Ethnicity

Following oral administration of a single dose of aprepitant, ranging from 40 mg to 375 mg, the $AUC_{0\text{-}24hr}$ and C_{max} are approximately 27% and 19% higher in Hispanics as compared with Caucasians. The $AUC_{0\text{-}24hr}$ and C_{max} were 74% and 47% higher in Asians as compared to Caucasians. There was no difference in $AUC_{0\text{-}24hr}$ or C_{max} between Caucasians and Blacks. These differences are not considered clinically meaningful. A population pharmacokinetic analysis of aprepitant in pediatric patients (6 months to 17 years) suggests that race has no clinically meaningful effect on the pharmacokinetics of aprepitant.

Renal Impairment

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

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

Hepatic Impairment

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

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

clinical or pharmacokinetic data in patients with severe hepatic impairment (Child-Pugh score greater than 9) *[see Use in Specific Populations (8.6)]*.

Body Mass Index (BMI)

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

Drug Interactions Studies

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

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

Effects of Fosaprepitant/Aprepitant on the Pharmacokinetics of Other Drugs

CYP3A4 Substrates

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

Corticosteroids:

Dexamethasone: Fosaprepitant administered as a single 150 mg intravenous dose on Day 1 increased the $AUC_{0\text{-}24hr}$ of dexamethasone, administered as a single 8-mg oral dose on Days 1, 2, and 3, by approximately 2-fold on Days 1 and 2 *[see Dosage and Administration (2.1), Drug Interactions (7.1)]*.

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

Chemotherapeutic agents:

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

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

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

CYP2C9 substrates (Warfarin, Tolbutamide):

Warfarin: A single 125-mg dose of oral aprepitant was administered on Day 1 and 80 mg/day on Days 2 and 3 to subjects who were stabilized on chronic warfarin therapy. Although there was no effect of oral aprepitant on the plasma AUC of R(+) or S(-) warfarin determined on Day 3, there was a 34% decrease in S(-) warfarin trough concentration accompanied by a 14% decrease in the prothrombin time (reported as International Normalized Ratio or INR) 5 days after completion of dosing with oral aprepitant *[see Drug Interactions (7.1)]*.

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

Other Drugs

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

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

Effect of Other Drugs on the Pharmacokinetics of Fosaprepitant/Aprepitant

Rifampin: When a single 375-mg dose of oral aprepitant was administered on Day 9 of a 14-day regimen of 600 mg/day of rifampin, a strong CYP3A4 inducer, the AUC of aprepitant decreased approximately 11-fold and the mean terminal half-life decreased approximately 3-fold *[see Drug Interactions (7.2)]*.

Ketoconazole: When a single 125-mg dose of oral aprepitant was administered on Day 5 of a 10-day regimen of 400 mg/day of ketoconazole, a strong CYP3A4 inhibitor, the AUC of aprepitant increased approximately 5-fold and the mean terminal half-life of aprepitant increased approximately 3-fold *[see Drug Interactions (7.2)]*.

Diltiazem: In a study in 10 patients with mild to moderate hypertension, administration of 100 mg of fosaprepitant as an intravenous infusion with 120 mg of diltiazem, a moderate CYP3A4 inhibitor administered three times daily, resulted in a 1.5-fold increase in the aprepitant AUC and a 1.4-fold increase in the diltiazem AUC.

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in Sprague-Dawley rats and in CD-1 mice for 2 years. In the rat carcinogenicity studies, animals were treated with oral doses ranging from 0.05 to 1000 mg/kg twice daily. The highest dose produced systemic exposures to aprepitant approximately equivalent to (female rats) or less than (male rats) the adult human exposure at the RHD of 150 mg. Treatment with aprepitant at doses of 5 to 1000 mg/kg twice daily caused an increase in the incidences of thyroid follicular cell adenomas and carcinomas in male rats. In female rats, it produced hepatocellular adenomas at 5 to 1000 mg/kg twice daily and hepatocellular carcinomas and thyroid follicular cell adenomas at 125 to 1000 mg/kg twice daily. In the mouse carcinogenicity studies, the animals were treated with oral doses ranging from 2.5 to 2000 mg/kg/day. The highest dose produced a systemic exposure approximately 2 times the adult human exposure at the RHD of 150 mg. Treatment with aprepitant produced skin fibrosarcomas at 125 and 500 mg/kg/day doses in male mice. Carcinogenicity studies were not conducted with fosaprepitant.

Mutagenesis

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

Impairment of Fertility

Fosaprepitant, when administered intravenously, is rapidly converted to aprepitant. In the fertility studies conducted with fosaprepitant and aprepitant, the highest systemic exposures to aprepitant were obtained following oral administration of aprepitant. Oral aprepitant did not affect the fertility or general reproductive performance of male or female rats at doses up to the maximum feasible dose of 1000 mg/kg twice daily (providing exposure in male rats lower than the exposure at the recommended adult human dose of 150 mg and exposure in female rats approximately equivalent to the adult human exposure).

14 CLINICAL STUDIES

14.1 Prevention of Nausea and Vomiting Associated with HEC in Adults

In a randomized, parallel, double-blind, active-controlled study, EMEND for injection 150 mg as a single intravenous infusion (N=1147) was compared to a 3-day oral EMEND regimen (N=1175) in patients receiving a HEC regimen that included cisplatin (≥70 mg/m^2). All patients in both groups received dexamethasone and ondansetron (see Table 11). Patient demographics were similar between the two treatment groups. Of the total 2322 patients, 63% were men, 56% White, 26% Asian, 3% American Indian/Alaska Native, 2% Black, 13% Multi-Racial, and 33% Hispanic/Latino ethnicity. Patient ages ranged from 19 to 86 years of age, with a mean age of 56 years. Other concomitant chemotherapy agents commonly administered were fluorouracil (17%), gemcitabine (16%), paclitaxel (15%), and etoposide (12%).

Table 11
Treatment Regimens in Adult HEC Trial*

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

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

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

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

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

The efficacy of EMEND for injection was evaluated based on the primary and secondary endpoints listed in Table 12 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 12
Percent of Adult Patients Receiving HEC Responding by Treatment Group and Phase — Cycle 1

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

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

14.2 Prevention of Nausea and Vomiting Associated with MEC in Adults

In a randomized, parallel, double-blind, active comparator-controlled study, EMEND for injection 150 mg as a single intravenous infusion (N=502) in combination with ondansetron and dexamethasone (EMEND regimen) was compared with ondansetron and dexamethasone alone (standard therapy) (N=498) (see Table 13) in patients receiving a MEC regimen. Patient demographics were similar between the two treatment groups. Of the total 1,000 patients included in the efficacy analysis, 41% were men, 84% White, 4% Asian, 1% American Indian/Alaska Native, 2% Black, 10% Multi-Racial, and 19% Hispanic/Latino ethnicity. Patient ages ranged from 23 to 88 years of age, with a mean age of 60 years. The most commonly administered MEC chemotherapeutic agents were carboplatin (51%), oxaliplatin (24%), and cyclophosphamide (12%).

Table 13
Treatment Regimens in Adult MEC Trial*

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

*EMEND for injection placebo and dexamethasone placebo (on Day 1) were used to maintain blinding.
†Dexamethasone was administered 30 minutes prior to chemotherapy treatment on Day 1. The 12 mg dose reflects a dosage adjustment to account

for a drug interaction with the EMEND for injection regimen *[see Clinical Pharmacology (12.3)]*.
‡The first ondansetron dose was administered 30 to 60 minutes prior to chemotherapy treatment on Day 1 and the second dose was administered 8 hours after first ondansetron dose.

The primary endpoint was complete response (defined as no vomiting and no rescue therapy) in the delayed phase (25 to 120 hours) of chemotherapy-induced nausea and vomiting. The results by treatment group are shown in Table 14.

Table 14
Percent of Adult Patients Receiving MEC Responding by Treatment Group

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

No. 3061 — Single-dose glass vial containing 150 mg of fosaprepitant as a white to off-white lyophilized powder for reconstitution. Supplied as follows:
NDC 0006-3061-00 1 vial per carton.

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

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

17 PATIENT COUNSELING INFORMATION

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

Hypersensitivity

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

Infusion Site Reactions

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

Drug Interactions

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

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

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

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

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

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

uspi-mk0517-iv-edta5-1804r004

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

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

What is EMEND for injection?

EMEND for injection is a prescription medicine used with other medicines that treat nausea and vomiting in patients 6 months of age and older to prevent nausea and vomiting caused by certain anti-cancer (chemotherapy) medicines.

- EMEND for injection is not used to treat nausea and vomiting that you already have.
- It is not known if EMEND for injection is safe and effective in children less than 6 months of age.

Who should not receive EMEND for injection?

Do not receive EMEND for injection if you:

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

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

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

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

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

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

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

How will I receive EMEND for injection?

Adults 18 years of age and older:

EMEND for injection will be given on Day 1 of chemotherapy treatment. It will be given to you by intravenous (IV) infusion in your vein about 50 to 60 minutes before you start your chemotherapy treatment.

Children 6 months to 17 years of age:

EMEND for injection will be given on Day 1 of chemotherapy treatment. It will be given to your child by intravenous (IV) infusion into a large vein through a type of IV line called a central venous catheter, about 1 hour to 1 ½ hours before the start of their chemotherapy treatment.

- Your child may also receive:

- capsules of EMEND or an oral suspension of EMEND on Days 2 and 3. If your child will receive either of these, see the Patient Information for EMEND capsules or EMEND for oral suspension for further information.

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

What are the possible side effects of EMEND for injection?

EMEND for injection may cause serious side effects, including:

- **Serious allergic reactions.** Allergic reactions can happen with EMEND for injection and may be serious. Tell your doctor or nurse right away if you have hives, rash, itching, flushing or redness of your face or skin, trouble breathing or swallowing, dizziness, a rapid or weak heartbeat, or you feel faint during or soon after you receive EMEND for injection, as you may need emergency medical care.
- Severe skin reactions, which may include rash, skin peeling, or sores, may occur.
- Infusion site reactions (ISR) at or near the infusion site have happened with EMEND for Injection.

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

In adults, the most common side effects of EMEND for injection include:

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

In children 6 months to 17 years of age, the most common side effects of EMEND for injection include:

- low red blood cell count
- low white blood cell count
- low blood platelet count
- low white blood cell count with a fever

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

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

General information about the safe and effective use of EMEND for injection.

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

What are the ingredients in EMEND for injection?

Active ingredient: fosaprepitant

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

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of **MERCK & CO., INC.,** Whitehouse Station, NJ 08889, USA
Manufactured by: Patheon Manufacturing Services LLC, 5900 Martin Luther King Jr. Highway, Greenville, NC 27834, USA
For patent information: www.merck.com/product/patent/home.html

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022023Orig1s017

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	April 3, 2018
From	Lisa Soule, M.D., Associate Director, Division of Gastroenterology and Inborn Errors Products
Subject	Division Director Summary Review
NDA/BLA #	NDA 22-023/S-017
Applicant Name	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Date of Submission	October 3, 2017
PDUFA Goal Date	April 3, 2018
Proprietary Name / Established (USAN) Name	Emend Fosaprepitant dimeglumine
Dosage Forms / Strength	150 mg fosaprepitant, lyophilized powder in a single-dose vial for reconstitution
Proposed Indication(s)	EMEND for injection, in combination with other antiemetic agents, is indicated in adults and pediatric patients 6 months of age and older for the prevention of: • acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin • delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)
Action/Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Cross-Discipline Team Leader	Insook Kim, Ph.D.
Medical Officer Review	Aisha Johnson, M.D., M.P.H., M.B.A/Anil Rajpal, M.D., M.P.H.
Pharmacology Toxicology Review	Yolanda Branch, Ph.D./Sushanta Chakder, Ph.D.
CMC Review/OBP Review	Hossein Khorshidi, Ph.D. (environmental analysis), David Lewis, Ph.D. (secondary review)
Clinical Pharmacology Review	Elizabeth Shang, Ph.D./Insook Kim, Ph.D./Justin Earp, Ph.D. (pharmacometrics)/Gilbert Burckart, Pharm.D.
Biostatistics Review	Ling Lan, Ph.D./George Kordzakhia, Ph.D.
Office of Prescription Drug Promotion	Meeta Patel, Pharm.D.
Division of Medication Error Prevention and Analysis	Sherly Abraham, R.Ph./Sarah Vee, Pharm.D.
Other: Division of Pediatric and Maternal Health	Amy Taylor, M.D., M.H.S./Hari Sachs, M.D./John Alexander, M.D., M.P.H. (pediatrics)
Other: Division of Medical Policy Programs, Patient Labeling Team	Karen Dowdy, RN, BSN/Sharon Williams, MSN, RN, BSN/LaShawn Griffiths, MSHS-PH, BSN, RN

OND=Office of New Drugs

1. Introduction

The Applicant submitted a supplemental NDA for fosaprepitant injection (Emend) for the prevention of chemotherapy-induced nausea and vomiting (CINV) associated with highly and moderately emetogenic chemotherapy (HEC and MEC, respectively) for use in pediatric patients ages 6 months to 17 years. Emend is currently approved under 3 NDAs, as follows:

- NDA 21-549 (**aprepitant capsules**, for oral use, a **3-day dosing regimen**), initially approved for adults in March 2003, is now indicated in patients **12 years of age and older** (pediatric indication approved in 2015), for prevention of:
  - acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy [HEC] including high-dose cisplatin
  - nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy [MEC; approved for adults in 2005]
- NDA 22-023 approved in January 2008, indicated in **adults** (fosaprepitant, for **injection**, a **single-day dosing regimen**), for prevention of:
  - acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy [HEC] including high-dose cisplatin
  - delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy [MEC]
- NDA 207-865 (aprepitant for **oral suspension**, a **3-day dosing regimen**), approved December 2015, indicated in patients **6 months of age and older**, for prevention of:
  - acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy [HEC] including high-dose cisplatin
  - nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy [MEC]

Fosaprepitant is the prodrug of aprepitant, which is a selective agonist of human Substance P/neurokinin 1 (NK_1) receptors. Fosaprepitant is completely converted to aprepitant within 30-60 minutes, and its antiemetic activity is attributable to aprepitant. Emend is intended to be given in combination with other antiemetic agents (dexamethasone and a 5-HT_3 antagonist).

The Applicant proposed the following pediatric regimens:

- single-day IV fosaprepitant regimen, to be given to patients receiving a **single-day course** of HEC or MEC
- a 3-day dosing regimen, to be given to patients receiving either **a single-day or a multi-day course** of HEC or MEC; the Applicant proposed that patients receive IV fosaprepitant on Day 1, with options to receive either IV fosaprepitant or oral aprepitant on Days 2 and 3

This submission is intended to fulfill the PREA post-marketing requirement (PMR) and to meet the terms of the Pediatric Written Request issued by FDA. The Applicant proposed to extrapolate the efficacy of the single-day pediatric IV regimen from the adult fosaprepitant regimen, and to bridge the 3-day pediatric IV regimen to the efficacy demonstrated with the 3-day pediatric oral aprepitant regimen, based on matching aprepitant exposures. The review of this application was conducted as a Standard review.

2. Background

CINV has been observed to occur both acutely after chemotherapy administration (i.e., within 0-24 hours) and as a delayed reaction (between 24-120 hours after chemotherapy). Aprepitant has been shown in animal models to inhibit CINV through actions in the central nervous system; animal and human studies have shown aprepitant to cross the blood-brain barrier and to occupy brain NK_1 receptors.

Dr. Johnson's review includes a listing of currently approved drugs for the prevention of CINV in pediatric patients. In contrast to adults, who frequently receive single-day chemotherapy regimens (and have an approved single-day regimen of fosaprepitant), children are more likely to receive multi-day chemotherapy in a given cycle. The pathophysiology of CINV, chemotherapeutic agents, and the response to antiemetic prophylaxis is otherwise similar between adults and children.

Emend (fosaprepitant for injection) was developed under IND 48,924. The NDA was approved on the second review cycle, in 2008, with a PREA post-marketing requirement for a study in adolescents and younger pediatric patients receiving emetogenic chemotherapy (HEC or MEC) to evaluate fosaprepitant PK, safety, and tolerability. Pediatric development is discussed further in Section 9.

3. CMC/Device

I concur with the OPQ recommendation for approval. No new CMC information was included in this submission. Following approval of the Emend for injection formulation for adults, FDA requested the Applicant to develop a formulation with a lower amount of ethylenediamenetetraacetic acid (EDTA) to support pediatric development. This "low EDTA" formulation (reduced from 18.8 mg to 5.4 mg per vial) was approved for adults in 2016 (Supplement 014) and is the formulation proposed in this submission for pediatric use. The following conclusions were made by the OPQ review team:

- The claim for Categorical Exclusion for the Environmental Assessment was granted.
- The CMC sections of the revised labeling are unchanged from the currently approved labeling.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

No new nonclinical studies were submitted in this application. Previous juvenile toxicology studies submitted in support of oral aprepitant for use in pediatric patients included an oral toxicity study of aprepitant in juvenile rats, and a 4-week intravenous injection toxicology study of fosaprepitant in juvenile dogs (this was Study 1 in the Pediatric Written Request; see Section 9). The NOAEL for aprepitant in the juvenile rat study was > 1,000 mg/kg BID. The 4-week juvenile dog study also assessed potential effects of EDTA; the NOAEL for fosaprepitant in this study was 4 mg/kg, while a dosage of 6 mg/kg/day was well-tolerated. There were no adverse effects attributable to EDTA.

Labeling of Sections 8.1, 8.2, and 13 was found to be acceptable.

5. Clinical Pharmacology

I concur with the clinical pharmacology review team's conclusion that the application is acceptable for approval of the specified dosing regimens (see Section 11).

Efficacy has been demonstrated previously for the adult single-day IV fosaprepitant regimen, and for the pediatric 3-day oral (po) aprepitant regimen. Therefore, the Applicant proposed to support the two dosing regimens (single-day and 3-day regimens) as follows:

> Single-day regimen for HEC and MEC:
>
> Efficacy was extrapolated from adult single-dose IV efficacy studies (Studies P017L and 031), based on similarity on the pathophysiology of CINV in adults and pediatric patients, similar response to NK1 antagonists, and comparable aprepitant exposure.
>
> Safety data to support the single-day regimen was obtained from the three clinical studies described below.
>
> 3-day regimen for HEC and MEC:
>
> Efficacy was bridged to the efficacy study for the 3-day pediatric oral aprepitant regimen (Study P208), based on exposure matching, given that the *in vivo* activity of fosaprepitant is attributable to aprepitant.
>
> There are no pediatric safety data based on a 3-day IV/IV/IV regimen.

Modeling and simulation of PK data from the aprepitant and fosaprepitant programs was utilized to select single-day fosaprepitant regimens that would provide exposure similar to that demonstrated to be efficacious in adults. The adult data are primarily based on subjects who received single-day chemotherapy; therefore, the proposed pediatric single-day regimen is limited to use with single-day (not multi-day) courses of chemotherapy.

Study 134 was a phase 1 study in pediatric patients 6 months to 17 years, evaluating PK, safety, tolerability and exploratory efficacy of aprepitant and fosaprepitant. Subjects received IV fosaprepitant either as a **single dose** (subjects > 12 years of age)**,** or as **Day 1** of a 3-day IV/po/po regimen (adolescent subjects).

Study 029 was a phase 2b randomized controlled trial (RCT) of a **single-day regimen** of fosaprepitant in subjects 0-17 years of age (administered with concomitant IV ondansetron, with or without dexamethasone). Study arms included 0.4 mg/kg (maximum of 20 mg), 1.2 mg/kg (maximum of 60 mg), and 3 mg/kg (maximum of 150 mg) of fosaprepitant. The fosaprepitant dosing regimens were intended to achieve aprepitant PK exposures (AUC and Cmax) similar to those in adults receiving single-day 20 mg, 60 mg, and 150 mg doses of IV fosaprepitant. Based on interim observation of lower exposures in pediatric patients < 12 years, a higher dose (5 mg/kg [maximum of 150 mg]) was added and evaluated in an open-label manner. In addition to assessing PK, safety and tolerability for the single-day regimen, safety in up to 5 additional cycles was also evaluated, at doses of 150 mg for adolescents and 3 mg/kg or 5 mg/kg (maximum of 150 mg) for patients < 12 years.

Study 044 was a phase 3 randomized controlled trial comparing a **single dose** of fosaprepitant + ondansetron to ondansetron alone in preventing CINV in pediatric patients. Adolescents received a single-day regimen of 150 mg fosaprepitant; patients < 12 years old received 5 mg/kg (maximum of 150 mg). The study was concluded prematurely following the approval of oral aprepitant for the pediatric population, based on data that confirmed similar efficacy of

aprepitant in adults and children. This information provided the rationale for extrapolating pediatric efficacy for fosaprepitant. Efficacy analyses were therefore not performed for the 71 of 180 planned subjects who completed the trial.

The Applicant proposed the following pediatric doses for the various ages/regimens:

Table 1 Proposed Pediatric Dosing and Dose Regimens

Age	Single-Day Fosaprepitant Regimen		
	Regimen Day 1		
12-17 years	150 mg IV over 30”		
2 to < 12 years	4 mg/kg (maximum 150 mg) IV over 60”		
6 months to < 2 years	5 mg/kg (maximum 150 mg) IV over 60”		
	3-Day Regimen (Fosaprepitant Day 1, Aprepitant Days 2-3)		
	Day 1	Day 2	Day 3
12-17 years	115 mg IV over 30”	80 mg aprepitant po	80 mg aprepitant po
6 months to < 12 years	3 mg/kg (maximum 115 mg) IV over 60”	2 mg/kg aprepitant po (maximum 80 mg)	2 mg/kg aprepitant po (maximum 80 mg)

Source: Based on Section 2.2, Emend for injection proposed labeling

The proposed doses for fosaprepitant were derived using an exposure-matching strategy based on the PK studies conducted following a single dose fosaprepitant, and modeling and simulation of PK parameters for aprepitant. Administration of multiple consecutive doses of IV fosaprepitant (i.e., a 3-day IV/IV/IV regimen) was not studied.

Data to support the single-day regimen:

Exposure was compared across studies for adults and adolescents. Predicted exposure in pediatric patients < 12 years of age, based on modeling and simulation, was compared to the same observed data in adults. Overall, AUC was higher in pediatric patients, and Cmax ranged from slightly lower to slightly higher (see Table 2), supporting the extrapolation of efficacy from adult data. As noted in the Clinical Pharmacology review, the concentration-time profiles for adults and adolescents were superimposable. For pediatric patients aged 6 months to < 12 years, the proposed infusion duration of 60” resulted in exposures comparable to those in adults receiving a 30” infusion.

Table 2 Observed and Simulated Aprepitant Exposures following Single-dose IV Infusion

Study Dose Age Group	Descriptive Statistics	$AUC_{0-\infty}$ ng°hr/mL	$AUC_{0-24\ hr}$ ng°hr/mL	C_{max} ng/mL	$C_{24\ hr}$ ng/mL
Observed Data					
P165 150 mg Healthy Adults	N	41	41	41	41
	Geometric Mean	**35,031**	**24,500**	**4,010**	**577**
P029 150 mg 12-17 y/o	N	3	12	12	12
	Geometric Mean	33,300	29,400	3,360	675
P134 150 mg 12-17 y/o	N	8	11	11	11
	Geometric Mean	42,000	30,000	5,380	769
Simulated Data					
4 mg/kg 6 to < 12 y/o	Geometric Mean	53,031	35,235	3,591	682
4 mg/kg 2 to < 6 y/o	Geometric Mean	37,909	28,205	3,080	444
5 mg/kg 6 months to < 2 y/o	Geometric Mean	40,021	30,125	3,116	481

Source: Based on Tables 1 and 2, Clinical Pharmacology review by Elizabeth Shang, Ph.D., dated March 31, 2018

Data to support the 3-day regimen:

Exposure data for the 3-day regimen was based on modeling and simulation of the following dosing regimens:

12 to < 17 years:

Day 1: 115 mg fosaprepitant IV or 125 mg aprepitant po

Days 2-3: 80 mg fosaprepitant IV or 80 mg aprepitant po

6 months to < 12 years:

Day 1: 3 mg/kg fosaprepitant IV or 3 mg/kg aprepitant po

Days 2-3: 2 mg/kg fosaprepitant IV or 2 mg/kg aprepitant po

As described in detail in the Clinical Pharmacology review, IV administration of fosaprepitant was predicted to result in similar AUC and up to 2-fold higher Cmax compared to oral aprepitant administration over the three-day regimen. The safety of the higher Cmax predicted for the Day 1 dose of the 3-day IV fosaprepitant regimen was addressed by safety data supporting the safety data obtained with the higher dose used in the single-day fosaprepitant IV regimen.

The Cmax for IV administration on Days 2 and 3 was predicted to be lower than that on Day 1, but still about 2-fold higher than the Cmax associated with oral administration of aprepitant on Days 2 and 3. Because no subjects received IV dosing of fosaprepitant on Days 2 and 3, there are no safety data available to support the safety of repeated administration resulting in this higher Cmax on Days 2 and 3 of the 3-day regimen, compared to that associated with the 3-day oral regimen.

The Pharmacometrics reviewers and the Applicant explored whether a longer infusion duration might reduce the Cmax while maintaining an AUC similar to that of oral administration. However, PK simulations indicated that an infusion duration of longer than 8 hours would be needed to match the Cmax of aprepitant following IV infusion to that of oral administration for Days 2 and 3, and this was deemed impractical. Therefore, while the proposed IV/IV/IV regimen would be expected to have acceptable efficacy, the safety of the higher Cmax has not been supported, and the review team recommends approval of a 3-day IV/po/po regimen.

Results of a thorough QT study conducted with IV fosaprepitant at up to 200 mg (1.3-fold the approved adult dose) also cover the maximum dose proposed for use in pediatric patients of 150 mg.

The Applicant was unable to assess the effects of fosaprepitant on dexamethasone exposures in children aged 0-1 year of age in Study 29 (see Section 9), due to the limited PK information obtained in this age group.

6. Clinical/Statistical-Efficacy

This NDA did not include studies that formally evaluated efficacy; rather, the Applicant sought to rely upon extrapolation of efficacy of the 1-day IV regimen from that demonstrated in adults who received similar aprepitant exposure in the setting of single-day chemotherapy. Further, the Applicant sought to support the 3-day IV regimen by bridging to efficacy demonstrated for the pediatric 3-day oral aprepitant regimen, given that the activity of the prodrug fosaprepitant is due to its metabolism into aprepitant, and given equivalent exposures obtained with the two routes of administration.

7. Safety

The safety review focused on subjects exposed to fosaprepitant in Studies 134, 029 and 044. As noted, subjects in these studies received only single-day dosing of fosaprepitant; regimens evaluated were either 1-day dosing, or a 3-day regimen consisting of IV on Day 1, followed by oral aprepitant on Days 2 and 3 (IV/po/po). There were a total of 139 subjects exposed to the doses proposed for the single-day regimen, and 199 exposed to the broader range of doses proposed for the 3-day IV regimen. A subset of subjects was treated over additional cycles (2-6 cycles). There were 30 subjects under age 2 years in the safety database, with a single subject under 6 months of age. The duration of safety follow-up over the three studies ranged from two to three weeks post-dosing.

There were no deaths in the first cycle of treatment; the three deaths that occurred in patients treated for 2-6 cycles were not considered drug-related. The most common serious adverse events in Cycle 1 and in Cycles 2-6 included febrile neutropenia, a known sequela to chemotherapy, and rates did not differ between treatment and control arms. Common AEs observed slightly more commonly in the fosaprepitant arms of the safety database compared to the control arms included febrile neutropenia, leukopenia, neutropenia and vomiting (based on 4 cases in the fosaprepitant arms and none in the control arms).

Among laboratory findings, hematologic changes likely to reflect the effects of chemotherapy were observed in both fosaprepitant and controls arms. A single case of drug-induced liver injury was observed in a patient receiving Cycle 3 of 3 mg/kg fosaprepitant (Day 109); the event resolved within 2 months. The Applicant did not provide detailed information about the

chemotherapeutic agent(s) used, other concomitant medications, or other possible factors associated with the observed increases in aminotransferases and bilirubin. Reports of elevation of these laboratory values are included in adverse reaction labeling for aprepitant.

Four subjects withdrew from the studies prior to completing both treatment periods due to an adverse event (AE); AEs included one case each of anaphylactic reaction, hypersensitivity, discomfort/flushing, and pyrexia. Regarding the three cases of potential hypersensitivity reactions, Dr. Johnson noted that the event reported as "hypersensitivity" would be characterized as anaphylaxis according to World Allergy Association guidelines, and the case of flushing and discomfort may have represented a hypersensitivity reaction; this would result in a total of three hypersensitivity reactions among all AEs, rather than the two the Applicant reported.

The Division of Pharmacovigilance queried the FAERS database for postmarketing AE reports occurring in association with off-label pediatric use of fosaprepitant IV. Five cases of anaphylaxis (3; all of whom were hospitalized) or anaphylactic shock (2) were reported:

- A 15 year old US patient who developed an acute anaphylactic reaction requiring oxygen, epinephrine and steroids, on his second dose of fosaprepitant
- An 11 year old US patient who developed difficulty breathing, vomiting and drop in systolic BP to 90 requiring epinephrine, on her third dose of fosaprepitant
- A 15 year old US patient who developed difficulty breathing and "turned purple" requiring epinephrine, steroids and antihistamines and an H2 blocker
- A 5 year old Japanese patient who developed anaphylactic shock on her first dose of fosaprepitant; she received no treatment, but fosaprepitant was discontinued after she had received 20 ml of the infusion
- A 15 year old Brazilian patient who developed anaphylactic shock within 5" of starting his first dose of fosaprepitant and was treated with steroids; he received fosaprepitant again three weeks later preceded by steroid prophylaxis, but experienced anaphylactic shock again, which was treated with diphenhydramine

Hypersensitivity, including anaphylaxis, is labeled in the Warnings and Precautions section of the Emend for injection labeling; while there is no evidence that these reactions occur more frequently in pediatric patients exposed to IV dosing, some postmarketing reports occurred after an initial problem-free exposure, which reinforces the concern about the absence of safety data to support three consecutive days of IV dosing.

The review team considered various approaches by which the 3-day IV regimen could be supported, including extending the duration of infusion to lower the Cmax. As noted in Section 5, this was not a feasible approach. An information request sought additional safety data from the Applicant to support 3-day IV dosing (e.g., from off-label use in pediatric patients), but the Applicant was not able to provide additional data. The Drug Use reviewers in the Office of Surveillance and Epidemiology indicated that use of IV fosaprepitant by patients under age 17 years comprises < 0.2% of all use.

Dr. Johnson concluded that the lack of safety data for fosaprepitant dosing on Days 2 and 3 of the proposed 3-day IV/IV/IV regimen does not permit approval of this regimen, given the higher Cmax demonstrated in modeling and simulation compared to the 3-day oral aprepitant

regimen. She recommended that the proposed option of a 3-day regimen comprising IV/po/po administration on Days 1-3, respectively, be approved.

The Applicant will be asked to provide data on the safety of a 3-day IV/IV/IV regimen in a postmarketing required trial (see Section 12); the occurrence of hypersensitivity reactions and liver enzyme elevations can be evaluated further in this trial.

8. Advisory Committee Meeting

The current submission relates to adding pediatric single-day and 3-day IV dosing regimens for an approved drug, which currently has approved 3-day oral regimens for adults and pediatrics, and a single-day IV regimen for adults. Therefore, advisory committee consideration was not warranted.

9. Pediatrics

During the review cycle for NDA 22-023, the Division advised the Sponsor that (b) (4) would agree to waive studies in pediatric patients < 6 months and to defer studies in older children. Dr. Kim's CDTL review describes the chronology of various PREA PMRs negotiated with the Applicant. The final PREA PMR 1663-3, issued in October 2016, required final study report submission by December 2017 of the following:

> A PK/PD study to characterize aprepitant PK parameters following administration of a single dose of intravenous fosaprepitant, in combination with a $5HT_3$ 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.
>
> Use modeling and simulation including the results of the above study to identify 1-Day and 3-Day intravenous fosaprepitant doses in pediatric patients 0 to 17 years of age that provide similar aprepitant PK exposures to pediatric aprepitant doses and exposures which have demonstrated acceptable safety and efficacy profiles in patients receiving single and multi-day chemotherapy regimens, respectively.

The Division issued a Written Request (WR) for pediatric studies on Feb. 2, 2009, which was subsequently amended in 2011, 2012, 2016 (associated with PMR 1663-3) and 2017. The final WR called for conduct of two studies, with final study reports to be submitted by Dec. 31, 2017. The studies were:

- Study 1: a 4-week IV toxicity study in juvenile dogs with at least 3 dose levels of fosaprepitant, to support the safety of EDTA disodium (b) (4) mg (b) (4) vial)
- Study 2: (conducted as Study 029) a single dose, randomized, PK and dose-ranging study of at least 3 dose levels of fosaprepitant, and placebo, to characterize aprepitant PK parameters and the exposure response relationship following intravenous fosaprepitant (age-appropriate I.V. formulation) in combination with a 5HT3 antagonist and dexamethasone in the pediatric patient age groups specified below. Available PK data from pediatric studies of aprepitant must be used to design Study 2. Study 1 must be completed and results reported to the Agency before children <12 years of age can be enrolled in Study 2.

Evaluate also the impact of intravenous fosaprepitant on the PK of dexamethasone in the pediatric age group 0 to 1 year.

The PK protocol may use a population PK approach.

Further, the Applicant was required to conduct modeling and simulation to identify single-day and 3-day IV fosaprepitant doses for pediatric patients ages 0 to 17 years that provide aprepitant exposures similar to the single-day IV regimen or the 3-day oral regimen in adults and pediatric patients, respectively.

The application was discussed at the Pediatric Exclusivity Board on February 28, 2018. Despite efforts by the Applicant, only one subject < 6 months of age was enrolled in the pediatric PK study, and no PK was obtained from this subject. As noted, the Applicant proposed that the indication be limited to pediatric patients 6 months of age and older. In addition, due to the absence of PK information in subjects between birth and 6 months of age, the Applicant was unable to evaluate the impact of fosaprepitant on the PK of dexamethasone. The Applicant further stated that of 5 subjects under one year of age enrolled into Study 134, none received dexamethasone, and that use of dexamethasone as part of the antiemetic regimen is rare in this age group. The WR allowed the option for the Applicant to fulfill the terms by providing documentation of diligent and reasonable efforts to enroll subjects across the full age range requested, and the Applicant documented its efforts to do so. Therefore, pediatric exclusivity was granted for this project.

The application was also discussed at the Pediatric Review Committee (PeRC) on March 7, 2018. As noted, while the modeling and simulation identified pediatric IV doses that matched the AUC of the pediatric oral formulation, the Cmax was approximately 2x higher for the IV formulation. Although the absence of safety data to support repeated IV dosing over the 3-day regimen does not permit approval of the IV/IV/IV regimen, it was concluded that the terms of the PREA PMR had been fulfilled. There is value in having the option of IV administration throughout the 3-day pediatric regimen (e.g., for pediatric patients who cannot tolerate oral dosing), and therefore, the Applicant will be required to conduct a post-marketing safety trial to obtain safety data that may support inclusion of a 3-day IV/IV/IV regimen in labeling in the future (see Section 12).

10. Other Relevant Regulatory Issues

Dr. Johnson's review includes the financial disclosure assessment; no investigators had disclosable financial interests or arrangements.

No inspections were requested of the Office of Study Integrity and Surveillance (OSIS) because no studies provided efficacy data relied upon for approval; there were no other issues of concern with the submitted studies that warranted inspection.

There are no other unresolved relevant regulatory issues.

11. Labeling

The major changes to labeling from that currently approved include addition of a pediatric indication in Section 1 and pediatric dosing instructions in Section 2. Because of the inability to obtain PK data on pediatric patients < 6 months of age, the Applicant proposed and FDA agreed that the IV regimens would be labeled for use in pediatric patients ages 6 months and

older. Similarly, given that the lowest body weight of subjects included in the safety database was 6.8 kg, the product will be labeled for use only by pediatric subjects weighing > 6 kg.

Major issues addressed during labeling discussions with the Applicant included the lack of safety data to support the proposed 3-day IV/IV/IV regimen, given the anticipated two-fold higher Cmax compared to oral dosing. The Applicant had originally proposed that the 3-day regimen could permit either IV or oral dosing on Days 2 and 3, but agreed that it would no longer seek approval of the IV dosing on Days 2 and 3. Thus, the 3-day regimen to be described in labeling is IV/po/po on Days 1, 2 and 3, respectively.

In the absence of specific data on the impact of fosaprepitant on the PK of dexamethasone, labeling regarding the concomitant use of dexamethasone will continue to recommend that 50% of the otherwise recommended dexamethasone dose be administered (consistent with existing labeling for fosaprepitant for adults and for aprepitant for adult and pediatric patients).

A labeling supplement (S-018) that added language to address new safety information regarding the risk of infusion site reactions was approved on March 26, 2018. The Applicant incorporated this new language in the currently proposed labeling.

Carton and container labeling was unchanged from that currently approved. Final agreement with the Applicant on labeling was reached on April 3, 2018, and recommendations by the primary and consulting review disciplines, including DPMH, DMEPA, DMPP and OPDP, have been incorporated into the labeling.

12. Decision/Action/Risk Benefit Assessment

- **Regulatory Action**

I agree with the recommendation of the CDTL, Insook Kim, Ph.D., and the other review disciplines that Emend for injection be approved for use in pediatric patients 6 months of age and above for prevention of CINV due to HEC and to MEC. The clinical and clinical pharmacology reviewers and team leaders recommended approval of the single-day IV regimen for pediatric patients aged 6 months and older who are receiving a single-day chemotherapy regimen. Although the Cmax for aprepitant seen after administration of IV fosaprepitant is higher than that of oral aprepitant on Day 1, the available safety data from Studies 134, 029 and 044 are adequate to provide reassurance about the safety of this higher Cmax.

With respect to the 3-day IV regimen, the review team concludes that the absence of pediatric safety data from multi-day IV dosing, given the higher Cmax observed on Days 2 and 3 (albeit lower than that observed on Day 1), precludes approval of a 3-day IV regimen. Instead, they recommended approval of a 3-day regimen to consist of IV dosing on Day 1, followed by oral dosing on Days 2 and 3.

I concur that the efficacy of the single-day IV regimen can be extrapolated from adult data, based on similar aprepitant exposure, and limited to the scenario in which chemotherapy is administered as a single-day regimen, as it was in the adult studies. The pathophysiology of CINV and the response to NK-1 receptor antagonists is similar in adults and pediatric patients. The safety data, based on 139 pediatric patients, supports the benefit/risk profile of this dosing regimen. Therefore, I recommend approval of labeling for this regimen for pediatric patients 6 months of age and above.

Regarding the 3-day dosing regimen, which would be used by pediatric patients receiving either a single-day or a multiple-day course of chemotherapy, the similar (or higher) aprepitant exposure observed with the IV dosing regimen compared to the oral regimen supports bridging the efficacy to that demonstrated for the 3-day oral aprepitant regimen. There are safety data from 199 pediatric patients to support the higher Cmax expected for the Day 1 IV administration compared to oral administration. However, there are no safety data on use of multi-day IV dosing to support the safety of the higher Cmax expected on Days 2 and 3 for IV dosing compared to oral dosing. Therefore, at this time, the 3-day regimen can be approved only as an IV/po/po dosing regimen. There are adequate safety data from Day 1 IV administration and from the 3-day oral dosing regimen to support this regimen.

- **Risk Benefit Assessment**

There are currently no IV NK-1 receptor antagonists approved in the pediatric population; aprepitant is approved only as a 3-day oral regimen. The data submitted in this efficacy supplement do not change the benefit/risk assessment of aprepitant/fosaprepitant in general, and do not raise any additional risks specific to the injectable formulation for use in pediatrics. However, in the absence of safety data to support the use of 3 consecutive days of IV dosing, which provides a higher Cmax each day compared to the 3-day oral regimen, the benefit/risk ratio of this specific regimen cannot be determined. Therefore, approval is limited to a single-day regimen of IV dosing, and a 3-day regimen that consists of IV dosing on Day 1, followed by oral aprepitant on Days 2 and 3. The benefit/risk analysis remains favorable for the agreed-upon indications.

- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies**

None are needed beyond labeling.

- **Recommendation for other Postmarketing Requirements and Commitments**

The Applicant has agreed to the following post-marketing requirement:

> Conduct a trial to evaluate the safety of multiple cycles of intravenous administration of fosaprepitant daily for three consecutive days for the prevention of chemotherapy-induced nausea and vomiting in pediatric patients 6 months to 17 years of age.

The agreed-upon milestones are:

- Draft Protocol Submission: 10/2018
- Final Protocol Submission: 04/2019
- Study/Trial Completion: 03/2021
- Final Report Submission: 09/2021

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/s/

LISA M SOULE
04/03/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022023Orig1s017

OFFICER/EMPLOYEE LIST

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 3, 2018

TO: Administrative file for NDA 22023/S-017 Emend (fosaprepitant) inj.

FROM: Mary Chung, Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products

SUBJECT: Officer/Employee List for NDA 22023/S-017 Emend (fosaprepitant) inj.

APPLICATION/DRUG: NDA 22023/S-017 Emend (fosaprepitant) injection

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

Abraham, Sherly
Alexander, John J.
Chakder, Sushanta
Dowdy, Karen
Earp, Justin
Kim, Insook
Kordzakhia, George
Lewis, David B.
Shang, Elizabeth
Soldatova, Lyudmila
Soule, Lisa
Strongin, Brian
Taylor, Amy
Williams, Sharon

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/s/

MARY H CHUNG
04/05/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022023Orig1s017

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 02, 2018
From	Insook Kim, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 22,023 Supplement 017
Applicant	Merck Sharp & Dohme Corp.
Date of Submission	October 2, 2017
PDUFA Goal Date	April 3, 2017
Proprietary Name / **Established (USAN) names**	EMEND for Injection Fosaprepitant dimeglumine
Dosage forms / Strength	Powder for injection solution
Proposed Indication(s)	for prevention of chemotherapy-induced nausea and vomiting (CINV) to pediatric patients 6 months and older • acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin. • delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)
Recommended:	*Approval*

EDR Location: \\CDSESUB1\evsprod\NDA022023\022023.enx

1. Introduction

In this supplemental NDA, the applicant proposes to extend the use of EMEND(fosaprepitant) for Injection to pediatric patients 6 months and older who are receiving highly or moderately emetogenic cancer chemotherapy for prevention of chemotherapy-induced nausea and vomiting (CINV). EMEND (fosaprepitant) for Injection has been approved since 2010 for prevention of CINV in adults receiving highly or moderately emetogenic cancer chemotherapy. Fosaprepitant is a prodrug of aprepitant and upon intravenous infusion, fosaprepitant is converted to aprepitant and is undetectable in plasma within 30 minutes in adults[1]. The antiemetic effects of fosaprepitant are attributed to aprepitant. Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK1) receptors. Aprepitant augments the antiemetic activity of the 5-HT3-receptor antagonist ondansetron and the corticosteroid dexamethasone and inhibits both the acute and delayed phases of cisplatin-induced emesis[2].
The approved dosage regimen of EMEND (fosaprepitant) for adult cancer patients is a single dose administration of 150 mg infused intravenously over 20 to 30 minutes completing the infusion approximately 30 minute prior to chemotherapy.

The pediatric studies in this submission were conducted in fulfillment of PREA PMR 1633-3 as below, and in response to the Written Request under BPCA.

[1] Clinical Pharmacology Review of original NDA 22023 dated 4/30/2007
[2] Product Label for EMEND (fosaprepitant dimeglumine) for Injection

1663-3
A PK/PD study to characterize aprepitant PK parameters following administration of a single dose of intravenous fosaprepitant, in combination with a $5HT_3$ 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.

Use modeling and simulation including the results of the above study to identify 1-Day and 3-Day intravenous fosaprepitant doses in pediatric patients 0 to 17 years of age that provide similar aprepitant PK exposures to pediatric aprepitant doses and exposures which have demonstrated acceptable safety and efficacy profiles in patients receiving single and multi-day chemotherapy regimens, respectively.

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

The following primary and consult reviews were used for this CDTL review:

Clinical Review (3/2/18)	Aisha Peterson Johnson, M.D./Anil Rajpal, M.D.
Clinical Pharmacology Review (3/31/18)	Elizabeth Shang, Ph.D./Justin Earp, Ph.D. /Insook Kim, Ph.D./ Gilbert Buckart, Pharm.D.
Statistical Review (3/2/18)	Ling Lan, Ph.D./George Kordzakhia, Ph.D.
Pediatric Labeling Review (3/5/18)	Amy M. Taylor, M.D./Hari Cheryl Sachs, M.D./John J. Alexander, M.D.
Office of Product Quality Review Review of Chemistry, Manufacturing, and Controls (3/7/18)	Hossein Khorshidi, Ph.D./David Lewis, Ph.D.
Pharmacology/Toxicology Review (3/2/18)	Yolanda R. Branch, Ph.D./Sushanta Chakder, Ph.D.
Division of Medication Error Prevention and Analysis Label and Labeling Review (3/1/18)	Sherly Abraham, R.Ph./Sarah K. Vee, Pharm.D.
Office of Prescription Drug Promotion Memorandum (2/28/18) Office of Medical Policy Patient Labeling Review (2/27/18)	Meeta Patel, Pharm.D. Karen Dowdy, RN/Meeta Patel, Pharm.D./ /Sharon Williams, RN.

2. Background

Fosaprepitant is approved for the prevention of chemotherapy-induced nausea and vomiting in adults under NDA 22023/S-004 (HEC) in 2010 and NDA 22023/S-006 (MEC) in 2016, respectively.
Emend (fosaprepitant dimeglumine) for injection is indicated for adults, in combination with other antiemetic agents, for the prevention of: 1) acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin; and 2) delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) in adults. The approved regimen in adults is a single dose of 150 mg fosaprepitant intravenously infused over 20 to 30 minutes approximately 30 minutes prior to chemotherapy. It has not been studied for treatment of established nausea and vomiting.

Fosaprepitant is a prodrug of aprepitant that can be administered intravenously (IV). Fosaprepitant is converted to aprepitant (within 30 minutes) after IV administration via the action of ubiquitous phosphatases, and the pharmacological effect of fosaprepitant is attributed to aprepitant, a neurokinin type 1 receptor antagonist.

Emend for Injection 115 mg was originally approved in 2008 as an alternative administration route for Day 1 of oral aprepitant three-day regimen, (given as EMEND for Injection 115 mg on Day 1 followed by EMEND oral capsules 80 mg on Days 2 and 3. The approval of EMEND for Injection 115 mg relied upon the demonstration of similar systemic exposure to aprepitant following a single dose of fosaprepitant 115 mg and aprepitant 125 mg. The three-day regimen with the intravenous fosaprepitant on Day 1 was discontinued after approval of single dose fosaprepitant 150 mg in 2010, not for safety or efficacy reasons.

Aprepitant (Emend capsule) is approved for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy (HEC) in 2003 and moderately emetogenic chemotherapy (MEC) in 2005 for adult patients. In 2015 EMEND (aprepitant) capsule for oral was approved for use in pediatric patients ages 6 months and older as a three-day regimen based on a randomized, double-blind, active comparator-controlled clinical study in pediatric patients aged 6 months to 17 years receiving HEC or MEC[3,4]. Refer to the Division Director's reviews of NDA 21549/S-25 Emend (aprepitant) oral capsule in adolescents approved on 8/28/2015 and NDA 207865 for Emend (aprepitant) oral suspension in patients less than 12 years old approved on 12/17/2015 for the basis of the approval of oral aprepitant for CINV in pediatric patients.

The recommended doses for the 3-day oral aprepitant regimen are 125 mg on Day 1 followed by 80 mg on Days 2 and 3 in adults and adolescent patients, and 3 mg/kg on Day 1 followed by 2 mg/kg on Days 2 and 3 in pediatric patients > 6 months and < 12 years old.

[3] Label for EMEND (aprepitant) capsule and oral suspension
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021549s027,207865s001lbl.pdf
[4] NDA 21549/S-025 Division Director Review by Dr. Griebel

In support of the proposed use of EMEND (fosaprepitant) for Injection in pediatric patients 6 months and older, the applicant conducted an open-label PK trial (Study 134)[5], a placebo-controlled phase 2b PK/PD trial (Study 029), and a phase 3 placebo-controlled trial (Study 044).

Upon the approval of 115 mg EMEND for Injection in 2008, a study was required in adolescents and younger pediatric patients receiving emetogenic chemotherapy (HEC or MEC) to evaluate fosaprepitant PK, safety, and tolerability (PREA PMR 1450-1).

Upon the approval of 150 mg EMEND for Injection in 2010, two pediatric studies were required for a single dose of intravenous fosaprepitant, i.e., a PK/PD study (PREA PMR 1663-1) and an adequate, placebo-controlled, superiority study to evaluate the safety and efficacy in pediatric patients ages 0 to 17 years (PREA PMR 1663-2)[6].

After the approval of oral aprepitant in pediatric patients, the Applicant proposed to extrapolate the efficacy of a single-day fosaprepitant regimen from adults to pediatric patients based on the similar systemic exposure to aprepitant, and requested release from the above PREA-PMRs. However, because multi-day emetogenic chemotherapy is more common in pediatric patients while fosaprepitant efficacy was established in adult patients receiving a single day chemotherapy, the Agency did not consider the extrapolation of the efficacy in adults to pediatric patients was appropriate. The applicant revised the proposal to support a 3-day IV fosaprepitant regimen in pediatric patients based on matching systemic exposures to aprepitant observed with the approved 3-day oral aprepitant regimen.

The Agency agreed that the efficacy of fosaprepitant in pediatric patients could be extrapolated from the efficacy of fosaprepitant in adult patients receiving single day chemotherapy and from the efficacy of aprepitant in pediatric patients receiving single day or multi-day chemotherapy regimens.

On October 13, 2016, the Agency granted the Applicant's request for release of PREA-PMRs 1450-1, 1663-1, and 1663-2, and issued a new deferred PREA-PMR 1663-3 and issued Amendment #3 to the WR. The pediatric development program[7] was revised to determine the pediatric dose for fosaprepitant based on a PK study for fosaprepitant conducted in pediatric patients ages > 6 months and older and the modeling and simulation to derive the pediatric doses resulting in the systemic exposures to aprepitant similar to those from the approved single dose fosaprepitant in adults receiving a single-day chemotherapy and the approved oral aprepitant doses in pediatric patients > 6 months and older receiving single-day or multi-day chemotherapy regimens.

As required by PMR 1633-3, the Applicant conducted a PK/PD study for a single dose fosaprepitant in pediatric cancer patients (Study 029) and conducted modeling and simulation

[5] The PK of intravenous fosaprepitant was studied as a 3-day fosaprepitant/aprepitant/aprepitant regimen in Study 134 and the results were submitted in support of oral aprepitant in pediatric patients in NDA 21549/S-25.
[6] NDA 022023/S-004 Supplement Approval Letter
https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/022023s004ltr.pdf
[7] Amendment #3 to the WR dated 10/13/16

to identify two dosing regimens, i.e., single- and 3-day regimen for intravenous fosaprepitant as shown below. For the 3-day fosaprepitant regimen, the Applicant proposed to allow substituting the doses on Days 2 and 3 for fosaprepitant with oral aprepitant pediatric doses. The Applicant proposed the fosaprepitant doses for the 3-day regimen based on not only the exposure matching but also in consideration of the potential dosing error. The proposed pediatric doses for the 3-day IV fosaprepitant regimen (b) (4) . The safety and efficacy trial (Study 044) for a single dose fosaprepitant in pediatric patients receiving single- and multi-day chemotherapy regimens was prematurely discontinued upon the decision to extrapolate the efficacy of fosaprepitant from pediatric oral aprepitant.

Please refer to the clinical review by Dr. Johnson for comprehensive regulatory background and marketing history.

Table 1 Proposed 3-Day IV/PO Fosaprepitant/Aprepitant Dosing Regimen and 1-Day Fosaprepitant Regimens by Age Group

(b) (4)

3. CMC/Device

The CMC reviewers, Drs. Hossein and Lewis, recommended approval of the supplement. The reviewers referred to the approval of Prior Approval Supplement (NDA 22,023/S-014) on December 2, 2016 for a fosaprepitant formulation with a reduced amount of ethylenediaminetetraacetic acid (EDTA) from 18.8 mg[8] to 5.4 mg per vial, proposed as an age-appropriate formulation for pediatric patients developed per the Agency's request for an age-appropriate formulation. The reviewers stated that the "reduced" EDTA formulation is currently being distributed for use in adults and will also be available to support use in pediatric patients, pending approval of this pediatric efficacy supplement. It was noted that the re-formulated product has been assigned a new NDC number since, for a period of time, both the original and the "reduced" EDTA formulation will be on the market and the new NDC number is appropriate.

[8] https://www.accessdata fda.gov/drugsatfda_docs/label/2014/022023s011lbl.pdf

Of note, both the original formulation and the "reduced" EDTA formulation were used in the clinical trials in pediatric patients. See Section 5 Clinical Pharmacology.

The CMC reviewers found the applicant's request for a *Categorical Exclusion from requirements to prepare an Environmental Assessment* under 21 CFR 25.31(b) acceptable as the estimated concentration of the drug substance at the point of entry into the aquatic environment, referred to as the Expected Introduction Concentration (EIC), is (b) (4) ppb which is below the allowed limit of 1.0 ppb. No CMC-related labeling changes are proposed in this supplement, and there are no recommended changes by the reviewers.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewers, Drs. Branch and Chakder, recommended approval. The reviewers concluded that the nonclinical studies submitted in the original and subsequent supplemental applications support the safety of Fosaprepitant (EMEND) injection in pediatric patients 6 months to 17 years of age for the prevention of MEC and HEC. The reviewers also noted that there are no novel excipients used in the Emend Injection, and there are no safety concerns for the excipients.

In this supplement, there were no new nonclinical studies submitted; however, the reviewers noted that two toxicology studies in juvenile animals were conducted in support of oral aprepitant and IV. fosaprepitant use in pediatric patients, i.e., an oral toxicity study of aprepitant in juvenile rats and a 4-week toxicity study of fosaprepitant formulation in juvenile dogs. Two juvenile animal toxicology studies were reviewed under the original submission of NDA 207865 in support of oral aprepitant approval in pediatric patients > 6 months and older by the FDA (refer to the Pharmacology and toxicology review by Dr. Chakder dated July 21, 2015). In addition, the previously submitted nonclinical studies with fosaprepitant and aprepitant were reviewed as part of the initial and supplemental marketing applications for use of aprepitant in adults.

Of note, the 4-week intravenous injection toxicity study in juvenile dogs was conducted in response to Study 1 in the Written Request to evaluate the potential toxicity of EDTA in fosaprepitant formulation.

The reviewers noted the following regarding the findings from the 4-week juvenile dog study with fosaprepitant.

> "The potential effects of EDTA in a clinical fosaprepitant formulation (TT#10-9017) and the toxicity and toxicokinetic of fosaprepitant were assessed in a 4-week intravenous injection toxicity study in juvenile beagle dogs. Beginning on postnatal day 14, juvenile dogs were intravenously administered fosaprepitant solution (2, 4, and 6 mg/kg/day) containing 0.125 mg/ml EDTA once daily for 4 weeks. There were no treatment related changes on electrocardiography, heart rate, blood pressure, or clinical pathology parameters. In the female dogs given 4 mg/kg/day and 6 mg/kg/day, fosaprepitant related histopathological changes noted were hypertrophy of the endometrium and myometrium within the horns and body of the uterus, hypertrophy of the cervical muscularis and edema of the lamina propria

and submucosa of the vagina. Treatment related histopathologic changes were observed in the testes in male dogs at 6 mg/kg/day (reduced size of Leydig cells in the testes) that correlated with decreased testicular weights. These fosaprepitant related changes in the female reproductive tract and Leydig cells in males were considered reversible and of minimal toxicological significance. In the dogs given 6 mg/kg/day, there was a decrease in heart weight that was not associated with any histopathological or electrocardiographic changes. All fosaprepitant treated dogs had microscopic findings at the injection sites related to the intravenous fosaprepitant formulation. There were no findings attributable to EDTA. The 4 mg/kg dose was the NOAEL, and the 6 mg/kg/day dose was a well-tolerated dose in this study."

Upon the conversion to aprepitant, fosaprepitant releases phosphate because fosaprepitant is a phosphorylated prodrug of aprepitant. Upon the conversion, 115 mg fosaprepitant releases 18.3 mg phosphate and meglumine 73 mg. Dr. Branch, the non-clinical reviewer, noted that after 28 day repeat dosing with fosaprepitant injection in juvenile dogs, there were no increases in phosphate levels.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology reviewers recommended approval of the single-dose fosaprepitant regimen, and the 3-day regimen for fosaprepitant on Day 1 followed by oral aprepitant on Days 2 and 3. The clinical pharmacology reviewers concluded that the proposed pediatric doses for IV fosaprepitant are acceptable to support the efficacy and safety of a single dose fosaprepitant injection. The fosaprepitant dose on Day 1 as part of the 3-day regimen is also acceptable for the safety and efficacy. The efficacy of the 3-day IV fosaprepitant regimen (IV/IV/IV) is supported by the comparable AUC and higher Cmax for aprepitant compared to those after oral aprepitant in pediatric patients ages > 6 months and < 17 years old. However, the reviewers commented that the Cmax will be higher on Days 2 and 3 compared to those after the 3-day oral aprepitant regimen after the 3-day IV fosaprepitant regimen, and the safety of the 3-day IV fosaprepitant regimen cannot be fully supported by the aprepitant 3-day regimen. As such the reviewers found that three consecutive fosaprepitant dosing is not acceptable without additional safety data due to the higher Cmax on Days 2 and 3.

Fosaprepitant is a prodrug of aprepitant and it is rapidly converted to aprepitant upon intravenous administration. In adults, fosaprepitant concentrations become undetectable within 30 minutes after dosing. As such the efficacy and safety of aprepitant is mainly attributed to aprepitant.

The doses for fosaprepitant were derived by an exposure-matching strategy based on the PK studies conducted following a single dose fosaprepitant, and the modeling and simulation of PK parameters for aprepitant. Of note, IV fosaprepitant was not studied as multiple consecutive doses. The extrapolation of efficacy based on comparable systemic exposures to aprepitant was supported by 1) the efficacy of fosaprepitant in adult cancer patients receiving single-day chemotherapy, and 2) the efficacy of aprepitant in pediatric patients aged 6 months and older receiving single-day or multi-day chemotherapy regimens.

For the single-dose fosaprepitant regimen, the pediatric dose for fosaprepitant was derived from matching systemic exposures (Cmax and AUC) to aprepitant to those in adult healthy subjects in cross-study comparisons. For the three-day regimen, the systemic exposure (AUC) of aprepitant following IV fosaprepitant was matched to those in pediatric patients received oral aprepitant in cross-study comparisons.

The infusion duration proposed for adolescents is 30 minutes, while infusion over 20-30 minutes is recommended in adults. In patients > 6 months and < 12 years old, a longer infusion duration of 1 hour was studied and is proposed. Consistently for adults, the completion of infusion of fosaprepitant approximately 30 minutes prior to chemotherapy is recommended, regardless of the infusion duration.

Compared to those after oral aprepitant, the Cmax for the proposed IV doses were about 1.8-2-fold higher on Days 1-3. The Applicant commented that an increase in the infusion duration to 2 hours lowered the Cmax about ~ 15%, and did not pursue the longer infusion time as it was impractical. In addition, the Applicant was concerned that the different infusion rates between Day 1 and Days 2 and 3 may be confusing to health care providers. The clinical pharmacology reviewers noted that the simulation of PK indicated that infusion duration of longer than 8 hours would be needed to match the Cmax of aprepitant following IV infusion to that of oral administration for Days 2 and 3 and this was deemed impractical. Although Cmax of aprepitant on Day 1 of the 3-day fosaprepitant IV regimen is also higher than that after oral aprepitant, the safety of single-dose fosaprepitant is supported by the safety dataset submitted to this supplemental NDA.

Of note, in adult patients, fosaprepitant was given as a combination therapy with dexamethasone, and a 5-HT_3 antagonist. However, in pediatric patients, use of dexamethasone was optional due to the difference in clinical practice, while patients received a 5-HT_3 antagonist in addition to fosaprepitant. In the label, the dosing of a selected concomitant 5-HT3 antagonist is included as a part of fosaprepitant regimen, but for a corticosteroid, a dose reduction is specified, "if a corticosteroid, such as dexamethasone is co-administered".

The dosing instructions regarding the concomitant administration of corticosteroids and 5-HT_3 antagonists for pediatric patients are appropriate and consistent with those for adult patients. The label will refer to the approved labels for concomitant 5-HT3 antagonists, while a 50% dose-reduction is recommended for dexamethasone. The duration of dosage reduction for concomitant dexamethasone differs by the fosaprepitant regimen, i.e., dosage reduction is specified for dexamethasone on Days 1 and 2 for the single-dose fosaprepitant regimen, and on Days 1 through 4 for the 3-day regimen, due to the duration of CYP3A4 enzyme inhibition.

The clinical pharmacology reviewers noted that the thorough QT study conducted with intravenous fosaprepitant at 200 mg (1.3-fold the approved adult dose) covers the Cmax in pediatric patients at 150 mg in adolescents, 4 mg/kg in patients ages 2-12 years old, and 5 mg/kg in patients ages 6 months to 2 years old.

The pharmacokinetics (PK) for fosaprepitant and aprepitant were studied following a single dose of fosaprepitant in pediatric patients 6 months and older in two studies; Study 029, a PK/PD

study for a single dose fosaprepitant, and Study 134, a PK study for fosaprepitant as the 3-day IV/PO/PO regimen. Refer to the Clinical Pharmacology Review for more details.

Cross-study comparison of systemic exposures to aprepitant and fosaprepitant across age groups in pediatric patients and healthy adults

Similar to adults, the concentrations of fosaprepitant after a single dose administration were neglectable within 15 to 30 minutes after the end of infusion in pediatric patients.

PK of fosaprepitant

Table 2 Summary of Plasma Fosaprepitant Cmax Values in Pediatric Patients Following a Single Dose of IV Fosaprepitant

Dose	Age Group (years)	Mean Cmax ± SD (ng/mL)
115 mg Infused over 15 minutes	Healthy Adults^	5635 ± 1544[#]
3 mg/kg Infused over 1 hour[*]	6 Months to < 2 (n = 7)	2756 ± 3364
	2 to < 6 (n = 8)	3034 ± 1718
	6 to < 12 (n = 8)	1654 ± 1995
150 mg Infused over 30 minutes[*]	12 to 17 (n = 11)	1310 ± 964

[*]Study P134
^ Historical data submitted to original NDA 22023.
[#] C_{15min}. Reported Cmax is 5900 ng/mL occurred at 10 minutes post the start of infusion, which was likely due to sampling error. Refer to Clinical Pharmacology Review of the original NDA published in 2008.

Source: Table 5 of the Clinical Pharmacology Review

PK of aprepitant at the proposed pediatric doses for fosaprepitant by regimen

In pediatric patients 2 to <12 years of age and in adolescents (12 - 17 years) following a single dose 3 mg/kg IV fosaprepitant and 150 mg IV, respectively, aprepitant exhibited a biphasic decline with a mean (%CV) terminal t½ ranging from 6.55 (55.3%) to 10.5 (9.6%) hours (Study P029). Similarly, the mean (%CV) terminal t½ of aprepitant was 7.94 (36%) hours in patients 6 months to < 2 years following a single dose of 5 mg/kg IV fosaprepitant.

Single-day regimen

Adolescents

The systemic exposures to aprepitant in adolescents following the 150 mg IV dose is shown in Table 3.

Table 3 Geometric Mean of Observed Aprepitant PK Parameters Following a Single Dose of 150 mg IV Infusion in Adolescent Patients and Healthy Adults

Source
and 11

Source: Table 1 of the Clinical Pharmacology Review;
Infused over 30 minutes for adolescents

6 months to < 12 years

Table 4 Geometric Mean of Simulated Aprepitant Following a Single Dose of 4 mg/kg IV Infusion in Pediatric Patients 2 to < 12 Years Old and 5 mg/kg IV Infusion in Patients 6 months to < 2 Years Old and Observed Aprepitant Following a Single Dose of 150 mg IV Infusion in Healthy Adults

Dose	Age Group (years)	AUC0-∞ (ng×hr/mL)	AUC0-24hr (ng×hr/mL)	Cmax (ng/mL)	C24hr (ng/mL)
4 mg/kg	6 to < 12	53031	35235	3591.4	682.25
4 mg/kg	2 to < 6	37909	28205	3080.2	443.78
5 mg/kg	6 months to < 2	40021	30125	3115.7	480.64
150 mg^	Healthy Adults	35031	24500	4010	577
^ Historical data from Study P165					
Source data: Section 2.7.2 Summary of Clinical Pharmacology, Table 2.7.2:11					

Source: Table 2 of the Clinical Pharmacology Review;
Infused over 60 minutes in pediatric patients aged 6 months to 12 years

Three-day regimen

Adolescents
The simulated systemic exposures to aprepitant after the following dosing regimens are shown in **Table 5:**

Adolescents:

- Day 1: Either 115 mg IV fosaprepitant or 125 mg oral aprepitant
- Days 2 and 3: Either 80 mg IV fosaprepitant or 80 mg oral aprepitant

6 months to < 12 years:

- Day 1: Either 3 mg/kg IV fosaprepitant or 3 mg/kg oral aprepitant

- Days 2 and 3: 2 mg/kg IV fosaprepitant or 2 mg/kg oral aprepitant

Table 5 The Geometric Mean of Simulated Systemic Exposures (AUC_{0-24h}, Cmax) to Aprepitant on (A) Day 1, and (B) Days 2-3 Following a Three-Day Regimen[1]

(A)

Day 1		
	AUC	Cmax
	(ng·h /mL)	(ng/mL)
Adolescents		
PO	17958	1152.8
IV	21083	2451
6- < 12 years		
PO	21354	1489.2
IV	25639	2686.5
2 - < 6 years		
PO	16398	1230.9
IV	20336	2307.3
6 months to -2 years		
PO	13431	1023.2
IV	16715	1872.1

(B)

PO
IV

Source: Reproduced from Table 3 of the Clinical Pharmacology review
[1] PO/PO/PO, IV/PO/PO, or IV/IV/IV regimens

6. Clinical Microbiology

No change in the currently marketed fosaprepitant dimeglumine (EMEND for Injection) formulation are proposed in the current application; therefore, a clinical microbiology review was not warranted.

7. Clinical/Statistical- Efficacy

The efficacy of the single day fosaprepitant regimen in pediatric patients receiving single-day of chemotherapy was extrapolated from adult patients receiving the single-day chemotherapy regimen based on the comparable systemic exposure to aprepitant between pediatric patients and adults. The efficacy of the 3-day fosaprepitant regimen in pediatric patients receiving multi-day chemotherapy was bridged to the efficacy of the 3-day oral aprepitant in pediatric patients receiving single or multiple-day chemotherapy regimens. The comparable systemic exposure to aprepitant following fosaprepitant administration supported the efficacy bridging. The efficacy of the 3-day IV/PO/PO regimen is based on matching aprepitant exposure for the fosaprepitant dose on Day 1 and using the same approved aprepitant oral doses for Days 2 and 3. Of note, the efficacy of a single dose fosaprepitant in pediatric patients receiving multiple-day chemotherapy was not established. The efficacy cannot be extrapolated from the efficacy of single dose fosaprepitant because the corresponding adult studies generally studied patients receiving single-day chemotherapy.

Since the efficacy relies on the extrapolation of the efficacy in adults and pediatric patients, statistical assessment of the data from the prematurely terminated phase 3 Study 044 was not performed by the Applicant or FDA statistics reviewers. By the time of study termination, there were 71 subjects who completed the trial out of the planned 180 subjects. The dose of fosaprepitant was 150 mg for adolescents, and 5 mg/kg for patients ages > 2 and < 12 years old. In this group, 73% of patients (52 out of 71 patients) received multiple-day chemotherapy. Only descriptive summaries of efficacy data were provided. No efficacy results from Study 044 will be included in Section 14 of the label. For more information, refer to the Statistical Review by Dr. Lan**.**

8. Safety

The clinical reviewers, Drs. Johnson and Rajpal, concluded that the submitted safety information for single-dose fosaprepitant does support the 1-day fosaprepitant regimen for pediatric patients and a 3-day fosaprepitant/aprepitant/aprepitant (IV/PO/PO) regimen. The safety of aprepitant for Days 2 and 3 is supported by pediatric studies conducted for the 3-day oral aprepitant regimen and post-marketing experience of oral aprepitant for the prevention of CINV. However, the clinical reviewers concluded that the safety of the proposed 3-day fosaprepitant IV regimen cannot be supported by the available safety data because there are no data to support the higher exposure (i.e., Cmax) on Days 2 and 3 following 3 consecutive doses of fosaprepitant. As such, the reviewers recommended approval of the single-day fosaprepitant regimen, and the 3-day IV/PO/PO regimen, but not of the 3-day IV/IV/IV regimen.

The clinical review noted that fosaprepitant labeling adequately describes the known risks associated with the use of fosaprepitant in adults. The labeled Warnings and Precautions include Clinically Significant CYP3A4 Drug Interactions, Hypersensitivity Reactions, Decrease in INR with Concomitant Warfarin, and Risk of Reduced Efficacy of Hormonal Contraceptives. Of these, only hypersensitivity reactions were observed in the safety population of pediatric patients reviewed for the current application. The clinical review noted that hypersensitivity reactions, including anaphylaxis, were observed at an incidence rate of 2% in the 199 patients of the primary safety population (Cycle 1 chemotherapy) for the current Application.

The reviewers noted that current EMEND for Injection labeling is adequate to instruct health care professionals (HCPs) to monitor patients during and after infusion. Labeling also instructs HCPs to discontinue the fosaprepitant infusion and administer appropriate medical therapy if hypersensitivity reactions are observed. Further, labeling warns HCPs not to reinitiate EMEND in patients who experience these symptoms with first-use. Of note, labeling will be updated to warn HCPs not to reinitiate EMEND for injection in patients who experience hypersensitivity reactions with previous use because not all cases occur on the initial administration.

The clinical review noted that there was a single case of a Hy's Law case (DILI)[9]. The potential DILI case was reported during optional cycle 3 of Protocol 029 in a 17-year-old patient who received 3 m/kg (150 mg) fosaprepitant. An AE of hepatoxicity was reported with an onset of

[9] Elevated aspartate transaminase (AST) or ALT ≥3X the upper limit of normal (ULN) and an elevated total bilirubin value ≥2X the ULN and, at the same time, an alkaline phosphatase <2X the ULN

Day 109. The investigator assessed this event as non-serious, and the event resolved within 2 months. Concomitant chemotherapeutics confounded the interpretation of this observation while the narrative was not available. Since fosaprepitant is converted to aprepitant, the labeling for fosaprepitant refers to the full prescribing information for EMEND capsules for complete safety information regarding studies performed with oral aprepitant. In the labeling of EMEND capsule, ALT increase (incidence rate $\geq$ 3%) and bilirubin increase (rare adverse event) are included. In the PMR safety study for the 3-day IV regimen, additional safety data will be collected in pediatric patients to inform the safety of multiple doses of fosaprepitant in pediatric patients.

Single-day regimen for fosaprepitant IV and 3-day regimen for IV fosaprepitant/oral aprepitant/oral aprepitant

The safety of the single day fosaprepitant IV regimen and the 3-day IV/PO/PO regimen in pediatric patients ages 6 months to 17 years is adequately supported by the safety data of single dose fosaprepitant and the 3-day oral aprepitant studied in pediatric patients. In adolescent patients, safety of a single dose fosaprepitant followed by oral aprepitant for subsequent two days was also evaluated. Of note, no patients received fosaprepitant for three consecutive days.

The pooled safety dataset that supported the single day IV regimen and the 3-day IV/PO/PO regimen was comprised of 199 pediatric patients receiving fosaprepitant during the first cycle of chemotherapy from three clinical studies. Most patients in the safety population were white and slightly more than half were male. The most common primary malignancies represented were sarcoma, CNS malignancy, bone-osteosarcoma, and neuroblastoma.

Supportive safety data (secondary safety population) is also available from cycles 2 through 6 of the Protocols 029 and 044. In the optional cycles (2 through 6) of protocols 029 and 044, only SAEs and non-serious AEs determined by the investigator to be drug-related or led to study discontinuation were required to be reported. Due to differences in safety reporting for these optional cycles, these data are not integrated with Cycle 1 data.

The safety profile of a single dose fosaprepitant was similar in the 199 pediatric patients who received fosaprepitant with that in adults as described in the current labeling.

Table 6 Pooled Dataset for Primary Safety Analysis, Protocols 134 Parts I and V, Protocol 029 (Cycle 1) and Protocol 044 (Cycle 1) [a]

Integrated Dataset	12 to 17 years of age	< 12 years of age	Total
To support 1-day dosing regimen	150 mg Includes data from Protocols: 134 Part IB (N=11) 029 (N=17) 044 (N=18)	5 mg/kg[b] Includes data from Protocols 029 (N=74) 044 (N=19)	N=139
Additional dataset to support 3-day[a] in addition to the safety	115 mg Includes data from	3 mg/kg Includes data from Protocols: 134 Part V (N=23)	N=60

dataset for 1-day dosing regimen	Protocol 134 Part1A (N=12)	029 (N=25)	
Control regimen	Includes subjects from the control regimen of Protocol 029 (N=35) and Protocol 044 (N=34) Of note no patients < 2 years old in control regimen		N=69

Source: Copied and modified from Table 5 from the Clinical Review.
[a] Patients received either a single dose fosaprepitant or fosaprepitant on Day1 followed by aprepitant on Days 2 and 3.
[b] The dose of 4 mg/kg is proposed for patients aged 2 to < 12 years old based on modeling and simulation for the single-day regimen. The safety data at 5 mg/kg in patients aged 2 to < 12 years supported the safety of 4 mg/kg in that age group.

Table 7 Extent of Exposure to Fosaprepitant by Dose in Cycle 1, All Subjects Treated, Protocols 134, 019, and 044 Combined [a]

6 to <12	
12 to 17	

Source: Reproduced from the Clinical Review
[a] 1-day supportive pool supported both 1-day regimen and 3-day regimen and included in 3-day supportive pool.

The clinical review summarized the safety results for death, SAEs, and the laboratory abnormality.

The reviewers noted that no death was observed in the primary safety population (Cycle 1), while three deaths occurred in the secondary safety population following optional cycles (2-6 cycles). None of the adverse events leading to these deaths was determined to be related to fosaprepitant.

Table 8 Deaths, Cycles 2-6, Protocols 044 and 029

029
029

Source: Table 12 from the Clinical Review.

Serious Adverse Events

The clinical review noted that 30.7% of patients had a serious adverse event (SAE) and the most commonly reported SAE was febrile neutropenia, which is a known adverse reaction associated with chemotherapy. The incidence of febrile neutropenia was similar across fosaprepitant and control regimens. No safety signals were observed in review of the SAE data. There did not appear to be any SAE with a substantial difference in incidence between the fosaprepitant and control regimen groups.

Significant Adverse Events

The most commonly reported Grade 3 AEs were febrile neutropenia and anemia. The incidence of anemia was greater in the control group than in the fosaprepitant group and is therefore not represented in Table 9, below. These events are consistent with a population of patients with cancer receiving chemotherapy. In general, the incidence of severe and life-threatening AEs was relatively similar between the fosaprepitant and control regimens.

Table 9 Subjects with Adverse Events by Maximum Toxicity Grade (Incidence ≥ 5% in One or More Treatment Groups), in Cycle 1, All Subjects as Treated, Protocols 134, 029 and 044 Combined, Incidence Greater than Control Group

count decr
Decreased

Source: Table 15 of the Clinical Review

Dropouts and/or Discontinuations Due to Adverse Effects

Table 10 Adverse Events Resulting in Discontinuation in Cycle 1, Protocols 134, 029 and 044

134
5)

Source: Table 14 of the Clinical Review

Dr. Johnson commented that the hypersensitivity reaction for the 13-year old patient (Study 044) should have been categorized as anaphylaxis, per World Allergy Organization guidelines.

- Safety dataset for the 3-day regimen for IV fosaprepitant/ fosaprepitant/ fosaprepitant

Of note, the 3-day IV/IV/IV regimen has not been studied either in adult patients or pediatric patients. The safety database was not adequate to support approval of use of fosaprepitant on Days 2 and 3 of the proposed 3-day regimen, the Cmax of aprepitant following fosaprepitant on Days 2 and 3 were higher than those after oral aprepitant on Days 2 and 3 while none of the patients received fosaprepitant on Days 2 or 3. The Applicant's 3-Day supportive safety pool included patients who received a single dose of fosaprepitant at doses similar to or higher than that proposed for Days 2 and 3 but included not patients who actually received fosaprepitant on Days 2 and/or 3.

(b) (4)

fosaprepitant is rapidly (<30 minutes) and completely converted to aprepitant, the lack of safety data from patients who have received three consecutive days of fosaprepitant is a concern given the higher aprepitant Cmax predicted through modeling and simulation.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

The pediatric exclusivity board meeting was held on 2/28/18. The review team concluded that the terms of the Written Request had been fairly met and recommended granting the pediatric exclusivity. The Exclusivity Board agreed and granted the pediatric exclusivity as of 3/23/18. Refer to the memo from the pediatric exclusivity board in DARRTS.[10]

The labeling of fosaprepitant for pediatric use was discussed at the Pediatric Research Committee meeting held on 3/7/18. The PeRC urged the review team to consider labeling of the product for the 3-day IV/IV/IV regimen for patients who may not tolerate oral aprepitant on Days 2 and 3 during chemotherapy. The PeRC noted that the WR did not specifically require safety data for the 3-day IV dosing regimen, and acknowledged additional safety data would be needed. The PeRC recommended that the review team consider labeling the product for 3-day IV dosing regimen, and obtaining the safety information post-approval. The PeRC agreed with the other proposed labeling based on the WR studies, including the labeling of the 3-day IV/PO/PO regimen.

The review team considered the PeRC's recommendations; however, remained concerned about the labeling of the 3-day IV regimen because the currently available safety data could not support

[10] Memo from Pediatric Exclusivity Board for NDA 022023/S-017 dated 3/23/18

the 3-day IV regimen although the efficacy of the 3-day IV regimen could be supported based the efficacy extrapolation from the 3-day oral aprepitant in pediatric patients. (b) (4) FDAAA PMR will be issued for a trial to evaluate the safety of three consecutive doses of fosaprepitant in patients receiving multiple chemo cycles (b) (4)

The PeRC considered the PREA PMR is fulfilled, and the review team concurs. In considering the fulfillment of PREA PMR and the WR, the Division considered the following:

1) Study of fosaprepitant in patients ages 0 < 6 months

Both PREA PMR 1663-3, and the WR required a PK/PD study in patients ages 0 to 17 years. The Applicant conducted a single-dose PK/PD study of fosaprepitant in combination with a 5-HT_3 antagonist and dexamethasone in pediatric patients ages 0 to 17 years (Study 029). A total of 23 subjects were enrolled across the planned 0 to <2 years age cohort. PK samples were analyzed for 22 subjects who received fosaprepitant and one patient who received dexamethasone. Of note, despite the Applicant's efforts, only 1 patient less than 6 months was enrolled and no PK was available from this patient. During the development program, the Applicant communicated to the Agency about its efforts to encourage enrollment of patients aged 0 < 6 months. The Agency agrees that the Applicant made diligent and reasonable efforts to encourage enrollment of patients aged 0 < 6 months.

2 to 6
6 to 1
years
12 to
years

Source: From DPMH Review.

2) Study of fosaprepitant in combination with a 5-HT3 antagonist and dexamethasone

In this PK/PD study, use of dexamethasone (administered IV) was not a standardized part of the anti-emetic regimen and was left to the discretion of the investigator. Similarly, dexamethasone was not a standardized part of the anti-emetic regimen in the clinical efficacy trial for oral aprepitant due to the difference in clinical practice for pediatric patients. If used, consistent with dexamethasone dosing in the adult fosaprepitant regimen, the dose was reduced by 50% based on aprepitant's drug-drug interaction with dexamethasone (via CYP3A4 inhibition), which results in increased systemic dexamethasone exposures in adults. The Applicant did not assess the effects of fosaprepitant on dexamethasone exposures in children aged 0-1 year as requested by the WR while only one patient received dexamethasone among patients < 2 years old in the PK/PD study.

3) Study with an age-appropriate formulation

An age-appropriate fosaprepitant formulation with a reduced EDTA content was developed, and used in the PK/PD study along with the originally approved high EDTA formulation. The reduced EDTA formulation was approval under NDA 22,023/S-014.

4) Identification of 3-Day intravenous fosaprepitant doses

The Applicant identified the doses for the 3-Day intravenous regimen that provide similar aprepitant exposures (AUC) that have demonstrated an acceptable efficacy profile in pediatric patients. However, the Applicant's proposed 3-Day intravenous regimen did not provide similar Cmax to that which demonstrated an acceptable safety profile. The Applicant conducted modeling and simulation of the PK for different infusion durations to better match the Cmax with oral aprepitant regimen; however, the Cmax could not be reduced with a practical infusion duration.

11. Other Relevant Regulatory Issues

Financial Disclosures

The clinical review notes that a list of clinical investigators were provided and there were no clinical investigators with disclosable financial interests or arrangements.

OSI inspection

The clinical review notes that OSI inspections were not indicated for the current supplement because no clinical efficacy study was relied upon for the determination of efficacy, combined with the lack of any other issues that needed to be resolved on inspection.

12. Labeling

See labeling discussions presented above in previous sections. Labeling recommendations from DPMH, OPDP, and DMEPA were incorporated.

The DMEPA reviewers concluded that the proposed PI is acceptable from a medication error perspective and noted that there were no proposed changes to carton labeling and container label.

The OPDP reviewer's recommendations on the proposed PPI were incorporated, and OPDP reviewers did not have comments on the PI.

The DPMH reviewers were consulted for the pediatric labeling and their recommendations were incorporated in Section 8.4 Pediatric Use of the labeling.

Major labeling recommendations are as follow:

Section 2 Dosage and Administration

The proposed doses for the single-day regimen in patients 6 months and older (> 6 kg) are shown in below Tables and are acceptable.

(b) (4)

(b) (4)

Section 8.4 Pediatric Use

The results of juvenile toxicity study of fosaprepitant in juvenile dogs will be included as below. In addition, the results of juvenile toxicity study of oral aprepitant in juvenile rats, which are included in Section 8.4 in the approved label for EMEND (aprepitant) capsule will be included in the EMEND for Injection label with further clarifications of the equivalent human ages to juvenile animal ages.

Juvenile Animal Toxicity Study

In juvenile dogs treated with fosaprepitant, changes in reproductive organs were observed. In juvenile rats treated with aprepitant, slight changes in sexual maturation were observed without an effect on reproduction. No effects on neurobehavior, sensory and motor function, or learning and memory were observed in rats.

In a toxicity study in juvenile dogs treated with fosaprepitant from postnatal day 14 (equivalent to a newborn human) to day 42 (approximately equivalent to a 2 year old human), decreased testicular weight and Leydig cell size were seen in the males at 6 mg/kg/day and increased uterine weight, hypertrophy of the uterus and cervix, and edema of vaginal tissues were seen in females from 4 mg/kg/day.

A study was also conducted in young rats to evaluate the effects of aprepitant on growth and on neurobehavioral and sexual development. Rats were treated at oral doses up to the maximum feasible dose of 1000 mg/kg twice daily (providing exposure in male and female rats lower than the exposure at the recommended pediatric human dose) from the early postnatal period (Postnatal Day 10 (equivalent to a newborn human) through Postnatal Day 58 (approximately equivalent to a 15 year old human)). Slight changes in the onset of sexual maturation were observed in female and male rats; however, there were no effects on mating, fertility, embryonic-fetal survival, or histomorphology of the reproductive organs. There were no effects in neurobehavioral tests of sensory function, motor function, and learning and memory.

Section 12.3 Pharmacokinetics
Pharmacokinetic parameters for aprepitant following fosaprepitant administration in pediatric patients will be included.

13. Recommendations/Risk Benefit Assessment

- Regulatory Action

I recommend approval of the single-day fosaprepitant regimen and the 3-day fosaprepitant/aprepitant/aprepitant regimen for the prevention of CINV in pediatric patients 6 months of age and older.

- Risk Benefit Assessment

The benefit of fosaprepitant for the prevention of CINV in pediatric patients outweighs the known risks. CINV is a potentially severe and debilitating side effect of chemotherapy. The availability of fosaprepitant for intravenous administration is beneficial to pediatric patients who cannot tolerate oral administration of aprepitant. The safety information does support the 1-day fosaprepitant regimen for pediatric patients receiving 1-day chemotherapy regimen and the 3-day fosaprepitant/aprepitant/aprepitant dosing regimen for pediatric patients receiving 1-day or multi-day chemotherapy regimen. The safety of aprepitant for Days 2 and 3 is supported by pediatric studies and post-marketing experience of oral aprepitant for the prevention of CINV. The safety profile of single dose fosaprepitant in pediatric patients ages > 6 months to 17 years is consistent with the labeled safety profile of fosaprepitant. The efficacy of fosaprepitant can be extrapolated from the efficacy of fosaprepitant in adults, and the efficacy of oral aprepitant in pediatric patients.

Although there are sufficient safety data to support administration of fosaprepitant IV on a single day followed by administration of aprepitant PO on Days 2 and 3 (the "IV/PO/PO" regimen), there are no safety data in this population for fosaprepitant IV daily for three consecutive days (the "IV/IV/IV" regimen) for prevention of CINV in pediatric patients ages > 6 months to 17 years. About 2-fold higher Cmax of aprepitant on Days 2 and 3 for the 3-day IV regimen compared to aprepitant PO administration based on systemic exposures in pediatric patients is a remaining safety concern for the "IV/IV/IV" regimen especially because no pediatric patients were treated with fosaprepitant for longer than one day in this program. Although the Day 1 fosaprepitant Cmax is higher than the simulated Cmax values on Day 2 and Day 3, the lack of safety data in patients who had received 3 consecutive days of fosaprepitant precludes a clinical recommendation to approve any regimen including fosaprepitant on Day 2 and/or Day 3. The extrapolation of safety data from single dose administration to three-day dosing is not appropriate. As such, the currently available safety information does not provide a sufficient basis for risk benefit assessment for the 3-day IV fosaprepitant regimen. The efficacy of the 3-day fosaprepitant regimen in pediatric patients can be bridged from the 3-day oral aprepitant regimen based on matching exposure for the Day 1 fosaprepitant dose and using the same oral aprepitant dose for Days 2 and 3.

A safety study will be required as a PMR (b) (4) regimen for pediatric patients who cannot tolerate oral administration on Days 2 and 3 under the "IV/PO/PO" regimen. The safety of the "IV/IV/IV" regimen, particularly hypersensitivity reactions including anaphylaxis and anaphylactic shock, will be studied in the PMR study.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

There were no safety issues identified in the pediatric studies that preclude approval of fosaprepitant for use in the pediatric population for the CINV indication. There were no safety issues for single-dose fosaprepitant as a single-day regimen or as part of 3-day regimen that warrant a Medication Guide, or a REMS.

- Recommendation for other Postmarketing Requirements and Commitments

The Applicant agreed to the following FDAAA PMR to evaluate the safety of three consecutive doses of fosaprepitant IV in pediatric patients during initial and repeat cycles of chemotherapy.

> Conduct a trial to evaluate the safety of multiple cycles of intravenous administration of fosaprepitant daily for three consecutive days for the prevention of chemotherapy induced nausea and vomiting in pediatric patients 6 months to 17 years of age.
>
> Draft Protocol Submission: 10/2018
> Final Protocol Submission: 04/2019
> Study/Trial Completion: 03/2021
> Final Report Submission: 09/2021

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/s/

INSOOK KIM
04/03/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022023Orig1s017

MEDICAL REVIEW(S)

Addendum to Clinical Review dated March 2, 2018 (NDA 22,301/S-017; EMEND for Injection; fosaprepitant dimeglumine)

PMR recommendation for fosaprepitant IV daily for three consecutive days (the "IV/IV/IV" regimen).

In consideration of the value of having a 3-day regimen and potential safety concerns, the Review Team determined that a PMR is needed.

The following PMR wording and milestone dates are taken from the PMR Template:

> "Conduct a trial to evaluate the safety of multiple cycles of intravenous administration of fosaprepitant daily for three consecutive days for the prevention of chemotherapy-induced nausea and vomiting in pediatric patients 6 months to 17 years of age."
>
> Draft Protocol Submission: 10/2018
> Final Protocol Submission: 04/2019
> Study/Trial Completion: 03/2021
> Final Report Submission: 09/2021

The following review issue and goal of the clinical trial is taken from the PMR Template:

> "We are concerned about the safety of the "IV/IV/IV" regimen, particularly hypersensitivity reactions including anaphylaxis and anaphylactic shock, because Cmax of aprepitant appeared to be about two fold higher on Days 2 and 3 after fosaprepitant IV administration (compared to aprepitant PO administration) based on predicted PK exposures in pediatric patients. A clinical trial is needed to evaluate the safety of the fosaprepitant "IV/IV/IV" regimen for prevention of CINV in pediatric patients ages 6 months to 16 years. Although there are sufficient safety data to support administration of fosaprepitant IV on a single day followed by administration of aprepitant PO on Days 2 and 3 (the "IV/PO/PO" regimen) for prevention of CINV in pediatric patients ages 6 months to 16 years, there are no safety data in this population for fosaprepitant IV daily for three consecutive days (the "IV/IV/IV" regimen)."

Recommendation: This Reviewer agrees with the PMR wording, milestone dates, review issue, and goal of the clinical trial as described above.

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/s/

ANIL K RAJPAL
04/03/2018

CLINICAL REVIEW

Application Type	Supplemental NDA
Application Number(s)	22,023/S-017, IND 48924
Priority or Standard	Priority
Submit Date(s)	02 October 2017
Received Date(s)	02 October 2017
PDUFA Goal Date	03 April 2018
Division/Office	DGIEP/ODE3
Reviewer Name(s)	Aisha Peterson Johnson, MD, MPH, MBA
Review Completion Date	March 2, 2018
Established/Proper Name	fosaprepitant dimeglumine
(Proposed) Trade Name	Emend for Injection
Applicant	Merck Sharp & Dohme Corp.
Dosage Form(s)	Solution for injection
Applicant Proposed Dosing Regimen(s)	• In pediatric patients (6 months to 17 years of age) receiving single or multi-day chemotherapy regimens of HEC or MEC, a 3-day intravenous regimen of EMEND for injection is recommended. ○ EMEND capsules or EMEND for oral suspension may also be used on Days 2 and 3 instead of EMEND for injection. • In pediatric patients (6 months to 17 years of age) receiving a single-day chemotherapy regimen, an alternative 1-day intravenous regimen of EMEND for Injection may be administered. EMEND for Injection is administered as an intravenous infusion through a central venous catheter over 30 minutes (12 years of age to 17 years) or over 60 minutes (6 months of age to less than 12 years) completing the infusion approximately 30 minutes prior to chemotherapy.
Applicant Proposed Indication(s)/Population(s)	EMEND for injection, in combination with other antiemetic agents, is indicated in adults and pediatric patients 6 months of age and older for the prevention of: • acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin. • delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).
Recommendation on Regulatory Action	Approval with modification to proposed dosing regimens to exclude fosaprepitant on Days 2 and 3 of the proposed 3-day regimen due to lack of safety data to support proposed 3-day fosaprepitant/fosaprepitant/fosaprepitant regimen

Recommended Indication(s)/Population(s) (if applicable)	Same as Applicant's proposed

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Executive Summary

1.1. Product Introduction

Trade Name: EMEND® for Injection
Generic Name: Fosaprepitant dimeglumine
Pharmacological Class: Neurokinin type 1 receptor antagonist
Fosaprepitant is a prodrug of aprepitant that can be administered intravenously (IV).
Fosaprepitant is converted to aprepitant (within 30 minutes) after IV administration via the action of ubiquitous phosphatases, and the pharmacological effect of fosaprepitant is attributed to aprepitant.

Proposed Dosing Regimen

Table 1. Proposed 3-Day IV/PO Fosaprepitant/Aprepitant Dosing Regimen and 1-Day Fosaprepitant Regimens by Age Group

Electronically copied and reproduced from Summary of Clinical Pharmacology, Table 2.7.2: 13

MO Comment:
Due to lack of safety data to support fosaprepitant dosing on Days 2 and 3 of the proposed 3-Day regimen, only regimens with fosaprepitant on Day 1 are recommended for approval. This issue will be discussed in detail in Section 8 of this review.

Currently approved indications

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

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

1.2. Conclusions on the Substantial Evidence of Effectiveness

Emend for Injection was found to be effective for prevention of CINV in pediatric patients receiving MEC and HEC. The efficacy of a 1-day fosaprepitant regimen in pediatric patients receiving one day of chemotherapy can be extrapolated from adult patients with similar exposures and receiving chemotherapy for a single day. The efficacy of a 3-day fosaprepitant regimen in pediatric patients receiving multi-day chemotherapy can be bridged from the approved pediatric 3-day oral aprepitant regimen based on matching aprepitant exposure for the fosaprepitant dose on Day 1 and using the same approved aprepitant oral dose for Day 2 and Day 3.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The benefit of fosaprepitant for the prevention of CINV in pediatric patients outweigh the known risks. Chemotherapy-induced nausea and vomiting (CINV) is a potentially severe and debilitating side effect of chemotherapy.

The safety profile observed in Protocols 134, 029, and 044 submitted in support of the current Application is consistent with the labeled safety profile of fosaprepitant. During these studies, pediatric patients were treated with fosaprepitant for no longer than one day. Exposure matching produced modeling and simulation results for Cmax values for the Day 2 and 3 fosaprepitant regimens that were 1.5- to 2-fold higher than observed with oral aprepitant. Although the Day 1 fosaprepitant Cmax is higher than the Day 2 and Day 3 Cmax simulated values, the lack of safety data in patients who had received 3 consecutive days of fosaprepitant recludes a clinical recommendation to approve any regimen including fosaprepitant on Day 2 and/or Day 3.. Therefore, the safety of the Applicant's proposed 3-Day fosaprepitant/fosaprepitant/fosaprepitant regimen is not supported by the safety information reviewed for this application. However, the safety information does support a 1-day fosaprepitant regimen for pediatric patients receiving 1-day chemotherapy and a 3-day fosaprepitant/aprepitant/aprepitant dosing regimen. The safety of aprepitant for Days 2 and 3 is supported

by pediatric studies and post-marketing experience of oral aprepitant for the prevention of CINV.

Fosaprepitant labeling adequately describes the known risks associated with the use of fosaprepitant in adults. The labeled Warnings and Precautions include Clinically Significant CYP3A4 Drug Interactions, Hypersensitivity Reactions, Decrease in INR with Concomitant Warfarin, and Risk of Reduced Efficacy of Hormonal Contraceptives. Of these, only hypersensitivity reactions were observed in the safety population of pediatric patients reviewed for the current Application.

Hypersensitivity reactions including anaphylaxis were observed at an incidence rate of 2% in the 199 patients of the primary safety population for the current Application. These reactions are of concern. The administration of fosaprepitant in a clinical setting by professionals trained to recognize these events can help to mitigate some of the risk of adverse outcome associated with these reactions. Current EMEND for Injection labeling instructs health care professionals (HCPs) to monitor patients during and after infusion. Labeling also instructs HCPs todiscontinue the fosaprepitant infusion and administer appropriate medical therapy if hypersensitivity reactions are observed. Further labeling warns HCPs not to reinitiate EMEND in patients who experience these symptoms with first-time use.

The efficacy of a 1-day fosaprepitant regimen in pediatric patients can be extrapolated from adult patients with similar exposures and receiving chemotherapy for a single day. The efficacy of a 3-day fosaprepitant regimen in pediatric patients can be bridged from the 3-day oral aprepitant regimen based on matching exposure for the Day 1 fosaprepitant dose and using the same oral aprepitant dose for Days 2 and 3.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Nausea and vomiting is a known adverse reaction associated with the use of chemotherapy agents • Highly emetogenic chemotherapy (HEC) agents are those associated with CINV in >90% of treated patients. Moderately emetogenic	Chemotherapy-induced nausea and vomiting (CINV) is a potentially severe and debilitating side effect of chemotherapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	chemotherapy (MEC) agents are those associated with CINV in 31% to 90% of patients.	
Current Treatment Options	• NK-1 receptor antagonists are a class of drug approved in adults for the prevention of CINV. The class is known to have a good safety profile and work in the delayed phase of CINV. • Aprepitant, the active metabolite of fosaprepitant, is approved as a 3-day regimen in pediatric patients • 5HT3 receptor antagonists (known to work for prevention of CINV in the acute phase) are approved for pediatric patients	• There is currently no intravenous NK-1 receptor antagonist approved in pediatric patients for the prevention of CINV.
Benefit	• EMEND for Injection is known to be effective for the prevention of CINV in adults. • Aprepitant, the active metabolite of fosaprepitant, is approved as 3-day regimen in pediatric patients for the prevention of CINV • CINV pathophysiology and response to NK1 receptor blockade is similar in adult and pediatric patients	It is appropriate to extrapolate efficacy from adults to pediatric patients for both 1-day fosaprepitant and 3-day fosaprepitant/aprepitant/aprepitant regimens.
Risk and Risk Management	• Labeled Warnings and Precautions include Clinically Significant CYP3A4 Drug Interactions, Hypersensitivity Reactions, Decrease in INR with Concomitant Warfarin, and Risk of Reduced Efficacy of Hormonal Contraceptives • The safety profile was similar in the 199 pediatric patients who received fosapepitant as part of Protocols 134, 029, and 044	The risks associated with the use of fosaprepitant is adequately described in current labeling.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Although multi-day chemotherapy was infrequently administered in the adult single dose IV fosaprepitant program, multi-day chemotherapy was commonly administered in the oral aprepitant pediatric development program. Protocol 208, the pivotal pediatric aprepitant safety and efficacy study, compared the 3-day oral aprepitant regimen versus the control regimen for the prevention of CINV in pediatric cancer patients. Eighty-six percent (86%) of the children enrolled in P208 (260 of 302 total subjects) received multi-day emetogenic chemotherapy; thus, there are considerable data available to justify the development of a multiday fosaprepitant regimen using model-based approaches. More importantly, the clinical benefit of aprepitant was demonstrated in children receiving either single or multiday chemotherapy.

2.2. Analysis of Current Treatment Options

Table 2. Summary of Prevention of CINV Products Approved for Pediatric Patients

Drug/Class	Indication	Pediatric Age Group
Ondansetron (Zofran) IV/ 5-HT3 receptor Antagonist	Prevention of CINV-HEC	6 months to 17 years
Palonosetron (Aloxi) IV/ 5-HT3 receptor antagonist	Prevention of CINV-HEC and CINV-MEC	1 month to 17 years
Aprepitant (Emend) oral	Prevention of CINV-HEC and CINV—MEC	6 months to 17 years

Reviewer's Table,

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

EMEND (oral capsules and oral suspension) Regulatory History

- Aprepitant (EMEND oral capsules) was approved on March 27, 2003 as part of a three day regimen for the prevention of acute and delayed chemotherapy induced nausea and vomiting (CINV) with initial and repeat courses of highly emetogenic chemotherapy (CINV-HEC) regimens in adults (NDA 21549/S-01).
- Efficacy supplement NDA 21549/S-008 was approved on October 28, 2005, for the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (CINV-MEC) in adults (NDA 21549/S-008).

- On August 23, 2015, aprepitant capsules were approved for use in pediatric patients ages ≥ 12 to 17 years (and patients less than 12 years who weight at least 30 kg) for the prevention of CINV associated with HEC and MEC (NDA 21549/S-025).
- Aprepitant oral suspension was approved on 17 December 2015 for prevention of chemotherapy induced nausea and vomiting in patients ages 6 months of age and older.

EMEND for Injection Brief Regulatory History

- On January 25, 2008, EMEND for Injection 115 mg (fosaprepitant dimeglumine) was approved in adults as an alternative administration route for Day 1 of the aprepitant oral 3-day regimen (EMEND for Injection 115 mg on Day 1 followed by EMEND oral capsules 80 mg on Days 2 and 3):
    - 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).
    - the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (CINV-MEC).

MO Comment:
The approval of EMEND for Injection 115 mg relied upon the demonstration of bioequivalence between fosaprepitant 115 mg and aprepitant 125 mg. The safety of the higher Cmax observed with fosaprepitant 115 mg was based upon previous clinical data for oral aprepitant 375 mg. The Sponsor did not pursue (b) (4) .

- On 12 November 2010, EMEND for Injection 150 mg was approved in adults as a single-day dosing regimen for CINV-HEC.

MO Comment:
The approval of the EMEND for injection 150 mg single day regimen for CINV-HEC in adults was based upon the results of a clinical trial showing fosaprepitant 150 mg single dose regimen was non-inferior to the approved aprepitant 3-day regimen (125 mg Day 1 and 80 mg on Days 2 and 3). The study did not include an adequate number of patients receiving MEC. Following the approval of the fosaprepitant 150 mg single dose, the Sponsor announced that beginning on 30 December 2010, sales of EMEND for Injection 115 mg would be discontinued. This action was not done as a result of safety or efficacy.

- On 10 February 2016, EMEND for Injection 150 mg was approved in adults as single -day dosing regimen for CINV-MEC, delayed phase only.

MO Comment:

The approval of the EMEND for injection 150 mg single day regimen for CINV-MEC in adults was based upon the results of a single adequate and well-controlled study showing fosaprepitant 150 mg single dose regimen was efficacious for the prevention of CINV-MEC for the delayed phase (>24-120 hours after chemotherapy). Efficacy was not shown during the acute phase.

3.2. Summary of Presubmission/Submission Regulatory Activity

Date	Relevant Regulatory History, pediatric fosaprepitant development program
02 Feb 2009	FDA Issued a single Written Request for aprepitant and fosaprepitant
8 April 2011	FDA issued Amendment #1 to the Written Request. Changes included eliminating apreptitant from current WR.
15 March 2012	FDA issued Amendment #2 to the WR
26 March 2012	FDA found the Sponsor's proposal to develop a pediatric fosaprepitant formulation with 5.4 mg of EDTA per vial acceptable (compared with 15.1 g EDTA per vial in the product marketed at that time)
22 March 2016	Type C, Teleconference • Sponsor proposed to extrapolate the efficacy of a single-day regimen of intravenous (IV) fosaprepitant from adults to pediatric patients based upon pharmacokinetic (PK) data showing similar aprepitant exposure observed in pediatrics in comparison to that of adults • FDA expressed concerns with the potential limitations of full extrapolation in the setting of multi-day chemotherapy given the differences in PK between one day IV dose regimen and 3- day oral dosing • FDA agreed that sponsor's revised proposal to obtain a 3-day IV fosaprepitant regimen in pediatrics based upon matching exposures observed with the approved multi-day oral aprepitant regimen in pediatrics appears reasonable • FDA stated that the amount of available safety data collected across the oral and IV pediatric programs *may be* sufficient to characterize the safety profile of a single -day regimen of fosaprepitant in the pediatric population (based on the age distribution of the observed data). • FDA agreed that diligent and reasonable efforts have been made to collect dexamethasone PK data in patients < 1 year of age as required as part of the WR.

14 June 2016	Sponsor requested release from the following Pediatric Research Equity Act (PREA) PMRs: <u>1450-1</u> A study in adolescents and younger pediatric patients receiving emetogenic chemotherapy (HEC or MEC) to evaluate fosaprepitant PK, safety, and tolerability. Final Report Submission: December 31, 2017 <u>1663-1</u> 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: August 2012 Study/Trial Completion: March 2017 Final Report Submission: August 2017 <u>1663-2</u> 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
13 July 2016	Type C, Meeting Canceled after preliminary comments deemed sufficient by Sponsor • FDA found Sponsor's proposal to extrapolate the efficacy of single dose IV fosaprepitant from adults to pediatric patients receiving single day chemotherapy regimens reasonable

	• FDA disagreed with the Sponsor's proposed (b) (4) [redacted]. • FDA confirmed that the planned size and nature of the proposed safety data base (including available data collected across the oral and IV pediatric programs) appears reasonable to characterize the proposed fosaprepitant single-day and 3-day regimens in pediatric patients. FDA qualified this confirmation by stating that the "adequacy of the safety data will be determined when the application is reviewed". • FDA recommended that the Sponsor conduct label comprehension studies to better define appropriate approach to labeling given the challenges seen in writing the Dosage and Administration section of the label
13 October 2016	FDA issued Amendment # 3 to the WR FDA granted the Sponsor's request for release of PMRs 1450-1, 1663-1,and 1663-2 and issued a new deferred PREA PMR described below: 1663-3 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. Use modeling and simulation including the results of the above study to identify 1-Day and 3-Day intravenous fosaprepitant doses in pediatric patients 0 to 17 years of age that provide similar aprepitant PK exposures to pediatric aprepitant doses and exposures which have demonstrated acceptable safety and efficacy profiles in patients receiving single and multi-day chemotherapy regimens, respectively. Final Report Submission: December 2017
18 Jan 2017	Type C FDA confirmed that diligent and reasonable efforts appear to have been made by the Sponsor to enroll patients less than 6 months of age. however, FDA declined to change the WR language of the youngest cohort (0-2 years of age) to document the importance of obtaining information in this age group.
27 Feb 2017	FDA issued Amendment # 4 to the WR

MO Comment: As described above, the current submission is being submitted to fulfill a PREA PMR and also a Written Request. The review team concluded that the Applicant fairly

responded to the written request (and any other relevant conclusions from the Ped Exclusivity Determination Checklist and/or the Ped Exclusivity Template). This Application was discussed at the FDA CDER OND Pediatric Exclusivity Board on 28 February 2018 and the Board agreed that the terms of the Written Request had been met and exclusivity will be granted.

3.3. Foreign Regulatory Actions and Marketing History

As of 10 May 2017, fosaprepitant 150 mg (single dose regimen) is registered and approved in more than 75 countries for prevention of CINV in adults. Although initially approved for use, most countries have deleted registration of the 115 mg dose of fosaprepitant, given the availability of the more convenient single day, 150 mg regimen. There are no records of any registration being revoked or withdrawn for safety reasons.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The OSI reviewer and OND review team concluded that OSI inspections are not indicated for the current supplement. This decision was based on the fact that no clinical efficacy study is being relied upon for the determination of efficacy combined with the lack of any other issues that need to be resolved on inspection.

4.2. Product Quality

No change in the currently marketed fosaprepitant dimeglumine (EMEND for Injection) formulation are proposed in the current Application.

4.3. Clinical Microbiology

No change in the currently marketed fosaprepitant dimeglumine (EMEND for Injection) formulation are proposed in the current Application.

4.4. Nonclinical Pharmacology/Toxicology

No change in the currently marketed fosaprepitant dimeglumine (EMEND for Injection) formulation are proposed in the current Application.

4.5. Clinical Pharmacology

Fosaprepitant is a neurokinin type 1 receptor antagonist. Fosaprepitant is a prodrug of aprepitant that can be administered intravenously (IV). Fosaprepitant is converted to aprepitant (within 30 minutes) after IV administration via the action of ubiquitous phosphatases, and the pharmacological effect of fosaprepitant is attributed to aprepitant. During each of the pharmacokinetic studies (Protocols 134, 029, and 044) submitted in support of the current Application, patients received fosaprepitant only once per cycle. For patients receiving multi-day chemotherapy in Study 134, patients were given oral aprepitant on Days 2 and 3. Study 029 was designed only to study single dose fosaprepitant. And the only phase 3 study, Study 044, was designed to study only single dose fosaprepitant. Study 044 was terminated early after consultation with FDA confirmed that the available PK, efficacy and safety data in the fosaprepitant and aprepitant programs were sufficient to support the approval of the proposed 1-day and 3-day IV fosaprepitant regimens.

Section 5.1 contains a table of the pharmacokinetic studies submitted in support of the current Application. Section 5.2 contains a discussion regarding the appropriateness of relying on simulation and modeling and extrapolation.

Section 7 contains additional details regarding the PK/PD studies submitted along with a review of the safety results of the pharmacokinetic studies. For a more detailed description of the pharmacokinetic studies and their results used to support bridging and extrapolation see the clinical pharmacology reviews in DARRTS.

4.6. Devices and Companion Diagnostic Issues

Not applicable

4.7. Consumer Study Reviews

Not applicable

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Sample Table. Listing of Clinical Trials Relevant to this NDA/BLA

Trial ID	Protocol	Trial Design	Regimen/ schedule/ route	Location of Trial Centers
2006-005515-10	Protocol 134	Phase 1, Multicenter, open-label, 5-part study to Evaluate the Pharmocokinetics, Safety, and Tolerability of Aprepitant and Fosaprepitant Dimeglumine in Pediatric Patients Receiving Emetogenic Chemotherapy	**Part IA:** Subjects 12-17 years of age. Day 1: 115 mg IV fosaprepitant with IV ondansetron ±IV dexamethasone. Days 2 and 3: 80 mg oral aprepitant and IV ondansetron ±IV dexamethasone. **Part IB:** Subjects 12-17 years of age. Day 1: 150 mg IV fosaprepitant with IV ondansetron ±IV dexamethasone. **Part IIA:** Subjects <12 years of age. Day 1: Oral aprepitant dose equivalent to 80 mg in adults with IV ondansetron ±IV dexamethasone. **Part IIB:** Subjects <12 years of age. Day 1: Oral aprepitant dose equivalent to 125 mg in adults with IV ondansetron ±IV dexamethasone. **Part III**: Subjects <12 years of age. Days 1-3: IV ondansetron ±IV dexamethasone. **Part IV:** Subjects <12 years of age. Day 1: Oral aprepitant at a dose equivalent to 125 mg in adults with IV ondansetron ± IV dexamethasone. Days 2 and 3: Oral aprepitant at a dose equivalent to 80 mg in adults with IV ondansetron ± IV dexamethasone. **Part V:** Subjects 6 months to <12 years of age. Day 1: IV fosaprepitant at a dose equivalent to 150 mg in adults with IV ondansetron ±IV dexamethasone.	Australia, Brazil, Canada, Colombia, France, Germany, Hungary, Israel, Mexico, Norway, Peru, Poland, Spain, Sweden, Switzerland, USA
2012-002340-	Protocol 029	A Phase 2b, Partially-Blinded, Randomized, Active Comparator-Controlled Study to Evaluate the Pharmacokinetics/Pharmacodynamics,	**Dose 1**: Fosaprepitant 150 mg (*43 randomized*) • Subjects 12 to 17 years old administered 150 mg • Subjects 2 to <12 years old administered a weight-adjusted dose of 3 mg/kg (not to exceed 150 mg)	Argentina, Austria, Brazil, Canada, Chile, Colombia,

24		Safety, and Tolerability of Fosaprepitant in Pediatric Subjects for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) Associated with Emetogenic Chemotherapy	**Dose 2**: Fosaprepitant 60 mg (44 randomized) • Subjects 12 to 17 years old administered 60 mg • Subjects 2 to <12 years old administered a weight-adjusted dose of 1.2 mg/kg (not to exceed 60 mg) **Dose 3**: Fosaprepitant 20 mg (*41 randomized*) • Subjects 12 to 17 years old administered 20 mg • Subjects 2 to <12 years old administered a weight-adjusted dose of 0.4 mg/kg (not to exceed 20 mg) **Dose 4**: Fosaprepitant 5 mg/kg (*74 randomized*) • Subjects 4 months to <12 years old administered a weight-adjusted dose of 5 mg/kg (not to exceed 150 mg) • Subjects 1 to <4 months old administered a weight-adjusted dose of 2.5 mg/kg • Subjects 0 to <1 month old administered a weight-adjusted dose of 1.25 mg/kg	Estonia, Germany, Greece, Hungary, Italy, Lithuania, Mexico, Peru, Portugal, Romania, Russia, South Africa, South Korea, Spain, Switzerland, Turkey, United Kingdom, Ukraine, United States
2014-001783-34	Protocol 44 (P044MK0517)	A Phase 3, Randomized, Placebo-Controlled Clinical Trial to Study the Efficacy and Safety of MK-0517/Fosaprepitant and Ondansetron Versus Ondansetron for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Pediatric Subjects Receiving Emetogenic Chemotherapy.	Cycle 1 and Optional Cycles 2 to 6 Age 0 to < 12 years: **Day 1**: Fosaprepitant 5 mg/kg (or age-specific adjustment not to exceed 150 mg), 90 minutes prior to initiation of the first emetogenic chemotherapy, via a central venous catheter, over a period of approximately 60 minutes + ondansetron (Cycle 1) or any 5-HT3 antagonist (Cycles 2 to 6), no later than 30 minutes prior to initiation of chemotherapy. Age 12 to 17 years: **Day** 1: Fosaprepitant 150 mg, 60 minutes prior to initiation of the first emetogenic chemotherapy, via a central venous catheter, over a period of	Chile, Colombia, Estonia, Finland, Greece, Hungary, Lithuania, Mexico, Netherlands, Norway, Poland, Russia, South Korea, Spain, Sweden, United Kingdom

			approximately 30 minutes + ondansetron (Cycle 1) or any 5-HT3 antagonist (Cycles 2 to 6), no later than 30 minutes prior to initiation of chemotherapy.	

5.2. Review Strategy

The Applicant did not submit the efficacy results of any well-controlled trials in support of the current Application. Instead, the Applicant is relying upon bridging and extrapolation. The Applicant uses the term "bridging" to refer to the inference that the efficacy of the proposed pediatric 3-day fosaprepitant regimen can be predicted from that demonstrated with the pediatric 3-day oral aprepitant regimen. This inference is possible given that the activity of fosaprepitant is attributable to aprepitant. For efficacy of the 1-day fosaprepitant regimen in children, the Applicant is relying upon extrapolation from efficacy demonstrated in adults. This extrapolation from adults to pediatric patients is only applicable to pediatric patients receiving a single day of chemotherapy.

Recently, similarities between adult and pediatric CINV pathophysiology and response to NK1 receptor antagonists were confirmed with the demonstration of aprepitant efficacy in children at exposures similar to those associated with safety and efficacy in adults. Based on these results, the efficacy of a 1-day fosaprepitant regimen in children can be extrapolated from that demonstrated in adults, given similar aprepitant exposures and comparable clinical circumstances (i.e., receipt of single-day emetogenic chemotherapy).

- Data suggest that the basic pathophysiology of CINV and CNS NK1 receptor distribution, affinity and density remain relatively stable throughout life.
- The substantial overlap of chemotherapeutic agents that cause CINV in adults and children suggests a common pathophysiology for CINV, regardless of age.
- Similarities in the prophylaxis and treatment of pediatric and adult CINV exist in established clinical practice and are reflected in published adult and pediatric oncology guidelines

The safety results from Studies 029, 033, and 129 were reviewed and are discussed in Section 6 of this review.

MO Comment:
The Sponsor's rationale for bridging and extrapolation are acceptable.

For the proposed 3-day pediatric regimen, bridging the pediatric 3-day fosaprepitant regimen to the approved pediatric 3-day oral aprepitant regimen is a scientifically rational approach suggested to the Sponsor by the FDA. The efficacy of the single day fosaprepitant pediatric dose was extrapolated from the efficacy of single dose fosaprepitant observed in adults.

While the AUCs of the bridged aprepitant and fosaprepitant doses (based on modeling and simulation) were relatively close, the Cmax (aprepitant) of the proposed fosaprepitant doses on each day are predicted to be 1.5-2x higher than those observed with oral aprepitant. The higher

Cmax was anticipated due to the differences in the route of administration (oral vs. intravenous). Safety information for the higher Day 1 Cmax is adequate from the PK studies used to support bridging and extrapolation. Given that no pediatric patients were given fosaprepitant on Days 2 or 3, there is inadequate safety data to support the higher Cmax predicted through simulation and modeling.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Protocol 044

Protocol 044 was planned as a phase 3 safety and efficacy study of single-dose fosaprepitant in pediatric patients for the prevention of chemotherapy-induced nausea and vomiting. However, the study was terminated early when the Applicant and the FDA reached agreement that no further studies were necessary and additional information to support approval could be obtained through modeling and simulation. Therefore, no efficacy information will be reviewed for this application.

Efficacy for the proposed 1-day fosaprepitant regimen will be extrapolated from the fosaprepitant 1-day regimen in adults. Efficacy for the proposed 3-day fosaprepitant regimen will be obtained by bridging to the 3-day aprepitant pediatric program by matching exposures.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

No efficacy trial data were reviewed as part of the current Application

7.2. Additional Efficacy Considerations

n/a

7.3. Integrated Assessment of Effectiveness

n/a

8. Review of Safety

8.1. Safety Review Approach

The safety results for the PK/PD Studies 134, 029, and the phase 3 efficacy and safety Study 044 will be discussed as part of the safety review. The primary safety population includes all patients who were exposed to fosaprepitant (any dose) in Protocols 134, 029, and 044 during Cycle 1. The supplemental safety population includes patients exposed during cycles 2 through 6.

PROTOCOL 134
Protocol 134 was a phase 1, multicenter, open-label, 5-part study to evaluate the pharmocokinetics, safety, and tolerability of aprepitant and fosaprepitant in pediatric patients receiving emetogenic chemotherapy. In Part I of the Study, 12-17 year old patients were treated with fosaprepitant. During Part IA, patients were treated with a 3-Day regimen of fosaprepitant on Day 1 and oral aprepitant on Days 2 and 3. During Part IB, patients were treated with 1-Day regimen of single dose fosaprepitant on Day 1 only.

Table 3. Protocol 134, Treatment Regimen Details

Study Part	Age Group Studied	Number of Patients Randomized	Treatment Regimen Day 1	Treatment Regimen Days 2 & 3
Part IA	12-17 years	43	115 mg IV fosaprepitant	80 mg oral aprepitant
Part IB	12-17 years	44	150 mg IV fosaprepitant	n/a
Part IIA	<12 years	n/a	Oral aprepitant dose equivalent to 80 mg in adults	n/a
Part IIB	<12 years	n/a	Oral aprepitant equivalent to 125 mg in adults	n/a
Part III	<12 years	n/a	n/a	n/a
Part IV	<12 years	n/a	Oral aprepitant at a dose equivalent to 125 mg in adults	Oral aprepitant at a dose equivalent to 80 mg
Part V	6 months to <12 years	23	IV fosaprepitant at a dose equivalent to 150 mg in adults	n/a

All aprepitant and fosaprepitant doses were accompanied by IV ondansetron ± dexamethasone
*During part III, patients were treated with ondansetron ± dexamethasone, only

PROTOCOL 029

Protocol 029 was a phase 2b, partially-blinded, randomized, active comparator-controlled study to evaluate the pharmacokinetics/pharmacodynamics, safety, and tolerability of single-dose fosaprepitant in pediatric subjects for the prevention of chemotherapy-induced nausea and vomiting (CINV). Protocol 029 was initially planned to include four treatment groups (administered with ondansetron ± dexamethasone):

- Control (placebo to fosaprepitant)
- Fosaprepitant 3 mg/kg (to a maximum of 150 mg),
- Fosaprepitant 1.2 mg/kg (to a maximum of 60 mg),
- Fosaprepitant 0.4 mg/kg (to a maximum of 20 mg).

The aim of the fosaprepitant dosing regimens was to achieve aprepitant PK exposures to match those seen in adults receiving 150 mg, 60, and 20 mg of single-day fosaprepitant IV. However, the interim analysis results revealed that while the plasma aprepitant concentrations in adolescents matched the adult targets, the plasma concentrations observed in patients <12

years of age were lower than seen in adults. Therefore, the protocol was amended to include an open-label treatment arm of fosaprepitant 5 mg/kg in pediatric patients <12 years of age in an effort to reach adult aprepitant targets.

Table 4. Protocol 029, Treatment Regimen Details

Adult Fosaprepitant Dose	Pediatric Dose Studied	Number of Patients Randomized
Fosaprepitant 150 mg	• Subjects 12 to 17 years old administered 150 mg • Subjects 2 to <12 years old administered a weight-adjusted dose of 3 mg/kg (not to exceed 150 mg)	43
Fosaprepitant 60 mg	• Subjects 12 to 17 years old administered 60 mg • Subjects 2 to <12 years old administered a weight-adjusted dose of 1.2 mg/kg (not to exceed 60 mg)	44
Fosaprepitant 20 mg	• Subjects 12 to 17 years old administered 20 mg • Subjects 2 to <12 years old administered a weight-adjusted dose of 0.4 mg/kg (not to exceed 20 mg)	41
Fosaprepitant 5 mg/kg*	• Subjects 4 months to <12 years old administered a weight-adjusted dose of 5 mg/kg (not to exceed 150 mg) • Subjects 1 to <4 months old administered a weight-adjusted dose of 2.5 mg/kg • Subjects 0 to <1 month old administered a weight-adjusted dose of 1.25 mg/kg	74

***** Fosaprepitant 5 mg/kg dose added after interim analysis

Protocol 044

Protocol 044 was initiated as a phase 3, randomized, placebo-controlled clinical trial comparing the combination of a single dose of fosaprepitant with ondansetron to ondansetron alone for the prevention of CINV in pediatric subjects receiving emetogenic chemotherapy. Dose selection was supported by PK/PD data from Protocol 134 and 029 (described above) along with data from the aprepitant pediatric development program.

Enrollment in Protocol 044 was closed early after the Applicant met with the FDA and it was

agreed that available PK, efficacy and safety data in the fosaprepitant and aprepitant programs were sufficient to support the approval of the proposed 1-day and 3-day fosaprepitant regimens. See regulatory history in Section 3.2 above.

Safety data from these three studies are reviewed. In general, the safety data are discussed as the 1-Day Supportive Pool and the 3-Day supportive Pool. The 1-Day Supportive Pool consists of pooled AE safety data from pediatric subjects who received fosaprepitant at or above the proposed 1-day fosaprepitant dose.

Safety Pooling Groups

The 1-Day Supportive Pool includes 139 pediatric subjects who received single-dose fosaprepitant 150 mg or 5 mg/kg in Protocol 134, and Cycle 1 of Protocols 029 and 044. The 3-Day Supportive Pool includes 199 patients from Protocols 029 and 044 who received a single IV fosaprepitant dose of 3 mg/kg, 5mg/kg or 150 mg or a 115 mg fosaprepitant dose as part of a 3-day IV/PO/PO regimen with oral aprepitant. It should be noted that these safety pooling groups are not discrete. All the patients in the 1-day Supportive Pool are also included in the 3-Day Supportive Pool. See Table 5 below.

Supportive safety data is also available from Cycles 2 through 6 of the Protocols 029 and 044. Due to differences in safety reporting for these optional cycles, these data are not integrated with Cycle 1 data. See Table 6 below.

Table 5. Pooled Dataset for Primary Safety Analysis, Protocols 134 Parts I and V, Protocol 029 (Cycle 1) and Protocol 044 (Cycle 1)

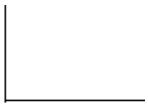

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Table 6. Integrated Dataset for Supplemental Safety Analysis, Protocols 029 and 044

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MO Comment:
The Applicant's 1-Day Supportive and 3-Day Supportive safety pools are appropriate. It should be noted that while the 3-Day safety Pool supports the proposed doses for the 3-day fosaprepitant pediatric regimen, no patients in the development program received fosaprepitant on Day 2 or Day 3. Therefore, proposed regimens with fosaprepitant dosing on Days 2 or 3 are not supported by safety data submitted as part of the current Application.

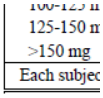
8.2. Review of the Safety Database

8.2.1. Overall Exposure

In total, 199 patients are included in the primary safety population and received at least a partial dose of fosaprepitant during Cycle 1. See

Table 7 below.

Table 7. Extent of Exposure to Fosaprepitant by Dose in Cycle 1, All Subjects Treated, Protocols 134, 019, and 044 Combined



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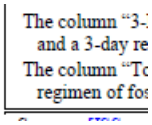
8.2.2. **Relevant characteristics of the safety population:**

Most patients in the safety population were white and slightly more than half were male. There were no patients less than 2 years of age. The most common primary malignancies represented were sarcoma, CNS malignancy, bone-osteosarcoma, and neuroblastoma.

Table 8. Subject Characteristics, All Subjects as Treated, Protocols 134, 029, and 044 Combined

Gastrointestina
Germ Cell
Head and Neck
Hematopoietic

Table 8 Continued



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8.2.3. **Adequacy of the safety database:**

The safety database was not adequate to support approval of fosaprepitant on Days 2 and 3 of the proposed 3-day regimen as none of the patients received fosaprepitant on Days 2 or 3. The Sponsor's 3-Day supportive safety pool included patients who received fosaprepitant doses similar to or higher than proposed for Days 2 and 3 and not patients who actually received fosaprepitant on Days 2 and/or 3.

MO comments:
Fosaprepitant is rapidly (<30 minutes) and completely converted to aprepitant. However, the lack of safety data from patients who have received three consecutive days of fosaprepitant given the higher Cmax predicted through modeling and simulation is a concern.

The database was adequate to support the approval of the single dose (single day) fosaprepitant regimen for pediatric patients receiving one-day chemotherapy and to support the approval of a 3-day regimen of fosaprepitant on Day 1 and aprepitant on Days 2 and 3. The safety of multiple days of aprepitant in pediatric patients is supported by pre-marketing data and postmarketing experience of aprepitant (EMEND oral) which is currently approved as a 3-day regimen for pediatric CINV.[1]

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There were no significant concerns with data integrity or submission quality. The electronic submission was easily navigable and well organized.

8.3.2. Categorization of Adverse Events

The All Subjects as Treated (ASaT) population was used for the analysis of safety and includes all randomized patients who received at least one dose of fosaprepitant. Events related to the efficacy endpoint (vomiting and dry heaves/retching) were not defined as AEs during the period of diary data collection (120 hours post-dose, cycle 1) unless Serious adverse event (SAE) criteria were met. In the optional cycles (2 through 6) of protocols 029 and 044, only SAEs and non-serious AEs determined by the investigator to be drug-related or led to study discontinuation were required to be reported.

MO Comment:
The difference in adverse event reporting requirements between Cycle 1 and Cycles 2 through 6 is the reason that these data are not pooled for the safety evaluation.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA, versions 16.1 and 19.0). All AEs were also categorized categorized by the investigator using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE).

8.3.3. Routine Clinical Tests

The safety variables assessed in Protocols 134, 044, and 029 included adverse events, vital signs, height, weight, physical examination, 12-lead ECG, laboratory safety assessments, and pregnancy testing. Laboratory safety tests included hematology, chemistry, and urinalysis.

[1] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=696f9e80-9cae-403b-de9e-078343ce4713

These safety assessments were conducted as outlined in Table 9,

Table 10, and Table 11 for Protocols 134, 044, and 029, respectively. See below.

MO Comment:
The frequency of assessing vital signs, height, weight, physical examination, 12-lead ECG, and laboratory measures was reasonable for Protocols 134, 044, and 029. The laboratory tests assessed were also appropriate given the known safety profile of fosaprepitant.

Table 9. Study Flow Chart, Protocol 134 (Parts I through V)

administrati
Ondansetron
Rescue therap
III, IV, and

Diary record
and use of r
Obtain and

Table 9 cont'd

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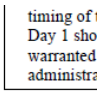
Table 10. Study Flow Chart, Protocol 044, Cycle 1

IV Ondanset
Optional Dex
Chemotherap
Adverse Eve

Table 10 cont'd


timing of
Day 1 sho
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administra

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Table 11. Study Flow Chart, Protocol 029, Cycle 1

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8.4. Safety Results

8.4.1. Deaths

Primary Safety Population

No subjects included in the primary safety population (Cycle 1 integrated dataset of Protocols 134, 044, and 029) died.

Secondary Safety Population

During and following the optional cycles of Protocols 029 and 044, three deaths occurred. Of these, one death occurred during the follow-up period. None of the adverse events leading to these deaths was determined by the investigator to be related to the study drug. See Table 12 below.

Table 12. Deaths, Cycles 2-6, Protocols 044 and 029

Study	Age (years)	Gender	Cycle of Onset	Adverse Event
044	14.6	Female	4	Sepsis
029	13.6	Female	4	Neutropenia
029	12.8	Male	Follow-up period	Metastases to lung

Reviewer's Table. Source, Summary of Clinical Safety Table 2.7.4:32

8.4.2. Serious Adverse Events

Primary Safety Population

In the primary safety population (both 3-Day and 1-Day Supportive Pools), 30.7 % of patients had a serious adverse event (SAE). The most commonly reported SAE was febrile neutropenia. The incidence of febrile neutropenia was similar across fosaprepitant and control regimens. This SAE is a known adverse reaction associated with chemotherapy.

No safety signals were observed in review of the SAE data. There did not appear to be any SAE with a substantial difference in incidence between the fosaprepitant and control regimen groups. See

Table 13 below.

Secondary Safety Population

Consistent with what was observed in Cycle 1, the most commonly reported SAEs in the optional Cycles 2 through 6 of Protocols 044 and 029 were in the Blood and lymphatic system disorders SOC, with febrile neutropenia occurring most frequently.

Table 13. Primary Safety Population, SAEs, Protocols 134, 044, and 029


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General
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Days 2

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8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Primary Safety Population (Cycle 1)
In the primary safety population (both 3-Day and 1-Day Supportive Pools), four patients (4/199) discontinued from a trial due to an adverse effect of the drug. It should be noted that all AEs resulting in discontinuation resolved.

Table 14. Adverse Events Resulting in Discontinuation in Cycle 1, Protocols 134, 029 and 044

Study	Age (years)	Gender	Study Day of Onset	Adverse Event	Duration
029	2.8	Female	1	Anaphylactic Reaction	10 minutes
044	7.3	Female	1	Discomfort, flushing	20 minutes
044	13.4	Male	1	Hypersensitivity	1 Hour
134 (Part 5)	2.6	Female	158	Pyrexia	4 hours

Reviewer's Table. Source, Summary of Clinical Safety Table 2.7.4:35

Patient narratives of Adverse Discontinuations
A 3-year-old girl (Study 134) with a diagnosis of medulloblastoma, experienced an SAE of pyrexia on Day 1 of Part V (Day 158 from entry into the study in Part III) post initiation of fosaprepitant and IV dexamethasone. She was treated with dipyrone, and the event resolved within 4 hours. The investigator assessed the event as moderate in intensity, with a toxicity grade of 1, and not related to study medication. Chemotherapy was cancelled and the rest of study medication regimen (ondansetron) was discontinued. The subject was discontinued from the study due to the AE of pyrexia.

A 13-year old white male (Study 044) with a diagnosis of soft tissue neoplasm NOS experienced an SAE of hypersensitivity reaction on Study Day 1 immediate after starting infusion of fosaprepitant 10 mg. The event was severe in intensity. The patient experienced shortness of breath, choking, red flushing of the head, cramping of the jaw and arms, and chest pain. The infusion was immediately stopped. Treatment of the event included hydrocortisone and clemastine fumarate. The event was considered resolved after 1 hour. Chemotherapy was continued according to the schedule. The subject was discontinued due to the AE of hypersensitivity reaction.

A 7-year old white male (Study 044) with a diagnosis of hematopoietic malignancy NOS experienced flushing and discomfort (Grade 2) on Study Day 1 during an infusion of fosaprepitant 100 mg. The event of flushing and discomfort reportedly lasted 20 minutes. No treatment was administered. Vital signs were normal.

A 2-year old white female (Study 029) with a diagnosis of bilateral congential retinoblastoma experienced an anaphylactic reaction with the symptoms of facial swelling, tachycardia, tachypnea, lower oxygen saturations, lip swelling, tongue edges swollen, erythema, red rash on chest, head and face. The event occurred three minutes into a 60-minute infusion. At this point, the patient had received approximately 7 mg of the fosaprepitant dose. The patient was randomized to the 5 mg/kg treatment arm. Study medication was discontinued and the patient began to improve 10 minutes after receiving treatment for anaphylactic reaction. Treatments included chlorpheniramine (administered approximately 4 minutes after the onset of the event) and hydrocortisone (administered approximately 2 hours and 20 minutes after the onset of the event). The event was considered resolved on Day 1. Fosaprepitant was permanently discontinued due to this event anaphylactic reaction.

Secondary Safety Population (Cycles 2 through 6)
No subjects in the optional Cycles 2 to 6 of Protocols 029 and 044 had an AE that resulted in discontinuation of study medication. Study 134 did not include optional Cycles 2 through 6.

MO Comment:
The 13-year old patient (Study 044) whose adverse discontinuation event was categorized as a hypersensitivity reaction should have been more specifically categorized as anaphylaxis, per World Allergy Organization guidelines.[2] The narrative for the adverse event of flushing and discomfort may also have been an event of hypersensitivity. The narrative did not contain adequate information to determine if the event should have been described as anaphylaxis. If we conservatively categorize each of these 3 events as hypersensitivity reactions, the incidence rate for hypersensitivity would be 1.5% (3/199). These events are already described in the Warnings and Precautions Section of the EMEND for Injection label. Therefore, no labeling changes based on these events is recommended.

> *Excerpt from Current EMEND for IV labeling*
>
> ***5.2 Hypersensitivity Reactions***
>
> *Serious hypersensitivity reactions, including anaphylaxis and anaphylactic shock, during or soon after infusion of fosaprepitant have occurred. Symptoms including flushing, erythema, dyspnea, hypotension and syncope have been reported [see Adverse Reactions (6.2)]. Monitor patients during and after infusion. If hypersensitivity reactions occur, discontinue the infusion and these symptoms with first-time use [see Contraindications (4)].[3]*

[2] http://www.bsaci.org/Guidelines/WAO_anaphylaxis_guideline_2012.pdf
[3] https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022023s014lbl.pdf

8.4.4. Significant Adverse Events

The NCI CTCAE Grades and their associated assignments of severity are listed below:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

Primary Safety Population (Cycle 1)

The most commonly reported Grade 3 AEs were febrile neutropenia and anemia. The incidence of anemia was greater in the control group than in the fosaprepitant group and is therefore not represented in **Table 15**, below. These events are consistent with a population of patients with cancer receiving chemotherapy. In general, the incidence of severe and life-threatening AEs was relatively similar between the fosaprepitant and control regimens.

Table 15. Subjects With Adverse Events by Maximum Toxicity Grade (Incidence ≥5% in One or More Treatment Groups), in Cycle 1, All Subjects as Treated, Protocols 134, 029 and 044 Combined, Incidence Greater than Control Group

Adverse Event	NCI CTAE Severity Grade	3-Day Supportive Pool n=199	Control Group n=69
Febrile neutropenia	3	29 (14.6)	9 (13.0)
	4	4 (2.0)	2 (2.9)
Leukopenia	3	6 (3.0)	2 (2.9)
	4	9 (4.5)	1 (1.4)
Neutropenia	3	15 (7.5)	3 (4.3)
	4	17 (8.5)	7 (10.1)
Nausea	3	1 (0.5)	0
	4	n/a	
Vomiting	3	4 (2.0)	0
	4	n/a	
Mucosal Inflammation	3	3 (1.5)	0
	4	n/a	
Pyrexia	3	1 (0.5)	0
	4	n/a	
AST increased	3	1 (0.5)	0
	4	n/a	
Neutrophil count decreased	3	8 (4.0)	1 (1.4)
	4	11 (5.5)	5 (7.2)
Platelet count decreased	3	6 (3.0)	2 (2.9)
	4	8 (4.0)	3 (4.3)
White blood cell count decreased	3	5 (2.5)	1 (1.4)
	4	3 (1.5)	4 (5.8)
Decreased appetite	3	4 (2.0)	1 (1.4)
	4	n/a	

Reviewer's Table. Source Table 2.7.4: 28, Summary of Clinical safety.

Secondary Safety Population (Cycles 2 through 6)

During Cycles 2 through 6, the most commonly reported Grade 3 AEs were febrile neutropenia and anemia, similar to what was seen in Cycle 1. Overall, the incidence of severe and life-threatening AEs was higher than was seen during Cycle 1. For example, the incidence of grade 3 febrile neutropenia was 23.6% during Cycles 2 through 6 compared with 13.0% in the 3-Day Supportive Group.

MO Comment:
The general trend of increased incidence of certain severe AEs is not unexpected given that many of the severe AEs were known to be associated with chemotherapy. The increased rate of severe AEs likely represents the cumulative effect of multiple rounds of chemotherapy.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Current EMEND for Injection labeling includes adverse reactions from clinical trials and from post-marketing reporting. See current EMEND labeling.

MO Comment:
The Adverse Reactions section of the current EMEND for Injection labeling is adequate. The Application does not contain any new safety information that is not currently reflected in EMEND for Injection labeling.

8.4.6. Laboratory Findings

Primary Safety Population (Cycle 1)
The treatment arms were generally balanced with respect to the number of subjects with a laboratory value outside of pre-specified limits. See Section 8.4.4 for a discussion of SAEs of laboratory abnormalities. The most notable laboratory abnormalities in both the fosaprepitant and control treatment arms were decreases in hematological measurements (WBCs, neutrophil count, platelet count, and hemoglobin,) and an increase in serum alanine transaminase (ALT).

Secondary Safety Population (Cycles 2 through 6)
Laboratory measurements were not required during Cycles 2 through 6.

Hepatic safety was monitored during the studies. Subjects with a liver function test result during the treatment and/or follow-up period that met predetermined criteria were reviewed. The normal range was defined at a site level by the site's local laboratory.

The criteria for a potential DILI case was an elevated aspartate transaminase (AST) or ALT ≥3X the upper limit of normal (ULN) AND an elevated total bilirubin value ≥2X the ULN AND, at the same time, an alkaline phosphatase <2X the ULN.

During Protocols 134, 029, and 044, a single case of DILI was reported. The case was reported during optional cycle 3 of Protocol 029. The patient was in the fosaprepitant 3 mg/kg treatment group. An AE of hepatoxicity was reported with an onset of Day 109. The investigator assessed this event as non-serious. The event resolved within 2 months.

Fosaprepitant has not been studied in patients with known severe hepatic impairment (Child-Pugh score greater than 9).

8.4.7. Vital Signs

No clinically significant changes in vital signs were reported in Protocols 134, 029, and 044.

8.4.8. Electrocardiograms (ECGs)

During Protocol 134, electrocardiograms were required only at baseline for subjects in Part I Step A. Subjects in Part I Step B and Part V received ECGs at baseline and post-treatment (Days 6 to 8).
During Protocol 029 (Cycle 1), ECGs were performed at baseline and on Days 6 to 8.
ECGs were not required in Cycles 2 to 6.

During Protocol 044, electrocardiograms were collected at baseline and at the follow-up/discontinuation visit (Day 15-17). ECGs were not required in Cycles 2 to 6.

No notable ECG findings were reported during Protocol l134, 029, and 044.

8.4.9. QT

The QT prolongation potential for fosaprepitant IV was evaluated in a previous study and no QT prolongation was detected for fosaprepitant 200 mg infused over 15 minutes. See current EMEND for Injection labeling.

8.4.10. Immunogenicity

N/a

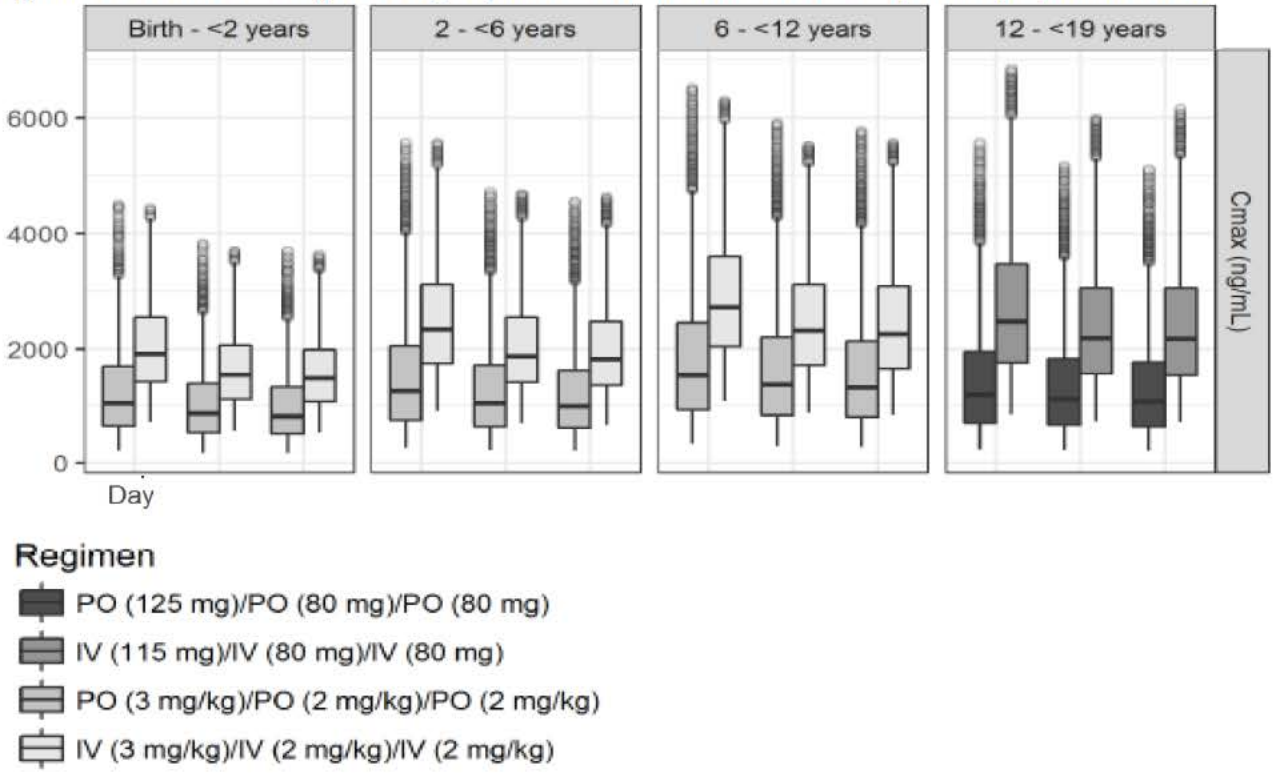
8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Increased Aprepitant C_{max} on Days 2 and 3

The Applicant used modeling and simulation to predict the fosaprepitant doses for Days 2 and 3 based on matching the aprepitant exposures of the approved 3-day EMEND oral regimen. The

aprepitant mean Cmax for the predicted fosaprepitant doses for each age group were 1.5 to 2-fold higher than the oral aprepitant mean Cmax for Days 2 and 3.

Figure 1. Predicted 3-Day IV PK Aprepitant Cmax vs Measured 3-Day oral Aprepitant Cmax



Source: clinical pharmacology Midcycle presentation by Dr. Elizabeth Shang

MO Comment:
The available safety data for the predicted higher Cmax values is limited to Day 1 of the proposed 3-Day (IV/IV/IV) regimen given that none of the fosaprepitant PK/PD or efficacy studies dosed patients with fosaprepitant past Day 1. While the Day 2 and Day 3 predicted Cmax values are less than what is seen for Day 1, this lack of patient safety data for fosaprepitant dosing on Days 2 and 3 cannot be overcome without an additional safety study.

The lack of safety data for patients receiving fosaprepitant on Days 2 and 3 of the proposed 3-day IV regimen was discussed with the Applicant during a teleconference on 13 February 2018. During the discussion, the Applicant decided to no longer pursue approval for any 3-day regimens involving dosing of fosaprepitant on days 2 or 3 given the lack of safety data. With this change, all proposed 3-day regimens would include only oral aprepitant on Days 2 and 3.

8.5.2. Safety Analyses by Demographic Subgroups

No demographic safety analyses by demographic subgroups were conducted given the small size of the safety data pool. Further subdividing this group would yield numbers too small to make inferences regarding safety.

8.6. Specific Safety Studies/Clinical Trials

N/A

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

N/A

8.7.2. Human Reproduction and Pregnancy

No pregnancies were reported during trials submitted in support of this Application.

8.7.3. Pediatrics and Assessment of Effects on Growth

The current Application is a pediatric supplement. All sections of this review pertain to the pediatric population.

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

N/A

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

As of 10 May 2017, fosaprepitant 150 mg (single dose regimen) is registered and approved in more than 75 countries for prevention of CINV in adults. Although initially approved for use, most countries have deleted registration of the 115 mg dose of fosaprepitant, given the availability of the more convenient single day, 150 mg regimen. There are no records of any registration being revoked or withdrawn for safety reasons.

The only country in which fosaprepitant has been approved for pediatric patients is Japan. In Japan, EMEND for Injection is approved as a single dose of 150 mg in patients 12 to 17 years of age and 3 mg/kg dose in patients 6 months to <12 years of age.

Since its licensure through 10 May 2017, post-marketing experience with fosaprepitant has

been reviewed based on an estimated exposure of (b) (4) patient courses (b) (4) of the 115 mg dose and (b) (4) of the 150 mg dose). The Applicant searched their own safety database for postmarketing reports, including spontaneous, literature and non-interventional study reports from market launch (14-Aug-2007) through 10 May 2017. A total of 4,983 (1,328 [27%] serious) spontaneous and non-interventional study reports for fosaprepitant received from HCPs and consumers were identified. Of these, 69 reports (12 serious [17%]) involved AEs in pediatric patients (17 years of age and younger); 67 cases were received from HCPs.

Most of the pediatric postmarketing cases were reported form Japan (25/69) where fosaprepitant is approved for pediatric patients. Of the 69 cases, most were nonserious and no safety signal was observed. Off-label use (41/69) and events related to hypersensitivity/anaphylaxis (7/69) were the most frequently reported AEs. See

Table **16** below.

Table 16 . Fosaprepitant Postmarketing Adverse Events in Pediatric Patients 20-Aug-2007 to 10-May-2017

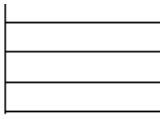


Table 15, cont'd

Vascular disord
Grand Total

*Indicates event

Electronically copied and reproduced from the Summary of clinical safety, Table 2.7.4: 72

See current EMEND for Injection labeling.

8.8.2. Expectations on Safety in the Postmarket Setting

It is expected that the postmarketing safety profile of fosaprepitant in pediatric patients will be consistent with the safety profile outlined in the current EMEND for Injection labeling.

8.8.3. Additional Safety Issues From Other Disciplines

No other safety issues are known that are not discussed in other areas of the review.

8.9. Integrated Assessment of Safety

The primary safety issue of this Application is the absence of safety data in patients receiving fosaprepitant on Days 2 or 3 of the proposed 3-day regimen. The doses for Days 2 and 3 were obtained using modeling and simulation. However, the doses should have been administered in

some patients so that the safety of repeat fosaprepitant dosing could be confirmed. The lack of a theoretical safety concern does not preclude the need to collect safety information.

9. Advisory Committee Meeting and Other External Consultations

N/A

10. Labeling Recommendations

10.1. Prescription Drug Labeling

See Approved labeling for details.

10.2. Nonprescription Drug Labeling

N/A

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not necessary based on information obtained in review of the current Application.

12. Postmarketing Requirements and Commitments

The current Application was submitted to fulfill PMRs. No additional PMRs are recommended in conjunction with approval of the current Application.

13. Appendices

13.1. References

See footnotes.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Protocol 134, 029, and 044

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: _____		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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AISHA P JOHNSON
03/02/2018

ANIL K RAJPAL
03/02/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022023Orig1s017

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	22023
Supporting document/s:	0139 (Supplement 17)
Sponsor's letter date:	October 2, 2017
CDER stamp date:	October 3, 2017
Product:	EMEND (fosaprepitant dimeglumide) for injection
Indication:	For the prevention of nausea and vomiting associated with moderately and highly emetogenic chemotherapy in pediatric patients
Sponsor:	Merck Sharp & Dohme Corp.
Review Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Reviewer:	Yolanda R. Branch, Ph.D.
Supervisor/Team Leader:	Sushanta Chakder, Ph.D.
Division Director:	Donna Griebel, M.D.
Project Manager:	Mary Chung, Pharm.D.

1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

From a nonclinical standpoint, an approval the NDA supplement is recommended.

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

The draft labeling of Emend generally conforms to the format specified under 21CFR 201.57(c)(14) Requirements for PLR (Physician's Labeling Rule) Prescription Drug Labeling. There are no recommended changes to the nonclinical sections of the proposed labeling.

Proposed Labeling:

8 USE IN SPECIFIC POPULATIONS

(b) (4)

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

1.2 Brief Discussion of Nonclinical Findings

No new nonclinical studies have been submitted in this supplement. The reports of the previously submitted nonclinical studies with fosaprepitant and aprepitant were reviewed as part of the initial and supplemental marketing applications for use of aprepitant in adults. In support of the approval of oral aprepitant use in pediatric patients 6 months to 17 years of age, an oral toxicity study of aprepitant was conducted in juvenile rats. In addition, a 4-week intravenous injection toxicity study in juvenile dogs was conducted with fosaprepitant. These reports were previously submitted and reviewed by the FDA under the original submission of NDA 207865 (dated July 21, 2015).

The potential effects of oral aprepitant on development, growth, behavior, and reproductive performance were assessed from postnatal day 10 through postnatal week 9 at doses of 0, 10, 250, or 1000 mg/kg b.i.d followed by a treatment free period through postnatal week 17 in juvenile rats. Aprepitant related effects observed were transient decreases in mean body weight gain and slight changes in clinical pathology parameters of all groups. On PND 28, there was a significantly early vaginal opening in the female rats given 250 and 1000 mg/kg aprepitant b.i.d. There was a significant delay in the preputial separation in the males at all doses of aprepitant when compared to the control. There were no treatment-related effects on mating performance, fertility, or embryonic/fetal survival and no treatment-related gross or histopathological changes in the ovaries, testes, prostate, pituitary, or adrenal glands at any time. Therefore, these findings were not considered to be adverse. Aprepitant related changes in the liver (increased organ weight and hepatocellular hypertrophy) and thyroid (increased organ weight and follicular cell hypertrophy) were similar to findings observed in adult rats and were considered to be secondary to hepatic enzyme induction and of minimal toxicological significance. Thus, the NOAEL for this study was ≥ 1000 mg/kg b.i.d.

The potential effects of EDTA in a clinical fosaprepitant formulation (TT#10-9017) and the toxicity and toxicokinetic of fosaprepitant were assessed in a 4-week intravenous injection toxicity study in juvenile beagle dogs. Beginning on postnatal day 14, juvenile dogs were intravenously administered fosaprepitant solution (2, 4, and 6 mg/kg/day) containing 0.125 mg/ml EDTA once daily for 4 weeks. There were no treatment related changes on electrocardiography, heart rate, blood pressure, or clinical pathology parameters. In the female dogs given 4 mg/kg/day and 6 mg/kg/day, fosaprepitant-related histopathological changes noted were hypertrophy of the endometrium and myometrium within the horns and body of the uterus, hypertrophy of the cervical muscularis and edema of the lamina propria and submucosa of the vagina. Treatment-related histopathologic changes were observed in the testes in male dogs at 6 mg/kg/day (reduced size of Leydig cells in the testes) that correlated with decreased testicular weights. These fosaprepitant related changes in the female reproductive tract and Leydig cells in males were considered reversible and of minimal toxicological significance. In the dogs given 6 mg/kg/day, there was a decrease in heart weight that was not associated with any histopathological or electrocardiographic changes. All fosaprepitant treated dogs had microscopic findings at the injection sites related to the intravenous fosaprepitant formulation. There were no findings attributable to EDTA. The 4 mg/kg dose was the NOAEL, and the 6 mg/kg/day dose was a well-tolerated dose in this study.

The results from the nonclinical studies support the use of aprepitant in pediatric patients for the prevention of Chemotherapy Induced Nausea and Vomiting (CINV).

2 Drug Information

2.1 Drug: EMEND (fosaprepitant dimeglumide) Injection

2.1.1 CAS Registry Number: 265121-04-8

2.1.2 Generic Name

Fosaprepitant

2.1.3 Code Name

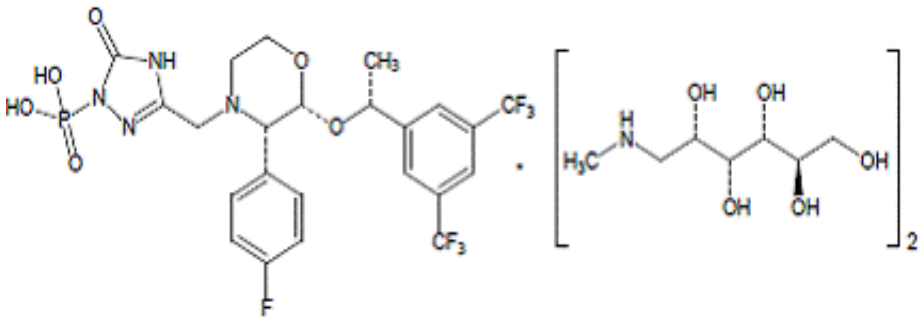
MK-0517

2.1.4 Chemical Name

Chemical name: 1-Deoxy-1-(methylamino)-D-glucitol[3-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-2,5-dihydro-5-oxo-1H-1,2,4-triaz ol-1-yl]phosphonate (2:1) (salt)

2.1.5 Molecular Formula/Molecular Weight: $C_{23}H_{22}F_7N_4O_6P \cdot 2(C_7H_{17}NO_5)$/1004.844

2.1.6 Structure



2.1.7 Pharmacologic class

Neurokinin 1 (NK1) receptor antagonist

2.2 Relevant IND/s, NDA/s, and DMF/s

N/A

2.3 Clinical Formulation

2.3.1 Drug Formulation

EMEND™ is a white to off-white powder that contains 245.3 mg of fosaprepitant dimeglumine equivalent to 150 mg fosaprepitant free base in each vial. Fosaprepitant is supplied for clinical use in 10-mL vials as a sterile, lyophilized preparation.

2.3.2 Comments on Novel Excipients

There are no novel excipients used in the Emend Injection, and there are no safety concerns for the excipients.

11 Integrated Summary and Safety Evaluation

In this NDA supplement, the Sponsor is seeking to extend the indication of Fosaprepitant (EMEND™) injection to pediatric patients 6 months to 17 years of age for the prevention of acute and delayed nausea and vomiting due to highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC). Fosaprepitant is a selective, potent Substance P/Neurokinin 1 (NK-1) receptor antagonist approved for the prevention of chemotherapy-induced nausea and vomiting (CINV). Fosaprepitant (prodrug) is rapidly dephosphorylated to the active moiety aprepitant, a selective, high affinity antagonist for NK-1 receptors. Aprepitant acts by inhibiting emesis induced by cytotoxic agents, such as cisplatin, via the central nervous system.

In support of the original and subsequent supplemental marketing applications, for oral aprepitant and for intravenous fosaprepitant in adults, comprehensive evaluations of the nonclinical pharmacology, pharmacokinetics, and toxicology of aprepitant and

fosaprepitant were completed. In support of the approval of oral aprepitant for use in pediatric patients 6 months to 17 years of age, an oral toxicity study of aprepitant was conducted in juvenile rats. In addition, a 4-week intravenous injection toxicity study in juvenile dogs was conducted with fosaprepitant to support IV dosing in pediatric patients.

In the juvenile rat toxicity study, the potential effects of aprepitant on development, growth, behavior, and reproductive performance were assessed following oral administration at doses of 0, 10, 250, or 1000 mg/kg b.i.d. Treatment related findings were significantly early vaginal opening in mid and high dose group females and significantly delayed preputial separation in all male groups. Test article-related changes in the liver (increased organ weight and hepatocellular hypertrophy) and thyroid (increased organ weight and follicular cell hypertrophy) were similar to findings observed in adult rats and were considered to be secondary to hepatic enzyme induction and to be of minimal toxicological significance. Thus, the NOAEL for this study was ≥ 1000 mg/kg b.i.d.

A 4-week IV toxicity study was conducted in juvenile beagle dogs to assess potential effects of EDTA present in the clinical formulation (TT #10-9017) and to determine the potential toxicity and toxicokinetic profile of fosaprepitant. Treatment-related histopathologic changes were observed in the testes in male dogs at 6 mg/kg/day (reduced size of Leydig cells) and in the reproductive tract of female dogs at 4 mg/kg/day and 6 mg/kg/day (endometrial and myometrial hypertrophy of the uterine horns and body, hypertrophy of the cervical muscularis, and edema of the lamina propria and submucosa of the vagina). These fosaprepitant related changes in the female reproductive tract and Leydig cells changes in males were reversible and considered to be of minimal toxicological significance. The 4 mg/kg dose was the NOAEL, and the 6 mg/kg/day dose was a well-tolerated dose in this study.

In conclusion, the nonclinical studies submitted in the original and subsequent supplemental marketing applications supports the safety of Fosaprepitant (EMEND™) injection in pediatric patients 6 months to 17 years of age for the prevention of MEC and HEC. From a nonclinical perspective, this supplemental NDA application is recommended for approval for its proposed use as indicated in the label.

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YOLANDA R BRANCH
03/02/2018

SUSHANTA K CHAKDER
03/02/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022023Orig1s017

STATISTICAL REVIEW(S)

MEMORANDUM OF STATISTICAL REVIEW

NDA #:	022-023
Supplement #:	017 (SDN 0139 & SN 0532) pediatric supplement efficacy
Related IND #:	48,924
Product Name:	Emend (fosaprepitant 150-mg) I.V.
Indication(s):	prevention of chemotherapy-induced nausea and vomiting (CINV) in pediatric patients 6 months and older
Applicant:	Merck Sharp & Dohme (Merck & Co.)
Dates:	Stamp date: 10/03/2017 Primary review due date: 3/5/2018 PDUFA date: 4/3/2018
Review Priority:	standard
Biometrics Division:	III
Statistical Reviewer:	Ling Lan, PhD
Concurring Reviewers:	George Kordzakhia, PhD
Medical Division:	DGIEP
Clinical Team:	Aisha Johnson, M.D., Anil Rajpal, M.D. (Team Leader)
Project Manager:	Mary Chung

Oral aprepitant (EMEND™) is a potent and selective NK1 receptor antagonist. It is approved for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) and highly emetogenic chemotherapy (HEC) in oncology patients 6 months and older under NDA 21-549 in 2014. Fosaprepitant is a water-soluble prodrug that is completely converted to aprepitant within the 30- to 60-minute duration of IV administration. Fosaprepitant is approved for the prevention of HEC and MEC in adults under NDA 22023/S-004 (HEC) in 2010 and NDA 22023/S-006 (MEC) in 2016, respectively.

This submission intends to fulfill the Written Request for pediatric exclusivity. The sponsor proposes to extrapolate the efficacy of the proposed pediatric 1-day fosaprepitant regimen from the adult fosaprepitant program and bridge the efficacy of the pediatric 3-day fosaprepitant regimen from that demonstrated with the pediatric 3-day oral aprepitant regimen.

This submission also included clinical data from a pre-maturely terminated phase 3 study, Study 044, and cited two studies in the ISE: a Phase IIb Study 029 and an open-label PK Study 134 (no CSRs or data sets were included for the two Phase II studies). For a summary

of the three pediatric studies, please refer to the Appendix. The dataset for Study 044 located at the link below:
\\CDSESUB1\evsprod\NDA022023\0139\m5\datasets\p044mk0517\analysis\legacy\datasets

The sponsor terminated Study 044 pre-maturely due to the approval of the oral aprepitant in a similar pediatric population. The study design did not pre-specify or assume an option for early stopping. By the time of study termination, there were 71 subjects who completed the trial out of the planned 180 subjects. The efficacy analyses were not performed by the sponsor, and no efficacy results were included in Section 14 of the proposed draft label. The sponsor stated that the dataset from Study 044 is not intended to support the applied indication. Since the efficacy relies on the extrapolation, statistical review team did not conduct further statistical assessment on the data of Study 044.

Appendix

Table 1: Summary of Trials to be Assessed in the Statistical Review

Trial ID Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings (Sponsor)
Study 044 MC, R, DB, PG, about 15 days main phase after maximum 28 days of screening phase and followed by maximum 6-month extension PC trial	Fosaprepitant + Ondansetron Versus Ondansetron alone N(1:1) = 37:34 Randomization stratified by age (<2 years, 2 to <6 years, 6 to <12 years and 12 to 17 years), HEC in Cycle 1 and use of dexamethasone in Cycle 1	Complete Response (CR) at the delayed phase, defined as no vomiting, no retching and no use of rescue medication in the >24 to 120 hours following initiation of emetogenic chemotherapy in Cycle 1. No formal hypothesis testing was performed.	Due to early termination of the trial, data from this study were decided not to be used to support the current marketing, i.e. not included in the proposed label, by the sponsor. Descriptive summaries were calculated for each treatment group and their difference on primary and key secondary endpoints.
Study 029 MC, open-label Phase 2b PK study	n=153 pediatric subjects from birth to <12 years old with no control arm	PK and safety endpoints	No study report
Study 303 MC, open-label, 6-month	Birth to 17 years old No control arm	PK and safety endpoints	No study report

* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, AC: active controlled

Source: Page 115 on Study 044 CSR

Source: Page 117 on Study 044 CSR

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LING LAN
02/28/2018

GEORGE KORDZAKHIA
03/02/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022023Orig1s017

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	22023/S-17
Link to EDR	\\CDSESUB1\evsprod\NDA022023\022023.enx
Submission Date	10/3/2017
Submission Type	Efficacy Supplement
Brand Name	Emend™ for Injection
Generic Name	Fosaprepitant dimeglumine
Dosage Form and Strength	Lyophilized powder (150 mg fosaprepitant) to be reconstituted for IV infusion
Route of Administration	Intravenous Infusion
Proposed Indication	In pediatric patients six months of age and older, combination with other antiemetic agents for the prevention of • acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin. • delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).
Applicant	Merck Sharp & Dohme Corp
Associated IND	048924
OCP Primary Reviewer	Elizabeth Shang, Ph.D., R.Ph. (Clinical Pharmacology and Pharmacometrics)
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1. EXECUTIVE SUMMARY

Fosaprepitant (Emend) for injection has been approved since 2008 for adults in combination with other antiemetic agents for the prevention of: 1) acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin; and 2) delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC). The approved regimen in adults is a single intravenous infusion of 150 mg fosaprepitant over 20 to 30 minutes approximately 30 minutes prior to chemotherapy. It has not been studied for the treatment of established nausea and vomiting. Fosaprepitant is a prodrug of aprepitant. Aprepitant (Emend) oral capsule and suspension have been approved for chemotherapy-induced nausea and vomiting (CINV) in adults (2003) and pediatric patients (2015) as a three-day oral regimen.

To support the proposed expansion of the indications to pediatric patients, the sponsor completed one phase 2b dose-ranging PK/PD study for a single-day regimen and one PK study including cohorts where 1) fosaprepitant IV was administered on Day 1 followed by oral aprepitant on Days 2 and 3 in adolescent patients; and 2) single-dose dose-ranging PK study of fosaprepitant IV was conducted in patients less than 12 years old. The sponsor proposed two dosing regimens for the use of fosaprepitant in pediatric patients 6 months and older: a single-day regimen and a three-day regimen.

The doses for both regimens were derived by using exposure-matching strategy since the efficacy of aprepitant has been established in 1) pediatric patients 6 months and older administered oral aprepitant in a three-day regimen, and 2) adult cancer patients receiving single-day regimen of fosaprepitant. For the single-day regimen, the dose for fosaprepitant was derived from matching systemic exposures (Cmax and AUC) in pediatric cancer patients to those in adult healthy subjects. For the three-day regimen, the systemic exposure (AUC) of aprepitant following IV fosaprepitant on Day 1 and oral aprepitant on Days 2 and 3 (IV/PO/PO) was matched to those in pediatric patients receiving three-day oral aprepitant (PO/PO/PO), an approved regimen in pediatric patients. Because the minimum body weight of subjects enrolled in the studies was 6.80 kg, the sponsor's proposal to not dose fosaprepitant for pediatric patients with body weight less than 6 kg is reasonable.

The sponsor initially also proposed a three-day regimen with fosaprepitant given on Days 1, 2, and 3 (IV/IV/IV). However, the option of using fosaprepitant IV for three consecutive days has been foundunacceptable based upon the review of PK data. The Cmax from the proposed IV administration on Days 2 and 3 with the same infusion duration as Day 1 was about 2-fold those from oral aprepitant administration. An infusion duration of 8 to16 hours is needed to match the Cmax of aprepitant following IV infusion to that following oral administration, and is thus considered impractical. In addition, there was no safety data for pediatric patients on Days 2 and 3 with higher Cmax of aprepitant. Thus, the review team recommends that only the three-day regimen with IV/PO/PO route be approved.

The data in this sNDA were also used to support the fulfillment of Postmarketing Requirement (PMR) under the Pediatric Research Equality Act (PREA) and the Pediatric Written Request (PWR).

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed this application and found this supplemental NDA acceptable from a clinical pharmacology perspective with the following recommendations on the dosage regimens. PREA PMR 1663-3 is fulfilled from a Clinical Pharmacology perspective.

The key review issue with specific recommendations/comments are summarized below:

Review Issues	Recommendations and Comments
Proposed one-day regimen	Acceptable
Proposed three-day regimen using IV/PO/PO	Acceptable
Proposed three-day regimen using IV/IV/IV or IV/IV/PO	Given that a) the Cmax from proposed IV on Days 2 and 3 with the same infusion duration as Day 1 was about 2-fold that from oral aprepitant administration, and b) there was no safety data for pediatric patients on Days 2 and 3 with higher Cmax of aprepitant, the review team recommends that only the three-day regimen with IV/PO/PO route be labeled.

1.2 Post-Marketing Requirements and Commitments

No Clinical Pharmacology related PMR or PMC.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK-1) receptors. Animal and human Positron Emission Tomography (PET) studies have shown that aprepitant crosses the blood brain barrier and occupies brain NK-1 receptors. Animal and human studies have shown that aprepitant augments the antiemetic activity of the 5-HT3 receptor antagonist ondansetron and the corticosteroid dexamethasone and inhibits both the acute and delayed phases of cisplatin-induced emesis. Fosaprepitant is a prodrug of aprepitant and accordingly, its antiemetic effects are attributable to aprepitant.

The pharmacokinetics (PK) for fosaprepitant and aprepitant were studied following a single dose of fosaprepitant in pediatric patients 6 months and older. In pediatric patients 2 to <12 years of age and in adolescents (12 - 17 years) following single dose 3 mg/kg IV fosaprepitant and 150 mg IV, respectively, aprepitant exhibited a biphasic decline with a mean (%CV) terminal half-life ($t_{½}$) ranging from 6.55 (55.3%) to 10.5 (9.6%) hours (Study P029). Similarly, the mean (%CV) terminal t1/2 of aprepitant was 7.94 (36%) hours in patients 6 months to < 2 years following single dose of 5 mg/kg IV fosaprepitant.

A summary for systemic exposures to aprepitant following fosaprepitant administration with proposed therapeutic doses in pediatric patients and healthy adults (comparator) is provided below. For details, see Section 3.2. Refer to the product label for detailed PK and PD information, intrinsic and extrinsic effects on fosaprepitant and aprepitant PK, as well as related dose adjustment in adults. Also refer to the oral Emend product label for the PK information in pediatrics. Excerpts of this information are provided in Section 3.2.

2.1.1 Single-day regimen

Adolescents

The systemic exposures to aprepitant in adolescents following 150 mg IV dose is shown in Table 1.

Table 1. Geometric Mean of Observed Aprepitant Following Single Dose of 150 mg IV Infusion in Adolescent Patients and Healthy Adults.

Study (Subjects)	Descriptive Statistics	AUC0-∞ (ng×hr/mL)	AUC0-24hr (ng×hr/mL)	Cmax (ng/mL)	C24hr (ng/mL)
P029 (12-17 years)	N	3	12	12	12
	Geometric Mean	33300	29400	3360	675
P134 (12-17 years)	N	8	11	11	11
	Geometric Mean	42000	30000	5380	769
P165^ (Healthy Adults)	N	41	41	41	41
	Geometric Mean	35031	24500	4010	577
^ Historical data					
Source data: Table 11-1 of CSR P029, Table 11-2 of CSR P134, Tables 11-1 and 11-2 of CSR P165					

6 months to < 12 years

Table 2. Geometric Mean of Simulated Aprepitant Following Single Dose of 4 mg/kg IV Infusion in Pediatric Patients 2 to < 12 Years Old and 5 mg/kg IV Infusion in Patients 6 months to < 2 Years Old and Observed Aprepitant Following Single Dose of 150 mg IV Infusion in Healthy Adults.

Dose	Age Group (years)	AUC0-∞ (ng×hr/mL)	AUC0-24hr (ng×hr/mL)	Cmax (ng/mL)	C24hr (ng/mL)
4 mg/kg	6 to < 12	53031	35235	3591.4	682.25
4 mg/kg	2 to < 6	37909	28205	3080.2	443.78
5 mg/kg	6 months to < 2	40021	30125	3115.7	480.64
150 mg^	Healthy Adults	35031	24500	4010	577
^ Historical data from Study P165					
Source data: Section 2.7.2 Summary of Clinical Pharmacology, Table 2.7.2:11					

2.1.2 Three-day regimen

The simulated systemic exposures to aprepitant after the administration of the following dosing regimens are shown in Table 3:

Adolescents:

- Day 1: Either 115 mg IV fosaprepitant or 125 mg oral aprepitant
- Days 2 and 3: Either 80 mg IV fosaprepitant or 80 mg oral aprepitant

6 months to < 12 years:

- Day 1: Either 3 mg/kg IV fosaprepitant or 3 mg/kg oral aprepitant
- Days 2 and 3: 2 mg/kg IV fosaprepitant or 2 mg/kg oral aprepitant

Table 3. The Geometric Mean of Simulated Systemic Exposures (AUC0-24h, Cmax, Cmin) to Aprepitant Following a Three-Day Regimen

Day 1				Day 2				Day 3			
	AUC	**Cmax**	**Cmin**		**AUC**	**Cmax**	**Cmin**		**AUC**	**Cmax**	**Cmin**
Adolescents											
PO	17958	1152.8	364.35	PO	17491	1097.1	376.96	PO	16833	1055.9	365.86
IV	20938	2424.5	424.79	PO	16820	1061.1	361.25	PO	16508	1036.1	359.34
IV	21083	2451	428.6	IV	20142	2154.7	391.75	IV	20127	2143.8	389.54
6 - < 12 years											
PO	21354	1489.2	384.31	PO	18832	1343.7	310.17	PO	18140	1291.9	298.9
IV	25659	2699.3	474.82	PO	19604	1403.9	321.35	PO	18260	1299.7	301.23
IV	25639	2686.5	474.92	IV	22704	2284	389.11	IV	22169	2235.5	377.58
2 - < 6 years											
PO	16398	1230.9	234.82	PO	13297	1034.9	167.56	PO	12710	987.39	160.23
IV	20196	2287.3	296.53	PO	13707	1070.8	172.06	PO	12724	988.1	160.66
IV	20336	2307.3	300.77	IV	16544	1860.1	219.27	IV	15941	1803.3	209.54
6 months to < 2 years											
PO	13431	1023.2	180.87	PO	10611	842.31	123.58	PO	10120	801.92	117.96
IV	16616	1864.4	227.82	PO	10915	870.12	126.6	PO	10125	802.06	118.2
IV	16715	1872.1	229.07	IV	13217	1495.5	159.94	IV	12674	1443.6	152.02

Units for AUC0-24h, Cmax, and Cmin are ng×hr/mL, ng/mL, ng/mL, respectively.

2.1.3 Fosaprepitant

Limited PK samples for fosaprepitant in pediatric patients were collected. The summary of the Cmax values is shown in Table 4. Since fosaprepitant is administered through IV infusion, the Tmax of fosaprepitant occurs at the end of infusion. Similar to adults, the concentrations of fosaprepitant were negligible within 15 to 30 minutes after the end of infusion in pediatric patients. For more details of fosaprepitant PK parameters, see Sections 3.2.2, 4.2.2.3, and 4.2.2.5.

Table 4. Summary of Plasma Fosaprepitant Cmax Values in Pediatric Patients Following a Single Dose of IV Fosaprepitant

Dose	Age Group (years)	Mean Cmax ± SD (ng/mL)
115 mg Infuse over 15 minutes	Healthy Adults^	5635 ± 1544[#]
3 mg/kg Infuse over 60 minutes	6 Months to < 2 (n = 7)	2756 ± 3364
	2 to < 6 (n = 8)	3034 ± 1718
	6 to < 12 (n = 8)	1654 ± 1995
150 mg Infuse over 30 minutes	12 to 17 (n = 11)	1310 ± 964

^ Historical data submitted to original NDA 22023.
[#] C_{15min}. Reported Cmax is 5900 ng/mL occurred at 10 minutes post the start of infusion, which was likely due to sampling error. Refer to Clinical Pharmacology Review of the original NDA published in 2008.

2.2 Dosing and Therapeutic Individualization

2.2.1 General Dosing

The doses for both regimens were derived by using exposure-matching strategy since the efficacy of aprepitant has been established in 1) pediatric patients 6 months and older receiving oral aprepitant in a three-day regimen for single or multi-day chemotherapy regimen, and 2) adult cancer patients receiving single day fosaprepitant for single-day chemotherapy regimen. For the single-day regimen, the dose for fosaprepitant was derived from matching systemic exposures (Cmax and AUC) in pediatric cancer patients to those in adult healthy subjects. For the three-day regimen, the systemic exposure (AUC) of aprepitant following IV fosaprepitant was matched to those in pediatric patients receiving oral aprepitant.

Single-day regimen for patients receiving single-day chemotherapy

The proposed doses for the single-day chemotherapy in patients 6 months and older (≥ 6 kg) and associated infusion durations are shown in Table 5 and are acceptable. The dosing instruction for the concomitant anti-emetics, corticosteroid, and 5-HT_3 antagonist is appropriate. Of note, unlike in adult patients for whom fosaprepitant is given as a combination therapy with dexamethasone and 5-HT_3 antagonist, the use of dexamethasone was optional for pediatric patients due to the difference in clinical practice. Nevertheless, when needed, dexamethasone dose should be reduced by half. The proposed infusion duration of 30 minutes in adolescents is similar to that in adult patients, i.e., 20 to 30 minutes, which is acceptable. In patients 6 months to < 12 years old, the infusion duration of one hour was proposed to reduce the Cmax. This is acceptable. The completion of infusion of fosaprepitant approximately 30 minutes prior to chemotherapy is proposed regardless of the infusion duration and age group. Since Emend is indicated for the prevention of delayed phase of CINV, this approach is acceptable.

Table 5. Single-Day Regimen for Single-Day Chemotherapy

Drug	Age	Regimen
EMEND for injection	12 Years to 17 Years	150 mg intravenously over 30 minutes,
	2 Years to less than 12 Years	4 mg/kg intravenously over 60 minutes (maximum dose 150 mg)
	6 Months to less than 2 Years	5 mg/kg intravenously over 60 minutes, (maximum dose 150 mg)
Dexamethasone	6 Months to 17 Years	If a corticosteroid, such as dexamethasone, is co-administered, administer 50% of the recommended corticosteroid dose on Days 1 and 2.
5-HT_3 antagonist	6 Months to 17 Years	See selected 5-HT_3 antagonist prescribing information for the recommended dosage

Three-day regimen for patients receiving multiple-day chemotherapy

For the three-day regimen given as IV/PO/PO, the systemic exposure (AUC) of aprepitant on Day 1 was matched to those in pediatric patients receiving oral aprepitant on Day 1. The simulated Cmax on Day 1 following IV infusion was about 2-fold the Cmax following oral administration. However, the safety profiles from adolescents receiving 150 mg IV (a dose 30% higher than 115 mg) and patients < 12 years old receiving 5 mg/kg IV (a dose 67% higher than 3 mg/kg) support the use of the IV dose on Day 1. The doses of 115 mg IV for adolecents and 3 mg/kg for patients < 12 years old on Day 1 for a three-day regimen are acceptable. The Cmax and AUC of aprepitant on Days 2 and 3 with oral aprepitant following IV fosaprepitant on Day 1 were similar to the pediatric patients who received the same oral doses on Days 2 and 3 following oral aprepitant dose on Day 1.

Table 6. Three-Day Regimen for Single-Day or Multi-Day Chemotherapy

Age Group	Drug	Day 1	Day 2	Day 3
12 Years to less than 17 Years	EMEND for injection	115 mg intravenously over 30 minutes	--	--
	EMEND capsules	--	80 mg orally	80 mg orally
6 Months to Less than 12 Years	EMEND for injection	3 mg/kg (maximum dose is 115 mg) intravenously over 60 minutes (maximum dose is 115 mg)	--	--
	EMEND for oral suspension	--	2 mg/kg orally (maximum 80 mg)	2 mg/kg orally (maximum 80 mg)
6 Months to 17 Years	Dexamethasone	If a corticosteroid, such as dexamethasone, is co-administered, administer 50% of the recommended corticosteroid dose on Days 1 through 4		
6 Months to 17 Years	5-HT_3 antagonist	See selected 5-HT_3 antagonist prescribing information for the recommended dosage		

The sponsor initially also proposed a three-day regimen with fosaprepitant given on Days 1, 2, and 3 (IV/IV/IV). However, the option of using fosaprepitant IV for three consecutive days was deemed unacceptable based upon the review of PK data. The Cmax from the proposed IV administration on Days 2 and 3 with the same infusion duration as Day 1 was about 2-fold those from oral aprepitant administration (Table 3, Table 25, Table 26, Units for AUC0-24h, Cmax, and Cmin are ng×hr/mL, ng/mL, ng/mL, respectively.

Table 27, Table 28). An infusion duration of 8 to16 hours is needed to match the Cmax of aprepitant following IV infusion to that following oral administration, and is thus considered impractical. In addition, there was no safety data for pediatric patients on Days 2 and 3 with higher Cmax of aprepitant. Thus, the review team recommends that only the three-day regimen with IV/PO/PO route be approved.

Details on how the review team reached the recommendation on these dosing regimens are in Section 3.3.1.1 and Section 3.3.1.2.

2.2.2 Therapeutic individualization

Not applicable.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The labeling recommendations included the revision of the dosing regimens based upon the review team's recommendations. Labeling revisions are ongoing. Please refer to the final approved labeling when available.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Proposed product

The proposed product is the currently approved fosaprepitant for injection. It is a sterile, lyophilized formulation containing fosaprepitant dimeglumine, a prodrug of aprepitant, a substance P/neurokinin-1 (NK-1) receptor antagonist, an antiemetic agent. Fosaprepitant dimeglumine is a white to off-white amorphous powder with a molecular weight of 1004.83 Da. It is freely soluble in water. Each vial of EMEND for injection for administration as an intravenous infusion contains 150 mg of fosaprepitant (equivalent to 245.3 mg of fosaprepitant dimeglumine) and the following inactive ingredients: edetate disodium (5.4 mg), polysorbate 80 (75 mg), lactose anhydrous (375 mg), sodium hydroxide and/or hydrochloric acid (for pH adjustment).

Approved therapy

Fosaprepitant 150 mg IV has been approved in adults as a single-day regimen since 2010 in the US. It was first approved in 2008 for the prevention of CINV in adults as a three-day regimen: 115 mg IV on Day 1 followed by oral aprepitant 80 mg on Days 2 and 3. This three-day regimen in adults was discontinued in 2010 not for safety or efficacy reasons.[1]

[1] https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=022023, last assessed on March 5, 2018.

Oral aprepitant has been approved in adults and pediatric patients as a three-day regimen since 2003 and 2015, respectively.

Table 7. Currently Approved Dosing Regimens of Fosaprepitant IV and Oral Aprepitant in Adults and Pediatric Patients.

Patient Population	Product	Route of Administration	Day 1	Day 2	Day 3
1-Day Regimen					
Adults	Fosaprepitant	IV infusion over 20 to 30 minutes	150 mg	n/a	n/a
3-Day Regimen					
Adults and Pediatric Patients 12 Years and Older	Aprepitant	PO	125 mg	80 mg	80 mg
Pediatric Patients 6 Months to Less than12 Years or Pediatric and Adult Patients Unable to Swallow Capsules	Aprepitant	PO	3 mg/kg Maximum 125 mg	2 mg/kg Maximum 80 mg	2 mg/kg Maximum 80 mg

Source data: Reviewer's summary

Other approved NK-1 receptor antagonists for CINV in adults include netupitant (one of the active ingredients in Akynzeo oral capsule) and rolapitant (Varubi). Neither of them has been approved in pediatric patients.

Clinical development program and relevant regulatory background

Studies completed to support the clinical development program

The fosaprepitant pediatric clinical development program consists of one Phase 1 trial (Study P134, Part I and Part V), one Phase 2b trial (Study P029) and one Phase 3 trial (Study P044). See Table 8 below. The program was initially designed to demonstrate efficacy, safety, and tolerability of fosaprepitant as a 1-day IV regimen and as part of a 3-day regimen (IV fosaprepitant given on Day 1 and oral aprepitant on Days 2 and 3) in children from birth to 17 years of age receiving HEC or MEC. While the pediatric fosaprepitant program was ongoing, the 3-day oral aprepitant regimen was approved for the prevention of CINV in children, confirming that NK-1 receptor blockade with aprepitant has similar antiemetic effects in children as in adults. Refer to PWR Amendment 4 issued in February 2017. Accordingly, the sponsor adjusted the scope of the fosaprepitant pediatric program based on the ability to extrapolate efficacy for pediatric patients, and the pivotal efficacy/safety phase 3 Study P044 for a single-day regimen was discontinued. Study P029 was conducted in response to Study 2 in the PWR, submitted in this sNDA related to the fulfillment of the PMR and PWR.

Also refer to the Division Director's reviews of NDA 21549/S-25 Emend oral capsule in adolescents approved on 8/28/2015 and NDA 207865 for Emend oral suspension in patients less than 12 years old approved on 12/17/2015 for the basis of the approval of oral aprepitant for CINV in pediatric patients. Results from Part II to Part IV of Study P134 were submitted to NDA 207865

for EMEND suspension and used to support the use of oral aprepitant suspension in pediatric patients less than 12 years old.

Table 8. Clinical Trials Used to Support the Proposed Indication in Pediatric Population

Trial ID	Phase	Country / Region	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
2012-002340-24 [Ref. 5.3.3.2: P029MK0517] Study P029	IIb	Worldwide (Europe, North and South America, Asia)	A Phase IIb, Partially-Blinded, Randomized, Active Comparator Controlled Study to Evaluate the Pharmacokinetics/ Pharmacodynamics, Safety, and Tolerability of Fosaprepitant in Pediatric Patients for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) Associated with Emetogenic Chemotherapy. Open-Label Cohort to Further Evaluate the Pharmacokinetics/ Pharmacodynamics, Safety, and Tolerability of Fosaprepitant in Pediatric Patients Birth to <12 Years Old	A multicenter, partially-blinded, randomized, parallel-group, PK/PD, dose-ranging study with an open label substantial amendment that allowed for dose adjustment and further assessment of fosaprepitant in younger age cohorts (0 to <12 years old)	**Fosaprepitant regimen** Fosaprepitant 150 mg, 60 mg, 20 mg, or 5 mg/kg (or age/weight-adjusted dose) IV, single-dose + ondansetron IV ± dexamethasone IV **Control regimen** Placebo for fosaprepitant (normal saline) IV, single-dose + ondansetron IV ± dexamethasone IV	Eligible subjects were male or female, between the ages of birth and 17 years (inclusive) with a documented malignancy scheduled to receive chemotherapeutic agent(s) associated with moderate, high, or very high risk of emetogenicity	Fosaprepitant 150 mg: 42 Fosaprepitant 60 mg: 43 Fosaprepitant 20 mg: 40 Fosaprepitant 5 mg/kg: 74 Control: 35

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
2006-005515-10 [Ref. 5.3.3.2: P134] Study P134	I	Australia, Brazil, Canada, Colombia, France, Germany, Hungary, Israel, Mexico, Norway, Peru, Poland, Spain, Sweden, Switzerland, USA	A Multi-center, Open-label, 5-Part Study to Evaluate the Pharmocokinetics, Safety, and Tolerability of Aprepitant and Fosaprepitant Dimeglumine in Pediatric Patients Receiving Emetogenic Chemotherapy	Multi-center, open-label, 5-part study	**Part IA:** Subjects 12-17 years of age. Day 1: 115 mg IV fosaprepitant with IV ondansetron ±IV dexamethasone. Days 2 and 3: 80 mg oral aprepitant and IV ondansetron ±IV dexamethasone. **Part IB:** Subjects 12-17 years of age. Day 1: 150 mg IV fosaprepitant with IV ondansetron ±IV dexamethasone. **Part IIA:** Subjects <12 years of age. Day 1: Oral aprepitant dose equivalent to 80 mg in adults with IV ondansetron ±IV dexamethasone. **Part IIB:** Subjects <12 years of age. Day 1: Oral aprepitant dose equivalent to 125 mg in adults with IV ondansetron ±IV dexamethasone. **Part III**: Subjects <12 years of age. Days 1-3: IV ondansetron ±IV dexamethasone. **Part IV:** Subjects <12 years of age. Day 1: Oral aprepitant at a dose equivalent to 125 mg in adults with IV ondansetron ± IV dexamethasone. Days 2 and 3: Oral aprepitant at a dose equivalent to 80 mg in adults with IV ondansetron ± IV dexamethasone. **Part V:** Subjects 6 months to <12 years of age. Day 1: IV fosaprepitant at a dose equivalent to 150 mg in adults with IV ondansetron ±IV dexamethasone.	Males/females Age: birth to 17 years of age scheduled to receive moderately or highly emetogenetic chemotherapy or a chemotherapy regimen not previously tolerated due to nausea and/or vomiting for a documented malignancy.	**Part IA** Three day regimen (fosaprepitant on Day 1 and aprepitant on Days 2 and 3, along with ondansetron): 12 subjects **Part IB** Single day regimen of fosaprepitant: 11 subjects **Part IIA** Single day regimen of aprepitant: 19 subjects **Part IIB** Single day regimen of aprepitant: 19 subjects **Part III** Three day regimen of ondansetron: 19 subjects **Part IV** Three day regimen of aprepitant: 20 subjects **Part V** Single day regimen of fosaprepitant: 23 subjects

Trial ID	Phase	Country / Region	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
2014-001783-34 [Ref. 5.3.5.1: P044MK0517] Study P044	III	Worldwide (Europe, North and South America, Asia)	A Phase III, Randomized, Placebo-Controlled Clinical Trial to Study the Efficacy and Safety of MK-0517/Fosaprepitant and Ondansetron Versus Ondansetron for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Pediatric Subjects Receiving Emetogenic Chemotherapy.	A randomized, placebo-controlled, parallel-group, multi-site, double-blind trial to evaluate the efficacy and safety of fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting (CINV) in pediatric patients receiving chemotherapeutic agent(s) associated with moderate or high risk of emetogenicity, or chemotherapy agent(s) not previously tolerated due to vomiting.	**Fosaprepitant regimen** Cycle 1: Day 1 Age 0 to < 12 years: Fosaprepitant 5 mg/kg (or age-specific adjustment not to exceed 150 mg) + ondansetron (Cycle 1) or any 5-HT3 antagonist (Cycles 2 to 6) ± dexamethasone IV 12 to 17 years: Fosaprepitant 150 mg + ondansetron (Cycle 1) or any 5-HT3 antagonist (Cycles 2 to 6) ± dexamethasone IV. **Control regimen** Cycle 1: Day 1 Age 0 to 17 years: Placebo for fosaprepitant (normal saline) + ondansetron (Cycle 1) or any 5-HT3 antagonist (Cycles 2 to 6) ± dexamethasone IV	Eligible patients were male or female, between the ages of birth and 17 years (inclusive) with a documented malignancy scheduled to receive chemotherapeutic agent(s) associated with moderate or high risk of emetogenicity	Fosaprepitant: 38 Control:37

Source data: Section 5.2 Tabular Listing of All Clinical Studies

The summary of doses studied in the clinical development program is provided in Table 9.

Table 9. Summary of Intravenous (IV) Fosaprepitant Regimens Studied in Study P029 and Study P134

Intravenous (IV) Regimens	Age Cohorts [yrs]			
	12 - 17*	6 - <12**	2 - <6**	0.5 - <2**
115 mg fosaprepitant Day 1, 80 mg oral aprepitant on Days 2 and 3	P134, Part I A	N/A	N/A	N/A
150 mg or 3.0 mg/kg (up to 150 mg)	P134, Part I B; P029; P044	P134, Part V; P029	P134, Part V; P029	P134, Part V; P029
5.0 mg/kg (up to 150 mg)	N/A	P029; P044	P029; P044	P029
60 mg or 1.2 mg/kg (up to 60 mg)	P029	P029	P029	N/A
20 mg or 0.4 mg/kg (up to 20 mg)	P029	P029	P029	N/A

*Fosaprepitant infused over 30 minutes

**Fosaprepitant infused over 60 minutes

Source data: Section 2.7.2 Summary of Clinical Pharmacology, Table 2.7.2:1

PREA PMR and PWR

Currently, the Postmarketing Requirement (PMR 1663-3) Study under the Pediatric Research Equity Act (PREA) is as follows: [2]

> "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. Use modeling and simulation including the results of the above study to identify 1-Day and 3-Day intravenous fosaprepitant doses in pediatric patients 0 to 17 years of age that provide similar aprepitant PK exposures to pediatric aprepitant doses and exposures which have demonstrated acceptable safety and efficacy profiles in patients receiving single and multi-day chemotherapy regimens, respectively."

Results from Study P029 and population PK analysis and simulation fulfilled the PMR of 1-day and 3-day regimens using fosaprepitant from a clinical pharmacology perspective. The Agency also considered that the sponsor provided a fair complete response to the PWR. For details, refer to Clinical Review and DPMH Review of this sNDA.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Refer to Section 2.1 for the mechanism of action of aprepitant.

Refer to the product label for detailed PK and PD information, intrinsic and extrinsic effects on fosaprepitant and aprepitant PK as well as related dose adjustment. An excerpt of clinical PK information in adults is summarized here based upon the approved fosaprepitant product label (Table 10). Note that the units for AUC and concentrations of apreppitant in the label are mcg·hr/mL and mcg/mL, respectively.

Table 10. Excerpt of PK from the Approved Fosaprepitant Product Label

12.3 Pharmacokinetics
Aprepitant after Fosaprepitant Administration
Following administration of a single intravenous 150-mg dose of fosaprepitant, a prodrug of aprepitant administered as a 20-minute infusion to healthy subjects, the mean AUC of aprepitant was 37.4 (± 14.8) mcg·hr/mL and the mean maximal aprepitant concentration was 4.2 (± 1.2)

[2] https://www.accessdata fda.gov/scripts/cder/pmc/index.cfm?StartRow=2&StepSize=1&Paging=Yes, last accessed March 5th, 2018

mcg/mL. Plasma concentrations of fosaprepitant are below the limits of quantification (10 ng/mL) within 30 minutes of the completion of infusion.

Distribution

Aprepitant is greater than 95% bound to plasma proteins. The mean apparent volume of distribution at steady state (Vd) was approximately 70 L in humans. Aprepitant crosses the blood brain barrier in humans *[see Clinical Pharmacology (12.1)]*.

Elimination

Metabolism

Fosaprepitant is converted to aprepitant in *in vitro* incubations with human liver preparations and in S9 preparations from multiple other human tissues including kidney, lung and ileum. Thus, it appears that the conversion of fosaprepitant to aprepitant can occur in multiple extrahepatic tissues in addition to the liver.

Aprepitant undergoes extensive metabolism. *In vitro* studies using human liver microsomes indicate that aprepitant is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19. Metabolism is largely via oxidation at the morpholine ring and its side chains. No metabolism by CYP2D6, CYP2C9, or CYP2E1 was detected.

In healthy young adults, aprepitant accounts for approximately 24% of the radioactivity in plasma over 72 hours following a single oral 300-mg dose of [^{14}C]-aprepitant, indicating a substantial presence of metabolites in the plasma. Seven metabolites of aprepitant, which are only weakly active, have been identified in human plasma.

Excretion

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

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

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

Renal impairment: No dose adjustment is needed as aprepitant is not renally excreted.

Drug interaction: Because of the quick conversion of fosaprepitant to aprepitant, drug interaction is likely to occur with drugs that interact with aprepitant. Aprepitant is a substrate, a weak inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9. Refer to Sections 7.1 and 7.2 of fosaprepitant label for detailed drug-drug interaction and dosage adjustment.

3.2.1 PK of aprepitant in pediatric patients

The PK of aprepitant following oral aprepitant administration in pediatric patients was evaluated in NDA 207865 (EMEND suspension) and NDA 21549/S-25 (EMEND oral capsule). An excerpt of clinical PK information in pediatric patients following oral Emend administration is provided below. Note that the units for AUC and concentrations of apreppitant in the label are mcg×hr/mL and mcg/mL, respectively.

Age: Pediatric Population

As part of a 3-day regimen, dosing of aprepitant capsules (125-mg/80-mg/80-mg) in 18 pediatric patients (aged 12 through 17 years) achieved a mean AUC0-24hr of 17 mcg×hr/mL on Day 1 with mean peak plasma concentration (Cmax) at 1.3 mcg/mL occurring at approximately 4 hours. The mean concentrations at the end of Day 2 (N=8) and Day 3 (N=16) were both at 0.6 mcg/mL.

As part of a 3-day regimen, weight-based dosing of aprepitant powder for oral suspension (3-mg/kg; 2- mg/kg; 2-mg/kg) in 18 pediatric patients aged 6 months to less than 12 years achieved a mean AUC0-24hr of 20.9 mcg×hr/mL on Day 1 with mean peak plasma concentration (Cmax) at 1.8 mcg/mL (N=19), occurring at approximately 6 hours. The mean concentrations at the end of Day 2 (N=18) and Day 3 (N=19) were 0.4 mcg/mL and 0.5 mcg/mL, respectively.

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

3.2.1.1 PK of aprepitant following fosaprepitant IV infusion

Adolescents

Following a single dose of fosaprepitant 150 mg IV infused over 30 minutes in adolescents, the mean AUC0-24hr of aprepitant ranged from 30400 ng×hr/mL to 30800 ng×hr/mL with mean Cmax ranged from 3500 ng/mL to 5870 ng/mL. The median Tmax was 0.5 hour.

Table 11. Descriptive Statistics of Observed Aprepitant Plasma Pharmacokinetic Parameters Following Administration of *150 mg* IV Fosaprepitant in Patients 12 to 17 Years Old

Study P029

12 to 17 Year-Olds	AUC0-∞ (hr*ng/mL)	AUC_{0-24hr} (hr*ng/mL)	C_{max} (ng/mL)	C_{24hr} (ng/mL)	C_{48hr} (ng/mL)	T_{max} (hr)	Apparent Terminal $t_{1/2}$ (hr)	CL/F (mL/min)
N	3	12	12	12	0	12	3	3
AM	33800	30400	3500	735	NR	0.546	10.5	76.2
SD	7180	8290	972	310	NR	0.144	1.0	16.2
ACV (%)	21.3	27.3	27.7	42.2	NR	26.3	9.6	21.2
Med	33200	29400	3730	714	NR	0.500	10.7	75.2
Min	26900	21300	1800	343	NR	0.500	9.39	60.6
Max	41200	48100	4600	1240	NR	1.00	11.4	92.9
GM	33300	29400	3360	675	NR	0.534	10.5	75.1
GCV (%)	21.6	26.1	32.7	46.0	NR	20.1	9.8	21.6

Study P134

12 to 17 Years	C_{max} (ng/mL)	T_{max} (hr)	C_{24hr} (ng/mL)	$AUC_{0-24\ hr}$ (hr*ng/mL)	C_{48hr} (ng/mL)	C_{72hr} (ng/mL)
N	11	11	11	11	10	11
AM	5870	0.64	825	30800	230	114
SD	2770	0.3	321	7020	324	186
Median	4960	0.5	742	31000	112	14.5
Min	2880	0.5	413	17800	BLQ	BLQ
Max	12300	1.5	1360	42200	1080	498

Source data: Summary of Clinical Pharmacology, Table 2.7.2:3 and Table 2.7.2:5

Following a single dose of fosaprepitant 115 mg IV infused over 30 minutes on Day 1 and 80 mg oral aprepitant on Days 2 and 3 in adolescents, mean AUC0-24hr was 19500 ng×hr/mL with mean Cmax on Day 1 reaching 3240 ng/mL. The median Tmax on Day 1 was 0.25 hour. The mean concentrations at the end of Days 2 and 3 were 310 ng/mL and 199 ng/mL, respectively.

Table 12. Descriptive Statistics of Observed Aprepitant Plasma Pharmacokinetic Parameters Following Administration of *115 mg* IV Fosaprepitant on Day 1 Followed by 80 mg Oral Aprepitant on Days 2 and 3 in Patients 12 to 17 Years Old

12 to 17 Years	C_{max} (ng/mL)	T_{max} (hr)	C_{24hr} (ng/mL)	$AUC_{0\text{-}24\ hr}$ (hr*ng/mL)	C_{48hr} (ng/mL)	C_{72hr} (ng/mL)
N	12	12	8	8	10	11
AM	3240	0.41	433	19500	310	199
SD	1280	0.27	318	8010	288	281
Median	3080	0.25	407	19300	171	84.9
Min	1650	0.25	133	9940	66.2	BLQ
Max	6210	1	1120	33100	904	796

Source data: Summary of Clinical Pharmacology, Table 2.7.2:2

2 to < 12 years

The PK parameters of aprepitant following 3 mg/kg fosaprepitant IV infused over 60 minutes in patients 2 to < 12 years are shown in Table 13.

Table 13. Descriptive Statistics of Observed Aprepitant Plasma Pharmacokinetic Parameters Following Administration of *3 mg/kg* IV Fosaprepitant in Patients 2 to < 12 Years Old

Study P134

6 - <12 years	C_{max} (ng/mL)	T_{max} (hr)	C_{24hr} (ng/mL)	$AUC_{0-24\ hr}$ (hr*ng/mL)	C_{48hr} (ng/mL)	C_{72hr} (ng/mL)
N	8	8	8	8	8	8
AM	2850	1.07	308	19500	37.5	NR
SD	641	0.11	240	6720	56.5	NR
Median	2830	1	210	16300	16.2	BLQ
Min	1800	1	100	14000	BLQ	BLQ
Max	3630	1.25	751	34000	159	92.5
2 - <6 years						
N	7	7	7	7	7	7
AM	2430	1.41	184	18300	NR	NR
SD	1100	0.83	189	11100	NR	NR
Median	2570	1.03	182	20600	BLQ	BLQ
Min	1260	1	BLQ	6190	BLQ	BLQ
Max	3880	3.27	462	36000	114	22.1

Study P029

6 to <12 Year-Olds[†]	AUC0-∞ (hr*ng/mL)	AUC_{0-24hr} (hr*ng/mL)	C_{max} (ng/mL)	C_{24hr} (ng/mL)	C_{48hr} (ng/mL)	T_{max} (hr)	Apparent Terminal $t_{1/2}$ (hr)	CL/F (mL/min)
N	8	14	14	14	0	14	8	8
AM	34300	29200	3550	589	NR	1.99	7.69	69.2
SD	20300	14300	2460	433	NR	1.62	2.09	66.4
ACV (%)	59.1	48.8	69.2	73.5	NR	81.6	27.2	95.9
Med	28400	29500	2700	550	NR	1.14	7.64	46.6
Min	10900	9650	1210	81.0	NR	0.533	4.39	34.0
Max	69000	60700	9190	1260	NR	6.00	11.9	231
GM	29200	26000	2930	419	NR	1.55	7.45	55.0
GCV (%)	69.0	54.9	69.5	119.9	NR	79.6	28.1	68.8
2 to <6 Year-Olds								
N	5	6	6	6	0	6	5	5
AM	15300	21800	2320	278	NR	2.29	6.55	66.2
SD	11100	22200	1540	398	NR	2.14	3.62	25.5
ACV (%)	72.9	101.8	66.1	142.9	NR	93.5	55.3	38.5
Med	9830	10600	1590	63.2	NR	1.00	4.96	63.6
Min	9530	9140	1020	33.5	NR	1.00	4.29	31.9
Max	35100	65100	4550	1020	NR	6.08	12.9	101
GM	13100	15900	1960	115	NR	1.68	5.95	61.8
GCV (%)	60.6	94.7	69.8	255.1	NR	97.5	48.2	45.0

Source data: Summary of Clinical Pharmacology, Table 2.7.2:4 and Table 2.7.2:5

The PK parameters of aprepitant following 5 mg/kg IV infused over 60 minutes in patients 2 to < 12 years old are shown in Table 14.

Table 14. Descriptive Statistics of Observed Aprepitant Plasma Pharmacokinetic Parameters Following Administration of *5 mg/kg* IV Fosaprepitant in Patients 2 to < 12 Years Old

6 to <12 Year-Olds	$AUC_{0-\infty}$ (hr*ng/mL)	AUC_{0-24hr} † (hr*ng/mL)	C_{max} (ng/mL)	C_{24hr} (ng/mL)	C_{48hr} (ng/mL)	T_{max} (hr)	Apparent Terminal $t_{1/2}$ (hr)	CL/F (mL/min)
N	13	23	24	24	11	24	13	13
AM	55300	47400	4400	1210	164	2.92	9.77	42.1
SD	11900	17300	1910	1000	124	5.09	2.49	12.7
ACV (%)	21.5	36.5	43.5	83.0	75.9	174.7	25.5	30.3
Med	55000	45200	4390	867	99.6	1.00	9.33	38.0
Min	36200	21800	1960	452	18.5	0.917	5.99	22.4
Max	73200	89300	10500	4950	391	24.5	14.5	62.8
GM	54100	44700	4090	992	120	1.57	9.47	40.3
GCV (%)	22.6	36.2	39.8	61.9	112.7	114.7	26.4	31.7
2 to <6 Year-Olds								
N	20	25	25	25	20	25	20	20
AM	46400	45000	4270	1060	232	1.90	9.27	31.8
SD	18600	23800	2370	1020	471	2.16	4.17	13.8
ACV (%)	40.1	52.9	55.4	96.3	202.6	114.1	45.0	43.5
Med	42800	36100	3950	577	50.8	1.00	8.21	27.7
Min	18600	16300	1500	194	0.00	0.917	5.61	12.8
Max	100000	131000	11300	4040	1970	9.33	22.9	72.0
GM	43300	40500	3800	738	NC	1.39	8.64	29.3
GCV (%)	39.0	47.2	51.0	99.9	NC	75.3	37.2	42.6

Source data: Summary of Clinical Pharmacology, Table 2.7.2:6

6 months to < 2 years

Following a single dose of fosaprepitant 5 mg/kg IV infused over 60 minutes in patients 6 months to 2 years old, the mean AUC0-24 hr of aprepitant was 36800 ng×hr/mL with mean Cmax of 3550 ng/mL. The median Tmax was 1.08 hours.

Table 15. Descriptive Statistics of Observed Aprepitant Plasma Pharmacokinetic Parameters Following Administration of *3 mg/kg* IV and *5 mg/kg* Fosaprepitant in Patients 6 Months < 2 Years Old

Study P134 – 3 mg/kg

0.5 - < 2 years	C_{max} (ng/mL)	T_{max} (hr)	C_{24hr} (ng/mL)	$AUC_{0\text{-}24\ hr}$ (hr*ng/mL)	C_{48hr} (ng/mL)	C_{72hr} (ng/mL)
N	7	7	6	6	6	6
AM	1700	1.13	150	11700	NR	NR
SD	636	0.17	103	6980	NR	NR
Median	1730	1	169	11300	BLQ	BLQ
Min	838	1	BLQ	1810	BLQ	BLQ
Max	2470	1.42	282	19800	50.8	19.8

Study P029 – 5 mg/kg

0 to <2 Year-Olds	$AUC_{0\text{-}\infty}$ (hr*ng/mL)	$AUC_{0\text{-}24hr}$ † (hr*ng/mL)	C_{max} (ng/mL)	C_{24hr} (ng/mL)	C_{48hr} (ng/mL)	T_{max} (hr)	Apparent Terminal $t_{1/2}$ (hr)	CL/F (mL/min)
N	16	21	22	21	10	22	16	16
AM	37200	36800	3550	691	352	2.01	7.94	24.2
SD	15800	21800	1500	852	929	2.10	2.86	11.9
ACV (%)	42.5	59.2	42.2	123.3	264.1	104.3	36.0	49.3
Med	35700	32500	3260	535	30.8	1.08	7.02	21.6
Min	12500	10200	1340	78.0	0.00	1.00	4.16	7.81
Max	81100	118000	7040	3970	2990	9.00	12.4	50.4
GM	34200	32700	3280	436	NC	1.50	7.46	21.6
GCV (%)	45.8	50.9	43.0	123.7	NC	76.5	38.0	53.8

Source data: Summary of Clinical Pharmacology, Table 2.7.2:4 and Table 2.7.2:6

Effects of sex and race on the PK of aprepitant

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

3.2.2 *PK of fosaprepitant following IV infusion*

The PK of fosprepitant 150 mg IV in adults was not evaluated. However, PK of fosaprepitant 115 mg IV in adults was evaluated in the original NDA. Following IV infusion of fosaprepitant 115 mg over 15 minutes, fosaprepitant plasma concentrations fell near or below the lower limit of quantitation (10 ng/mL) within 30 minutes after the end of infusion and conversion of fosaprepitant to aprepitant was nearly complete. The exact identity of the enzyme(s) involved in the conversion of fosaprepitant to aprepitant has not been identified but is thought not to involve the CYP family of enzymes. Mean fosaprepitant Cmax was approximately 5900 ng/mL and mean AUC was 1483 ng×hr/mL after 115 mg IV infusion over 15 minutes. The elimination half-life for fosaprepitant

was estimated to be 2 to 3 minutes. Refer to the Clinical Pharmacology Review of the original NDA approved in 2008.

The PK of fosaprepitant in patients ≤ 17 years old is summarized in Table 16. The Tmax occurred at the end of infusion. The variability of Cmax of fosaprepitant in patients < 2 years are particularly large with Cmax ranging from 20.2 ng/mL (minimum) to 7260 ng/mL (maximum). The cause is unknown. However, altered conversion of IV administered prodrugs in infants has been observed.[3,4] The values of Cmax across all age groups appear to be much lower than the historical value of 5900 ng/mL in adults receiving single dose of 115 mg IV infused over 15 minutes which was reported in the original NDA. The concentrations of fosaprepitant were negligible with 15 to 30 minutes after the end of infusion. Due to limited sampling time for fosaprepitant, AUC values were not estimated. The effect of age and weight on Cmax of fosaprepitant was not explored, either.

[3] G. Burckart, F.F. Barrett, A.R. Straughn, and S.R. Ternullo, Chloramphenicol Clearance in Infants. J Clin Pharmacol. 1982; 22:49-52.
[4] G. Burckart, F.F. Barrett, R. Della Valle, and M.C. Meyer, Chloramphenicol Dosage and Pharmacokinetics in Infants and Children. J Clin Pharmacol. 1983; 23:106-112.

Table 16. Summary of Plasma Fosaprepitant Cmax and Tmax Values Following Fosaprepitant IV Single Dose (Study P134)

Dose	Age Range		Tmax (hr)	Cmax (ng/mL)
3 mg/kg Infuse over 1 hour§	6 Months to <2 Years Old	N	7	7
		Mean	1.13	2756
		SD	0.175	3364
		Median [min – max]	1.00 [1.00 – 1.42]	159 [20.2 – 7260]
	2 to <6 Years Old	N	7	8
		Mean	1.05	3034
		SD	0.089	1718
		Median [min – max]	1.02 [1.00 – 1.25]	3292 [BLQ – 5240]
	6 to <12 Years Old	N	8	8
		Mean	1.04	1654
		SD	0.088	1995
		Median [min – max]	1.00 [1.00 – 1.25]	910 [357 – 6200]
150 mg Infuse over 30 minutes‡	12 to 17 Years Old	N	11	11
		Mean	0.614	1310
		SD	0.251	964
		Median [min – max]	0.5 [0.5 – 1.33]	1020 [26.6 – 3300]
	§ In patients < 12 years old: the PK samples were collected at pre-dose, 1 hour (at the end of fosaprepitant infusion), 1.25 hour (30 minutes prior to chemotherapy), 1.75 hour ((at the start of chemotherapy), and 2.25 hour (30 minutes after the chemotherapy). ‡ In patients 12 to 17 years old: the PK samples were collected at pre-dose, 0.5 hour (at the end of fosaprepitant infusion), 0.75 hour (30 minutes prior to chemotherapy), 1.3 hour (at the start of chemotherapy), 1.8 (30 minutes after the chemotherapy). BLQ: below limit of quantification Source data: Clinical Study Report P134, Table 2-6 and Table 2-19, Tables 11-3 and 11-16			

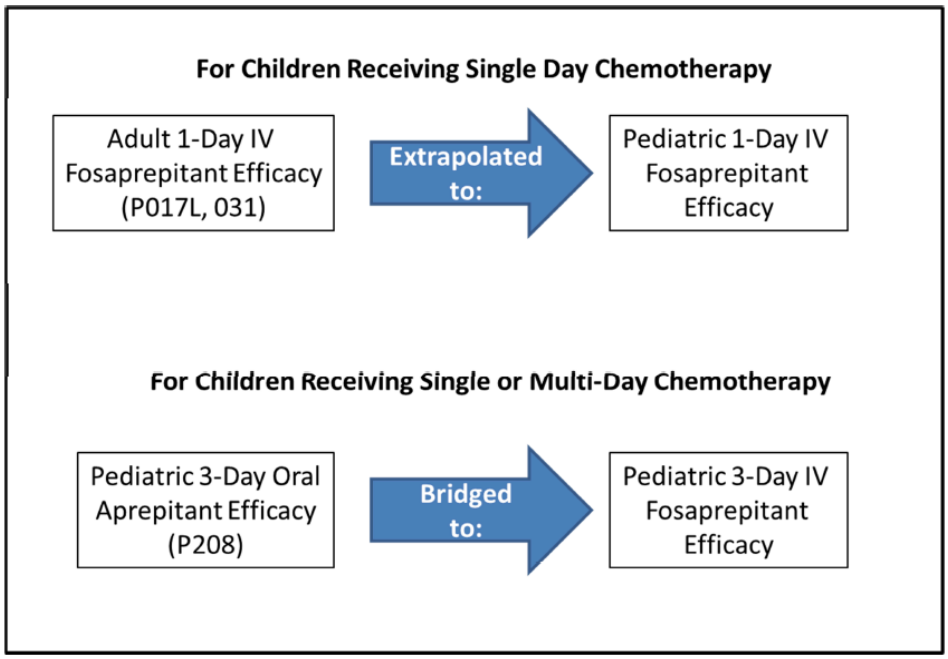
3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

As mentioned in Section 3.1, the 3-day oral aprepitant regimen was approved for the prevention of CINV in children based upon efficacy and safety data obtained in pediatric patients while the pediatric fosaprepitant program was ongoing. This also confirmed that NK-1 receptor blockade with aprepitant has similar antiemetic effects in children as in adults and allows using exposure-matching strategy to identify doses of fosaprepitant in pediatric patients.

The bridging scheme is showed in Figure 1.

Figure 1. Efficacy Extrapolation/Bridging for One-Day and Three-Day Pediatric Fosaprepitant Regimens



Source data: Section 2.5 Clinical Overview, Figure 2.5:1

3.3.1.1 Single-day regimen

The dose selection for single-day regimen is based solely upon matching the systemic exposures (Cmax and AUC) of aprepitant in patients ≤ 17 years to healthy adults. Studies P029 and P134 also provided safety data for single dose fosaprepitant in pediatric cancer patients.

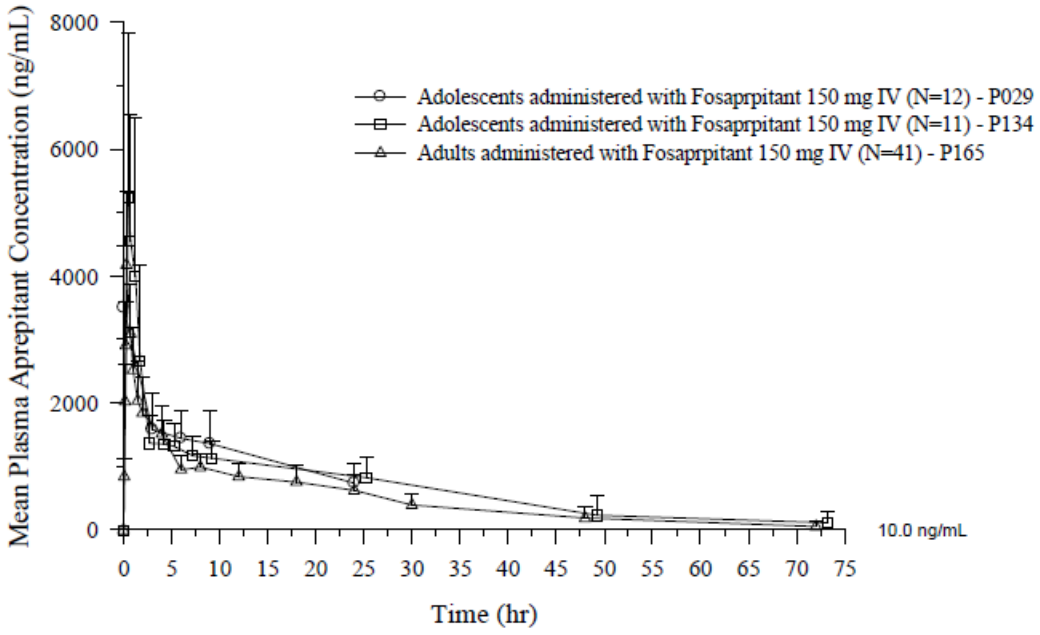
The sponsor's proposed single-day regimen is as follows:

Drug	Age	Regimen
EMEND for injection	12 Years to 17 Years	150 mg intravenously over 30 minutes, completing the infusion approximately 30 minutes prior to chemotherapy
	2 Years to less than 12 Years	4 mg/kg (maximum dose 150 mg) intravenously over 60 minutes, completing the infusion approximately 30 minutes prior to chemotherapy
	6 Months to less than 2 Years	5 mg/kg (maximum dose 150 mg) intravenously over 60 minutes, completing the infusion approximately 30 minutes prior to chemotherapy
Dexamethasone**	6 Months to 17 Years	If a corticosteroid, such as dexamethasone, is co-administered, administer 50% of the recommended corticosteroid dose on Days 1 and 2.
5-HT_3 antagonist	6 Months to 17 Years	See selected 5-HT_3 antagonist prescribing information for the recommended dosage

3.3.1.1.1 Adolescents (12 to 17 years)

PK similarity was demonstrated by comparing the PK parameters from Studies P029 and P134 to those obtained in healthy adult subjects receiving single150 mg fosaprepitant IV (Study P165) (Table 17). The concentration – time profiles of aprepitant were superimposable (Figure 2).

Figure 2. Mean Concentration-Time Profiles (± Standard Deviation) of Aprepitant from Adolescents in Study P134 and Study P029 Receiving 150 mg Fosaprepitant and Healthy Adult Subjects Receiving the Same Dose in Study P165



Source data: Summary of Clinical Pharmacology, Figure 2.7.2:3

Overall, the Cmax achieved in adolescents ranged from 84% to 134% of the Cmax achieved in the healthy adults. Concentrations at 24 hours post dose (C24hr) in adolescents were 17 to 33% more than that in the healthy adults. The AUC0-inf ranged from 95% to 120 % of that achieved in the adults. The AUC0-24hr was 20 to 23% more than that in the healthy adults. Given that these are cross-study comparisons, the systemic exposures (AUC and C24) to aprepitant are considered comparable.

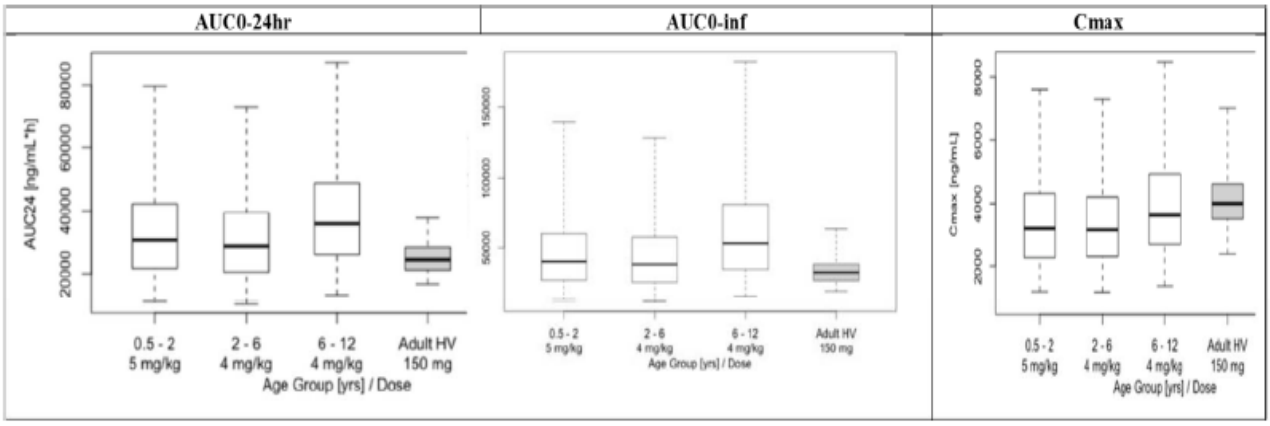
Table 17. Descriptive Statistics in key PK Parameters of Observed Aprepitant Following Single Dose of 150 mg IV Infusion in Adolescent Patients and Healthy Adults.

Study (Subjects)	Descriptive Statistics	AUC0-∞ (ng×hr/mL)	AUC0-24hr (ng×hr/mL)	Cmax (ng/mL)	C24hr (ng/mL)
P029 (12-17 years)	N	3	12	12	12
	Arithmetic Mean	33800	30400	3500	735
	CV%	21.3	27.3	27.7	42.2
	Geometric Mean	33300	29400	3360	675
P134 (12-17 years)	N	8	11	11	11
	Arithmetic Mean	43600	30800	5870	825
	CV%	26.8	22.8	47.1	38.9
	Geometric Mean	42000	30000	5380	769
P165 (Healthy Adults)	N	41	41	41	41
	Arithmetic Mean	37375	25105	4154	--
	CV%	39.5	23.0	27.7	--
	Geometric Mean	35031	24444	4005	577
--: not reported					
Source data: Table 11-1 of CSR P029, Table 11-2 of CSR P134, Tables 11-1 and 11-2 of CSR P165					

3.3.1.1.2 6 months to < 12 years

The comparison of systemic exposures (AUC and Cmax) to aprepitant in pediatric patients < 12 years and adults is provided in Figure 3.

Figure 3. Comparison of Observed 1-day 150 mg IV Fosaprepitant Regimen in Adult Healthy Subjects and Model- Simulated Aprepitant PK Parameters (AUCinf, AUC24, Cmax) After Administration of 4 mg/kg in Pediatric Subjects 2 to 12 Years Old and 5 mg/kg in <2 Years Old Subjects



Source data: Figure 23 in Section 4.3.1.5

3.3.1.1.2.1 6 to < 12 years

The AUC0-inf, AUC0-24hr, Cmax, and C24hr in patients aged 2 to 6 years following 3 mg/kg IV dose were all lower than that in the healthy adult subjects receiving 150 mg IV dose (Table 18). Similar pattern was observed in the patients aged 6 to < 12 years except AUC0-24hr from Study P029 (Table 19).

Table 18. Cross-Study Comparison of Observed Systemic Exposures to Aprepitant Following Single 3 mg/kg IV Infusion over 60 Minutes in Pediatric Patients (2 to < 6 years) to Healthy Adult Subjects Given 150 mg IV Infusion over 30 Minutes (Study P165)

PK Parameter	Study	Age Group	N	Geometric Mean
AUC0-∞ (ng•hr/mL)	P029	2 to <6 years	5	13100
	P134 (Part V)		6	19800
	P165	Adult	41	35100
AUC0-24hr (ng•hr/mL)	P029	2 to <6 years	6	15900
	P134 (Part V)		7	15200
	P165	Adult	41	24500
Cmax (ng/mL)	P029	2 to <6 years	6	1960
	P134 (Part V)		7	2200
	P165	Adult	41	4010
C24hr (ng/mL)	P029	2 to <6 years	6	115
	P134 (Part V)		--	--
	P165	Adult	41	577
Source data: Clinical Study Reports P029 and P134				

Table 19. Cross-Study Comparison of Observed Systemic Exposures to Aprepitant Following Single 3 mg/kg IV Infusion over 60 Minutes in Pediatric Patients (6 to < 12 years) to Healthy Adult Subjects Given 150 mg IV Infusion over 30 Minutes (Study P165)

PK Parameter	Study	Age Group	N	Geometric Mean
AUC0-∞ (ng•hr/mL)	P029	6 to <12 years	8	29200
	P134 (Part V)		8	22500
	P165	Adult	41	35100
AUC0-24hr (ng•hr/mL)	P029	6 to <12 years	14	26000
	P134 (Part V)		8	18700
	P165	Adult	41	24500
Cmax (ng/mL)	P029	6 to <12 years	14	2930
	P134 (Part V)		8	2780
	P165	Adult	41	4010
C24hr (ng/mL)	P029	6 to <12 years	14	419
	P134 (Part V)		8	239
	P165	Adult	41	577
Source data: Clinical Study Reports P029 and P134				

3.3.1.1.2.2 2 to < 6 years

PK simulation analysis showed that systemic exposures would be comparable to the adults if a 4 mg/kg IV infusion over 60 minutes in patients aged 2 to < 6 years is given (Table 20).

Table 20. Simulated Aprepitant Exposure in Pediatric Patients Age 2 to < 6 Years vs Observed in Healthy Adults

	Geometric Mean				Ratio of Geometric Mean (ped/adults)		
	2 to < 6 years (Simulated)			Adults (Observed)			
Dose (mg/kg)	4	3.5	3	150 mg	4	3.5	3
AUC0-24hr	28205	24190	20249	24500	1.15	0.99	0.83
Cmax	3080.20	2690.5	2301.3	4010	0.77	0.67	0.57
C24	443.78	366.93	293.93	577	0.77	0.64	0.51
C48	83.933	65.661	49.231				
C72	15.877	11.752	8.2471				
AUCinf	37909	32069	26436	35100	1.08	0.91	0.75
Source Data: Population PK Modeling and Simulation Report, Table II- 2					Reviewer's analysis		

Simulation analysis showed that systemic exposures would be comparable to the adults if a 3.5 mg/kg IV infusion over 60 minutes in patients age 6 to < 12 years is given (Table 21). On the other hand, the predicted AUC0-24hr following a 4 mg/kg dose is 44% higher than that in adults. However, 4 mg/kg dose is also reasonable given that 5 mg/kg dose was studied in this age group and found to have an acceptable safety profile. The Agency also believe that a simplified dosing regimen, i.e. 4 mg/kg for the ages ranging from 2 to < 12 years, instead of 3.5 mg/kg for 6 to < 12 years and 4 mg/kg for 2 to < 6 years, may help avoid potential medication error.

Table 21. Simulated Aprepitant Exposure in Pediatric Patients Age 6 to < 12 Years vs Observed in Healthy Adults

	Geometric Mean				Ratio of Geometric Mean (ped/adults)		
	6 to < 12 years (Simulated)			Adults (Observed)			
Dose (mg/kg)	4	3.5	3	150 mg	4	3.5	3
AUC0-24hr	35235	30301	25446	24500	1.44	1.24	1.04
Cmax	3591.4	3137.9	2684.8	4010	0.90	0.78	0.67
C24	682.3	570.4	463.1	577	1.18	0.99	0.80
C48	181.2	144.9	111.6				
C72	48.1	36.8	26.9				
AUCinf	53031	44860	36981	35100	1.51	1.28	1.05
Source Data: Population PK Modeling and Simulation Report, Table II- 3					Reviewer's analysis		

3.3.1.1.2.3 6 months to < 2 years

The AUC0-inf, AUC0-24hr, Cmax, and C24hr in patients aged 6 months to < 2 years following 3 mg/kg IV dose were all lower than that in the healthy adult subjects receiving 150 mg IV dose

(Table 22). The AUC0-inf, AUC0-24hr, Cmax, and C24hr following 5 mg/kg IV were comparable to that in the healthy adults. Simulation also showed that 5 mg/kg would provide similar exposures to those in adults.

Table 22. Cross-Study Comparison of Observed Systemic Exposures to Aprepitant Following Single 3 mg/kg and 5 mg/kg IV Infusion over 60 Minutes in Pediatric Patients (6 Months to < 2 years) to Healthy Adult Subjects Given 150 mg IV Infusion over 30 Minutes (Study P165)

PK Parameter	Study	Age Group	Does (mg/kg)	N	Geometric Mean
AUC0-∞ (ng•hr/mL)	P029	< 2 years	5	16	34200
	P134 (Part V)		3	6	10600
	P165	Adult	150§	41	35100
AUC0-24hr (ng•hr/mL)	P029	< 2 years	5	21	32700
	P134 (Part V)		3	6	9170
	P165	Adult	150§	41	24500
Cmax (ng/mL)	P029	< 2 years	5	22	3280
	P134 (Part V)		3	7	1580
	P165	Adult	150§	41	4010
C24hr (ng/mL)	P029	< 2 years	5	21	436
	P134 (Part V)		3	--	--
	P165	Adult	150§	41	577
Source data: Clinical Study Reports P029 and P134; --: Not reported; §: unit in mg					

Simulation analysis showed that systemic exposures would be comparable to the adults when a 5 mg/kg IV infusion over 60 minutes in patients aged 6 months to < 2 years is given (Table 23).

Table 23. Simulated Aprepitant Exposure in Pediatric Patients Age 6 months to < 2 Years vs Observed in Healthy Adults

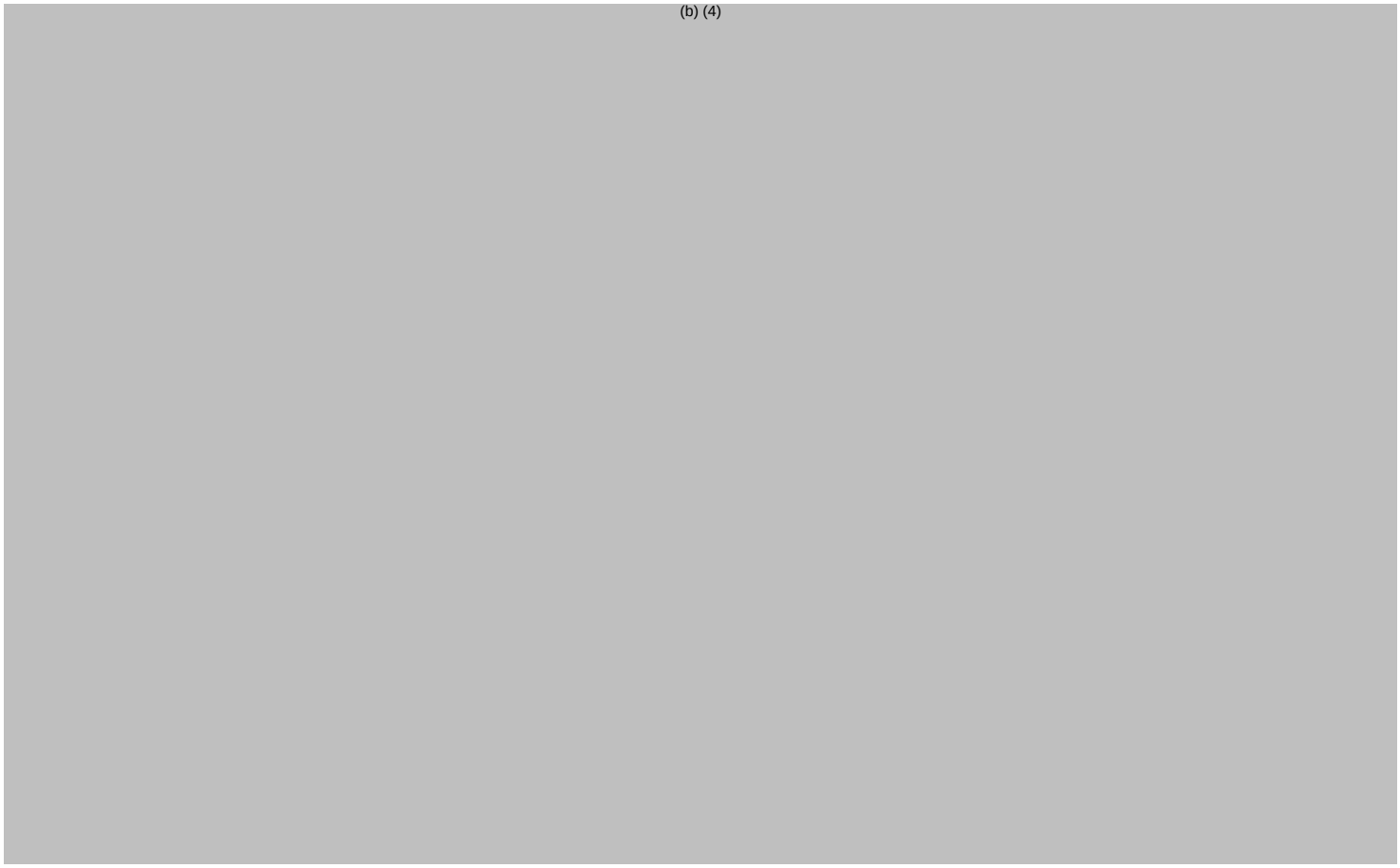
	Geometric Mean				Ratio of Geometric Mean (ped/adults)		
	6 months < 2 years (Simulated)			Adults (Observed)			
Dose (mg/kg)	5	4.5	4	150 mg	5	4.5	4
AUC0-24hr	30125	26688	23300	24500	1.23	1.09	0.95
Cmax	3115.7	2800.5	2485.7	4010	0.78	0.70	0.62
C24	480.6	413.8	349.5	577	0.83	0.72	0.61
C48	90.8	74.8	60.1				
C72	17.2	13.5	10.3				
AUCinf	40021	35072	30260	35100	1.14	1.00	0.86
Source data: Population PK Modeling and Simulation Report, Table II- 1					Reviewer's analysis		

3.3.1.2 Three-day regimen

Three-day regimen using oral Emend has been approved in pediatric patients age 6 months and older since 2015. The Agency agreed that the efficacy of a 3-day IV fosaprepitant regimen for the pediatric patients could be extrapolated from oral aprepitant by identifying an IV dose regimen to match aprepitant exposures in pediatric subjects for each day of the 3-day oral aprepitant regimen through PK modeling. The 3-day IV regimen may include 3-day IVs (IV/IV/IV) or IV/PO/PO regimens. Refer to Preliminary Comments of July 13, 2016 issued under IND 048924. The sponsor proposed a three-day IV regimen with an option to substitute the second and third day dose with oral aprepitant.

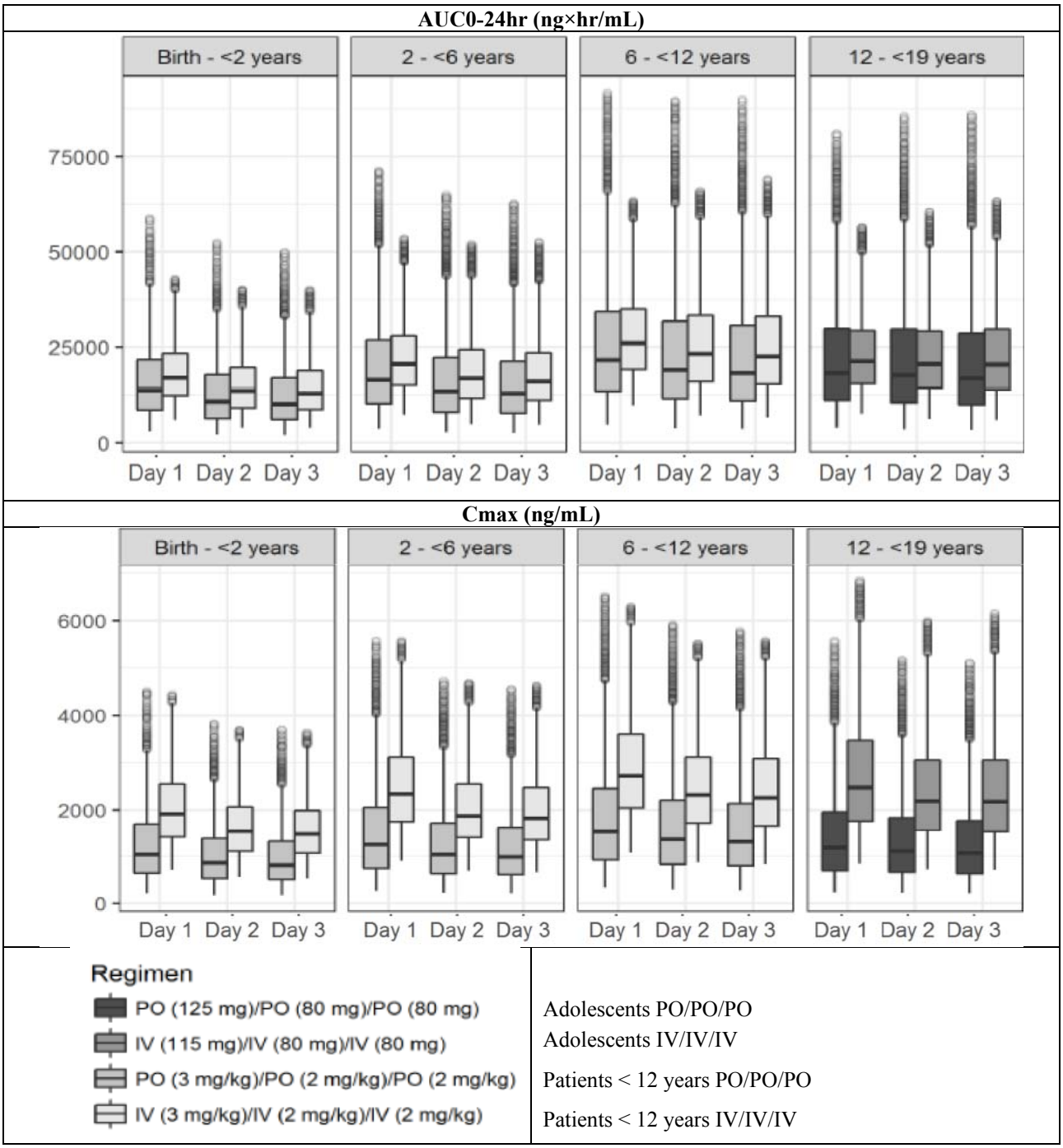
The sponsor's initial proposed three-day regimen is as follows:

(b) (4)



Comparison of systemic exposures (AUC and Cmax) to aprepitant following IV/IV/IV or PO/PO/PO regimen is provided in the Figure 4.

Figure 4. Comparison of 3-day Oral Aprepitant Regimens in Adolescent (125 mg on Day 1 and 80 mg on Days 2 and 3) and Pediatric Subjects <12 Years Old (3 mg/kg on Day 1 ad 2 mg/kg on Days 2 and 3) with Simulated 3-day IV Fosaprepitant Regimens, 115 mg on Day 1 and 80 mg on Days 2 and 3 in Adolescents and 3 mg/kg and 2 mg/kg on Days 2 and 3 in Pediatric Subjects < 12 Years Old



Source data: Figure 24, Section 4.3.1.5

3.3.1.2.1 Adolescents (12 to 17 years)

Fosaprepitant 115 mg IV on Day 1 and aprepitant 80 mg PO using Emend oral suspension on Days 2 and 3 were studied in adolescent cancer patients. The observed AUC0-24hr on Day 1 was 26% higher than that in the three-day oral regimen in adolescents given aprepitant 125 mg on Day 1 and aprepitant 80 mg on Days 2 and 3 (Study P097, oral capsules used). The observed Cmax of aprepitant on Day 1 was 183% higher than that in the three-day oral regimen. Although the Cmax is much higher following IV dosing (Table 24), the safety of the higher Cmax is supported by the acceptable safety profile in adolescents given single dose of 150 mg IV infusion.

Table 24. The Observed AUC, Cmax, and Cmin (C24hr, C48hr, and C72hr) in 12 to 17 Years from Studies P134 and P097

Dose (mg) (Days 1/2/3)		AUC0-24hr (hr*ng/ml)	Cmax (ng/ml)	C24hr (ng/mL)	C48hr (ng/mL)	C72hr (ng/mL)
IV/PO/PO (115/80/80) (Study P134[♯])	N	8	12	8	10	11
	AM	19500	3240	433	310	199
	CV%	41.1	39.4	73.6	93.1	141
	GM	18000	3030	348	210	--
PO/PO/PO (125/80/80) (Study P097[§])	N	18	18	9	9	16
	AM	16648.5	1268.6	512.4	624.7	595.8
	CV%	42.9	60.2	48.9	75.6	92.2
	GM	14318	1070	449.7	460.6	367.0

[♯] Oral suspension was used on Days 2 and 3.
[§] Oral capsules were used. Results submitted to NDA 21549/S-25 for EMEND oral capsule
AM: arithmetic mean; GM: Geometric mean; --: not reported
Source data: Reviewer's summary table based upon the sponsor's clinical study reports to NDA 21549/S-25 and NDA 22023/S-17

For both studies (P134 and P097), the Cmax on Days 2 and 3 were not measured. PK samplings for Days 2 and 3 were only for trough concentrations (Cmin), i.e. C24hr, C48hr, and C72hr. Cross-study comparison showed that Cmin at Hour 24 and Hour 48 from IV/PO/PO group were 22.5% and 54.4% lower than the PO/PO/PO regimen, respectively.

Reviewer's comment: Emend oral capsules have been approved for patients 12 years and older. Emend oral suspension has been approved for patients < 12 years old. The two formulations are not interchangeable due to lack of a dedicated bioequivalence study. Population PK analysis showed that CL is similar between the two oral formulations. Therefore, even though the suspension was used in adolescents on Days 2 and 3 (Part I, Study P134), Emend oral capsule is recommended on Days 2 and 3 for the IV/PO/PO regimen.

The simulated geometric means of systemic exposures to aprepitant from three different types of three-day regimens (IV/IV/IV 115/80/80 mg, IV/IV/PO 115/80/80 mg, IV/PO/PO 115/80/80 mg) and corresponding differences in exposures compared to PO/PO/PO (125/80/80 mg) regimen are shown in Table 25.

Table 25. The Simulated Geometric Means of Aprepitant Following IV/PO/PO, IV/IV/PO, and IV/IV/IV and Corresponding Ratios Compared to Simulated Values from PO/PO/PO Regimen.

	Day 1				Day 2				Day 3			
		AUC0-24h	Cmax	Cmin		AUC 0-24h	Cmax	Cmin		AUC0-24h	Cmax	Cmin
PO/PO/PO	PO	17958	1152.8	364.35	PO	17491	1097.1	376.96	PO	16833	1055.9	365.86
IV/PO/PO	IV	20938	2424.5	424.79	PO	16820	1061.1	361.25	PO	16508	1036.1	359.34
IV/IV/PO	IV	20938	2424.5	424.79	IV	19996	2132.7	387.79	PO	16783	1057.6	360.32
IV/IV/IV	IV	21083	2451	428.6	IV	20142	2154.7	391.75	IV	20127	2143.8	389.54
Geometric mean ratio, PO/PO/PO as reference												
	Day 1				Day 2				Day 3			
IV/PO/PO	IV	1.17	2.10	1.17	PO	0.96	0.97	0.96	PO	0.98	0.98	0.98
IV/IV/PO	IV	1.17	2.10	1.17	IV	1.14	1.94	1.03	PO	1.00	1.00	0.98
IV/IV/IV	IV	1.17	2.13	1.18	IV	1.15	1.96	1.04	IV	1.20	2.03	1.06

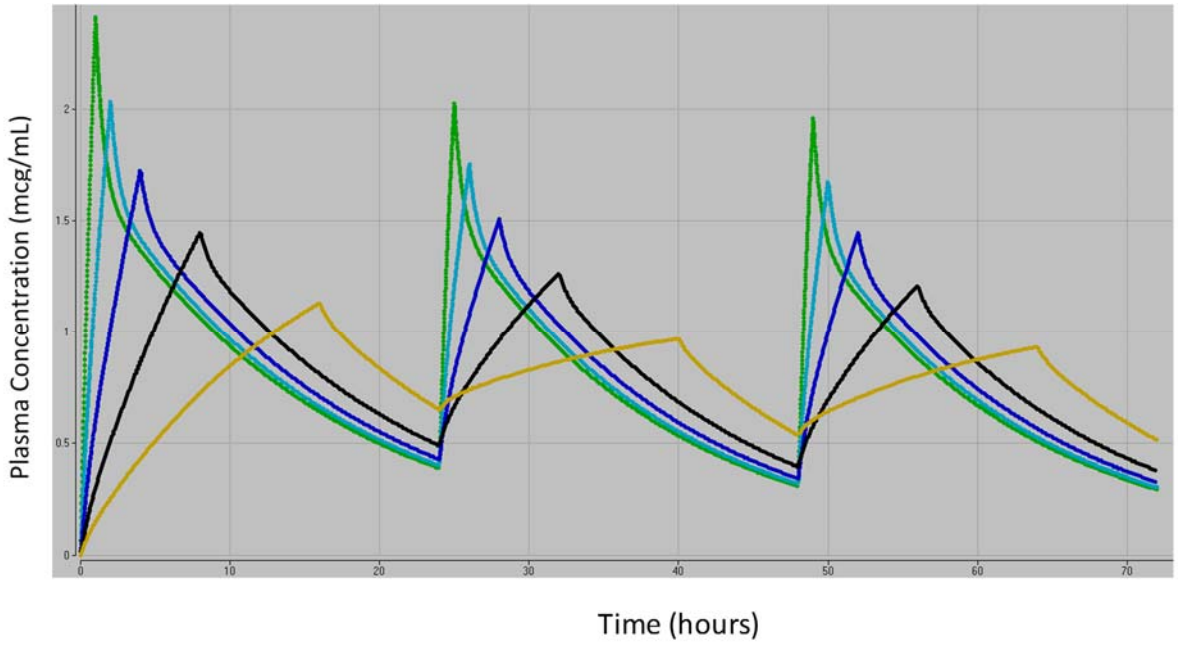
Units for AUC0-24h, Cmax, and Cmin are ng×hr/mL, ng/mL, ng/mL, respectively.

The simulated AUC0-24 and Cmin on Day 1 following IV infusion were 17% higher than those achieved following oral administration on Day 1. The AUC, Cmax, and Cmin of aprepitant on Days 2 and 3 with 80 mg oral aprepitant following IV fosaprepitant on Day 1 were similar to the adolescents who received the same oral doses on Days 2 and 3 following 125 mg oral aprepitant dose on Day 1.

The simulated Cmax on Day 1 following IV infusion was about 2-fold the Cmax following oral administration. However, as discussed earlier, the safety profile from adolescents receiving 150 mg, a dose 30% higher than 115 mg, was acceptable. The dose of 115 mg IV on Day 1 for a three-day regimen is acceptable.

The simulated values of Cmax on Days 2 and 3 following IV infusion were still about 2-fold the Cmax following oral administration. As fosaprepitant IV given beyond Day 1 has never been studied in pediatric patients, there is no safety data to support the 2-fold increase in Cmax when fosaprepitant IV is given repetitively for additional two days even though the simulated Cmax values on Days 2 and 3 were not higher than on Day 1. In order to reduce the Cmax values by 50% the infusion duration needs to be increased significantly beyond 60 minutes on Days 2 and 3 (**Error! Reference source not found.**).

Figure 5. Population PK Predicted Time Course of Plasma Aprepitant Concentrations (mcg/mL) after IV/IV/IV 115/80/80 mg Dosing in Adolescents for Various Infusion Durations



Infusion duration: Green represents 1 hour, light blue 2 hours, blue 4 hours, black 8 hours, yellow/tan 16 hours
Source data: Reviewer's analysis using Berkeley Madona software

Given that adjustment, because infusion duration on Days 2 and 3 duration will be different from Day 1, potential medication errors could occur. Consequently, the Agency and the sponsor agreed that IV infusion on Days 2 and 3 would be impractical in clinical settings. Thus, only the three-day regimen of IV/PO/PO is acceptable.

3.3.1.2.2 6 months to < 12 years

The three-day regimen with IV dosing on Day 1 has not been studied in pediatric patients < 12 years.

The simulated geometric means of systemic exposures to aprepitant from three different types of three-day regimens (IV/IV/IV 3/2/2 mg/kg, IV/IV/PO 3/2/2 mg/kg, IV/PO/PO 3/2/2 mg/kg) and corresponding differences in exposures compared to PO/PO/PO (3/2/2 mg/kg) regimen are shown in Table 26, Units for AUC0-24h, Cmax, and Cmin are ng×hr/mL, ng/mL, ng/mL, respectively.

Table 27 and Table 28, respectively.

Table 26. The Simulated Geometric Means of Aprepitant Following IV/PO/PO, IV/IV/PO, and IV/IV/IV and Corresponding Ratios Compared to Simulated Values from PO/PO/PO Regimen: 6 to < 12 years

	Day 1				Day 2				Day 3			
		AUC0-24h	Cmax	Cmin		AUC0-24h	Cmax	Cmin		AUC0-24h	Cmax	Cmin
PO/PO/PO	PO	21354	1489.2	384.31	PO	18832	1343.7	310.17	PO	18140	1291.9	298.9
IV/PO/PO	IV	25659	2699.3	474.82	PO	19604	1403.9	321.35	PO	18260	1299.7	301.23
IV/IV/PO	IV	25659	2699.3	474.82	IV	22733	2293.2	389.45	PO	19099	1363.3	313.21
IV/IV/IV	IV	25639	2686.5	474.92	IV	22704	2284	389.11	IV	22169	2235.5	377.58
Geometric mean ratio, PO/PO/PO as reference												
	Day 1				Day 2				Day 3			
IV/PO/PO	IV	1.20	1.81	1.24	PO	1.04	1.04	1.04	PO	1.01	1.01	1.01
IV/IV/PO	IV	1.20	1.81	1.24	IV	1.21	1.71	1.26	PO	1.05	1.06	1.05
IV/IV/IV	IV	1.20	1.80	1.24	IV	1.21	1.70	1.25	IV	1.22	1.73	1.26

Units for AUC0-24h, Cmax, and Cmin are ng×hr/mL, ng/mL, ng/mL, respectively.

Table 27. The Simulated Geometric Means of Aprepitant Following IV/PO/PO, IV/IV/PO, and IV/IV/IV and Corresponding Ratios Compared to Simulated Values from PO/PO/PO Regimen: 2 to < 6 years

	Day 1				Day 2				Day 3			
		AUC 0-24h	Cmax	Cmin		AUC0-24h	Cmax	Cmin		AUC0-24h	Cmax	Cmin
PO/PO/PO	PO	16398	1230.9	234.82	PO	13297	1034.9	167.56	PO	12710	987.39	160.23
IV/PO/PO	IV	20196	2287.3	296.53	PO	13707	1070.8	172.06	PO	12724	988.1	160.66
IV/IV/PO	IV	20196	2287.3	296.53	IV	16364	1841.7	215	PO	13146	1023.6	165.15
IV/IV/IV	IV	20336	2307.3	300.77	IV	16544	1860.1	219.27	IV	15941	1803.3	209.54
Geometric mean ratio, PO/PO/PO as reference												
	Day 1				Day 2				Day 3			
IV/PO/PO	IV	1.23	1.86	1.26	PO	1.03	1.03	1.03	PO	1.00	1.00	1.00
IV/IV/PO	IV	1.23	1.86	1.26	IV	1.23	1.78	1.28	PO	1.03	1.04	1.03
IV/IV/IV	IV	1.24	1.87	1.28	IV	1.24	1.80	1.31	IV	1.25	1.83	1.31

Units for AUC0-24h, Cmax, and Cmin are ng×hr/mL, ng/mL, ng/mL, respectively.

Table 28. The Simulated Geometric Means of Aprepitant Following IV/PO/PO, IV/IV/PO, and IV/IV/IV and Corresponding Ratios Compared to Simulated Values from PO/PO/PO Regimen: 6 months to < 2 years

	Day 1				Day 2				Day 3			
		AUC 0-24h	Cmax	Cmin		AUC0-24h	Cmax	Cmin		AUC0-24h	Cmax	Cmin
PO/PO/PO	PO	13431	1023.2	180.87	PO	10611	842.31	123.58	PO	10120	801.92	117.96
IV/PO/PO	IV	16616	1864.4	227.82	PO	10915	870.12	126.6	PO	10125	802.06	118.2
IV/IV/PO	IV	16616	1864.4	227.82	IV	13140	1487.9	159.19	PO	10428	828.5	121.17
IV/IV/IV	IV	16715	1872.1	229.07	IV	13217	1495.5	159.94	IV	12674	1443.6	152.02
	Geometric mean ratio, PO/PO/PO as reference											
	Day 1				Day 2				Day 3			
IV/PO/PO	IV	1.24	1.82	1.26	PO	1.03	1.03	1.02	PO	1.00	1.00	1.00
IV/IV/PO	IV	1.24	1.82	1.26	IV	1.24	1.77	1.29	PO	1.03	1.03	1.03
IV/IV/IV	IV	1.24	1.83	1.27	IV	1.25	1.78	1.29	IV	1.25	1.80	1.29

Units for AUC0-24h, Cmax, and Cmin are ng×hr/mL, ng/mL, ng/mL, respectively.

The simulated AUC0-24 and Cmin on Day 1 following IV infusion were 20% to 26% higher than those achieved following oral administration on Day 1. The simulated Cmax on Day 1 following IV infusion was about 2-fold the Cmax following oral administration. However, as discussed earlier, the safety profile from patients < 12 years old receiving 5 mg/kg IV, a dose 67% higher than 2 mg/kg, was acceptable. The dose of 3 mg/kg IV on Day 1 for a three-day regimen is acceptable.

The AUC, Cmax, and Cmin of aprepitant on Days 2 and 3 with 2 mg/kg oral aprepitant following IV fosaprepitant on Day 1 were similar to the those who received the same oral doses on Days 2 and 3 following 3 mg/kg oral aprepitant dose on Day 1.

Similar to what was found in the adolescent group, the simulated values of Cmax on Days 2 and 3 following IV infusion were still close to 2-fold the Cmax following oral administration. As fosaprepitant IV given beyond Day 1 has never been studied in pediatric patients, there is no safety data to support the near 2-fold increase in Cmax when it is given repetitively for additional two days. It is noteworthy that Cmax values on Days 2 and 3 were not higher than on Day 1. In order to lower the Cmax values, the infusion duration would also have to be increased significantly beyond 60 minutes on Days 2 and 3. As such, infusion duration on Days 2 and 3 would be different from Day 1 which may potentially lead to mediation errors. The Agency and the sponsor agreed that IV infusion on Days 2 and 3 were impractical in clinical settings. Thus, only the three-day regimen of IV/PO/PO would be approved.

3.3.1.3 Fosaprepitant

The safety of fosaprepitant IV in pediatric patients was deemed to be acceptable. Refer to Clinical Review of the supplement NDA 22023/S-17 for details.

According to the sponsor, the fosaprepitant level on Day 1 following 115 mg IV in adolescents in the three-day regimen (IV/PO/PO) was not reported in Study P134 because the samples were mishandled. However, single dose fosaprepitant 150 mg IV in adolescents was evaluated (Table 16). No safety issue was found to be associated with single dose fosaprepitant in this age group. No safety issue was found to be associated with 115 mg fosaprepitant IV on Day 1 of the three-day regimen in this age group even though the systemic exposures to fosaprepitant following 115 mg IV were not available.

The three-day regimen (IV/PO/PO) was not studied in patients < 12 years. However, 3 mg/kg and 5 mg/kg were studied in the single-day regimen and were found to be safe. Fosaprepitant levels following 3 mg/kg single dose were evaluated (Table 16). The proposed dose of 3 mg/kg IV on Day 1 was also lower than 5 mg/kg studied in the single-day regimen in patients < 12 years.

3.3.1.4 Cardiac Electrophysiology

A single 200 mg dose of fosaprepitant had no effect on the QTc interval. Maximum aprepitant concentrations after a single 200 mg dose of fosaprepitant were 4- and 9-fold higher than that achieved with oral EMEND 125 mg and 40 mg (for PONV), respectively.[5] QT prolongation with the oral EMEND dosing regimens for CINV and PONV is not expected. The maximum proposed dose for pediatric patients is 150 mg IV which is 30% lower than 200 mg dose.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

No. See discussion in Section 3.3.1.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No. Population PK analysis showed that sex and race do not affect systemic exposures of aprepitant. The dosing regimens for fosaprepitant IV have factored in the effect of age and body weight on the PK.

[5] Fosaprepitant product label (rev 8/2017) and aprepitant product label (rev 5/2017)

The CL of aprepitant increases with the increase of body weight. Across the range of pediatric body weights, CL change nearly 2-fold. For 150 mg IV aprepitant administered to a 9-year old with the body weight of 29.7 kg (median age and weight in the 6 to 12 years old group, Table 40), the predicted CL of aprepitant is 2.50 L/hr. For the same dose in a 9-year old with body weight of 68.4 kg (maximum weight in the 6 to 12 years old group, Table 40), the predicted CL is 4.67 L/hr.

The V2 (central compartment) of aprepitant decreases with the increase of age. The V2 for a 9-year old with a body weight of 29.7 kg is predicted to be 19.8 L. The V2 for a 6-year old with the same body weight is predicted to be 21.5 L.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Food-drug Interactions

Since fosaprepitant is administered by intravenous infusion, a food-effect study is not conducted as food-drug interactions are not anticipated nor applicable.

Drug-drug interactions

Yes. This has been addressed in the current approved label for oral aprepitant. Also see Section 3.2.

Dosage adjustment for a corticosteroid e.g. dexamethasone

Similar to what is recommended for oral aprepitant in pediatric cancer patients[6], a 50% dose reduction is recommended if a corticosteroid, such as dexamethasone, is co-administered. In the clinical trials evaluating PK and PK/PD of aprepitant following fosaprepitant IV, the dexamethasone dose was set to be reduced by 50%. This is because both aprepitant and dexamethasone are the substrates of CYP3A4 enzymes while aprepitant is also a moderate CYP3A4 inhibitor. In adults, co-administration of aprepitant resulted in a significant 2-fold increase in dexamethasone AUC and Cmax. Co-administration of single oral dose of aprepitant with midazolam given IV (a sensitive CYP3A4 substrate) resulted in a 1.5-fold increase in midazolam AUC. A 2.3-fold increase in midazolam AUC was observed when midazolam was given orally with a single dose of oral aprepitant. Fosaprepitant is quickly converted to aprepitant, thus, has minimal drug-drug interaction potential. Taken together, the proposed dose reduction of dexamethasone in pediatric patients is reasonable.

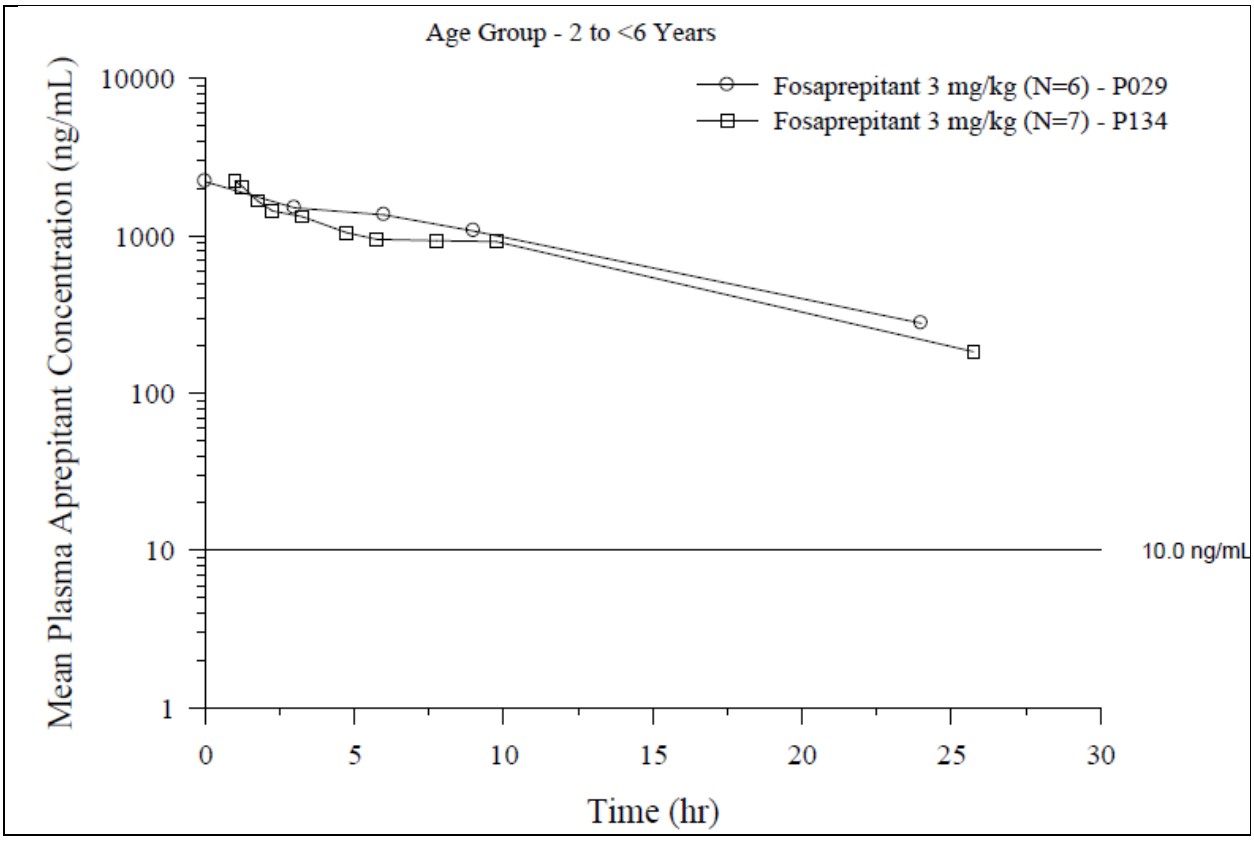
[6] Approved product label of oral aprepitant, Section 14.3

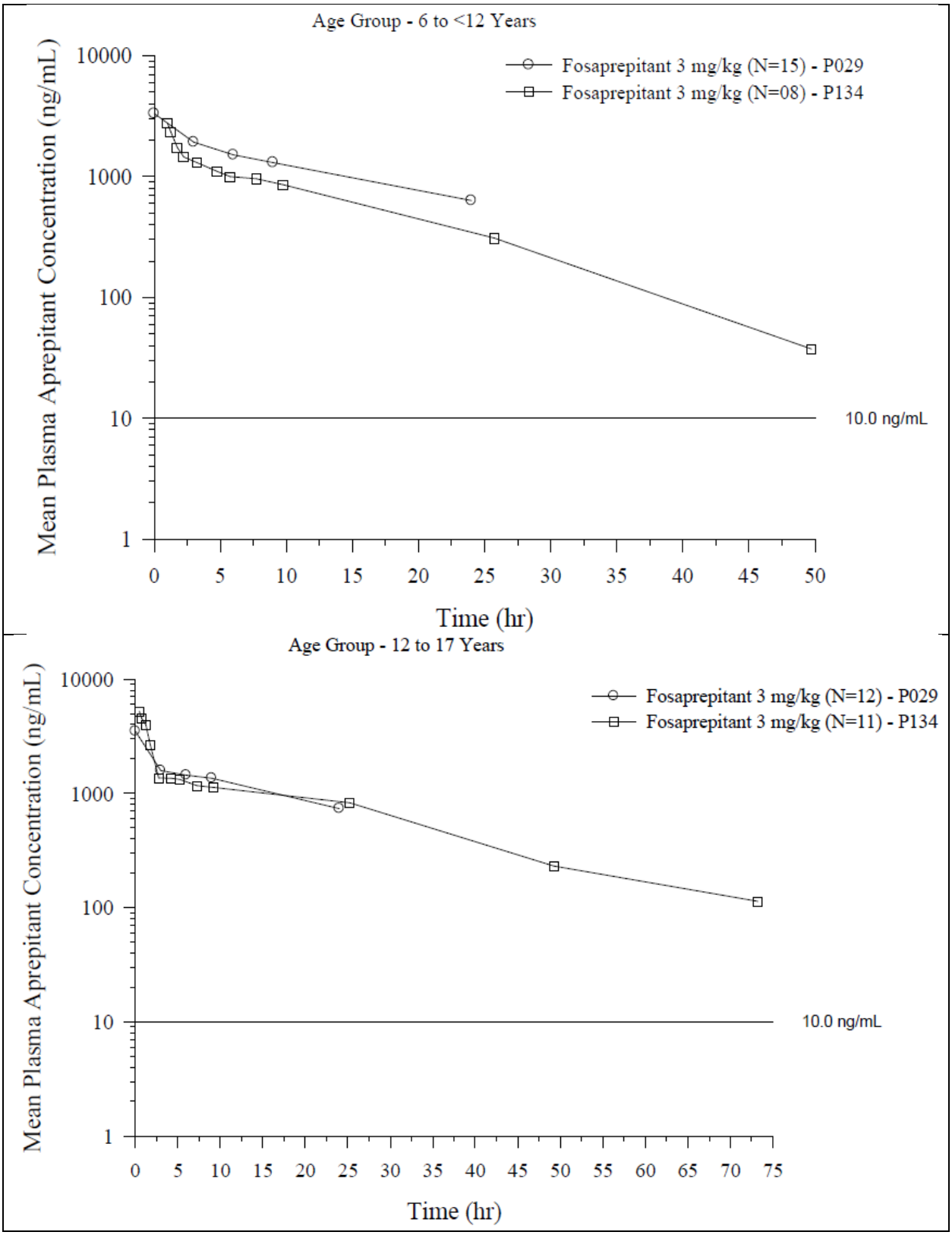
Effect of excipient -EDTA

The to-be-marketed formulation of fosaprepitant for pediatric patients is the currently approved formulation for use in adults. It contains 5.4 mg edetate disodium (EDTA) in a 150 mg dose vial ("reduced EDTA" formulation) which has been approved since 12/2/2016 (NDA 22023/S-14). This formulation was used in Study P029. However, fosaprepitant used in Study P134 was the "original" marketed IV fosaprepitant formulation approved in 2009 in adults. The formulation included 18.8 mg EDTA in a 150 mg dose vial ("high EDTA" formulation, "original EDTA" formulation).

The effect of EDTA in terms of "reduced" formulation vs "high" formulation on systemic exposures of aprepitant in pediatric population is negligible. As EDTA is not expected to affect the PK of aprepitant and the bioavailability of intravenous injection is 100%, the "reduced EDTA" formulation (NDA 22023/S-14) was approved without a relative bioavailability study. The cross-study comparison of the concentration-time profiles following 3 mg/kg of aprepitant in patients 2 to 12 years old and 150 mg in adolescents showed that the concentration-time profiles were superimposable except for age group of 6 to < 12 years (Figure 6). However, this difference could be due to an imbalance of the subject numbers between the two studies. Population PK analysis (Section 4.3) also found that the systemic exposures of aprepitant from "reduced" formulation is similar to that from "high" formulation.

Figure 6. Concentration-Time Profiles of Aprepitant in Adolescents Receiving 150 mg Fosaprepitant and 2 to < 12 Years Old Receiving 3 mg/kg (up to 150 mg) in Study P134 ("Original" EDTA, aka "High" EDTA) and Study P029 ("Reduced" EDTA) Across All Age Groups.

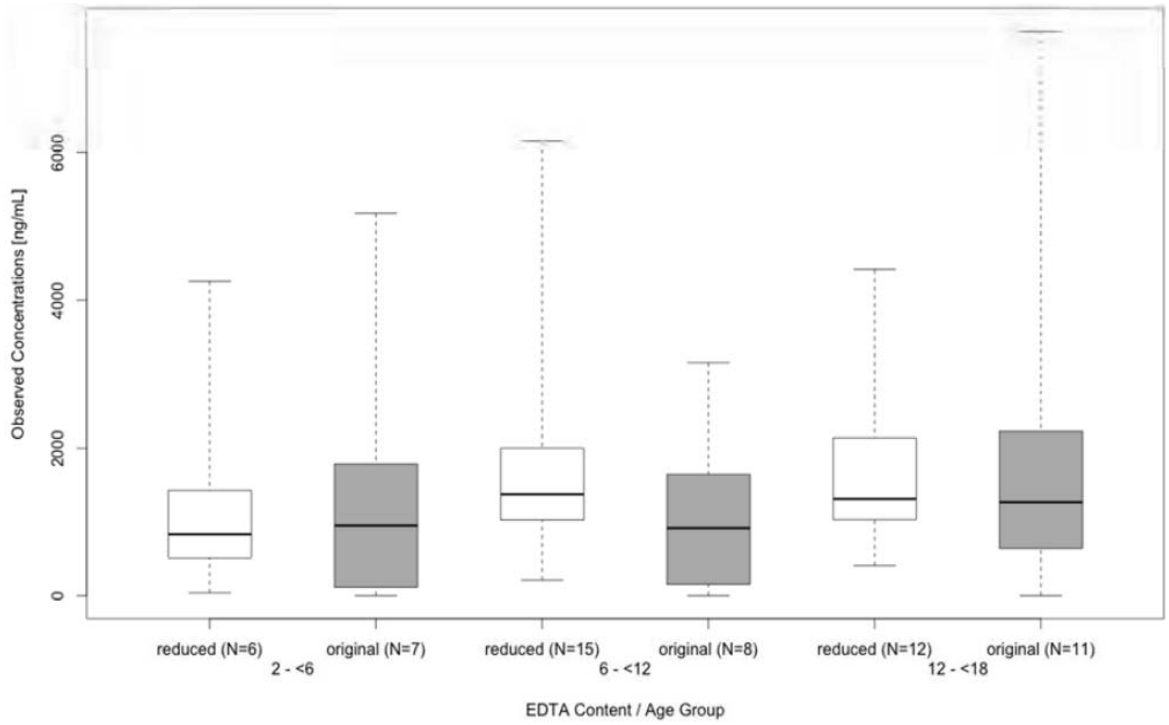




Source data: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Figure 2.7.1:2
10.0 ng/mL: LLOQ

In addition, the distributions of the observed concentrations from both studies were comparable (**Error! Reference source not found.**).

Figure 7. Distribution of Observed Aprepitant Concentration Data Following IV Administration of 3 mg/kg Fosaprepitant in Study P029 (Reduced EDTA) and Study P134 (Original EDTA, aka. High EDTA) in Pediatric Patients 2 – 17 Years Old



Source data: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Figure 2.7.1:3

4. APPENDICES

4.1. Summary of Bioanalytical Method Validation and Performance

Plasma aprepitant (MK-0869) was measured by an adequately validated high performance liquid chromatography with tandem mass spectrometric detection (HPLC-MS/MS) with acceptable accuracy and precision. Both methods showed in Table 29 were reviewed and deemed to be acceptable. Refer to Clinical Pharmacology Review of NDA21549/S-025 (Efficacy Supplement of Emend oral capsules) and original NDA 207865 (Emend oral suspension) for details.

Table 29. Laboratories That Developed and Validated the Bioanalytical Methods and Performed the Analyses

Laboratory	Laboratory Method	Matrix	Study Supported	Analyte	Laboratory Address
Merck Research Laboratories	DM-359O	Plasma	P097	MK-0869	770 Sumneytown Pk, West Point, PA 19486
(b) (4)	09BASM032V2	Plasma	P029, P044, P134, P148	MK-0869	(b) (4)

Source data: 2.7.1 Summary Of Biopharmaceutic Studies/Associated Analytical Methods (Pediatric), Table 2.7.1: 4

Plasma fosaprepitant (MK-0517) was measured by a validated high performance liquid chromatography with tandem mass spectrometric detection (HPLC-MS/MS) in the positive ion mode using a Heated Nebulizer interface. The analytical method numbered 12BAS0234 was performed by (b) (4) in 2014. The concentration range of detection was 10.000 – 5000.000 ng/mL with an r^2 of 0.9978. The intra-day, inter-day precision and accuracy, recovery were within acceptable range. Free-Thaw stability and twelve-months stability at ≤ 20°C and ≤70°C were also within acceptable range.

4.2. Individual Study Review

4.2.1 Study P029

Title: A Phase IIb, Partially-Blinded, Randomized, Active Comparator-Controlled Study to Evaluate the Pharmacokinetics/Pharmacodynamics, Safety, and Tolerability of Fosaprepitant in Pediatric Patients for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) Associated with Emetogenic Chemotherapy

Subtitle: Open-Label Cohort to Further Evaluate thePharmacokinetics/Pharmacodynamics, Safety, and Tolerability of Fosaprepitant in Pediatric Patients Birth to <12 Years Old

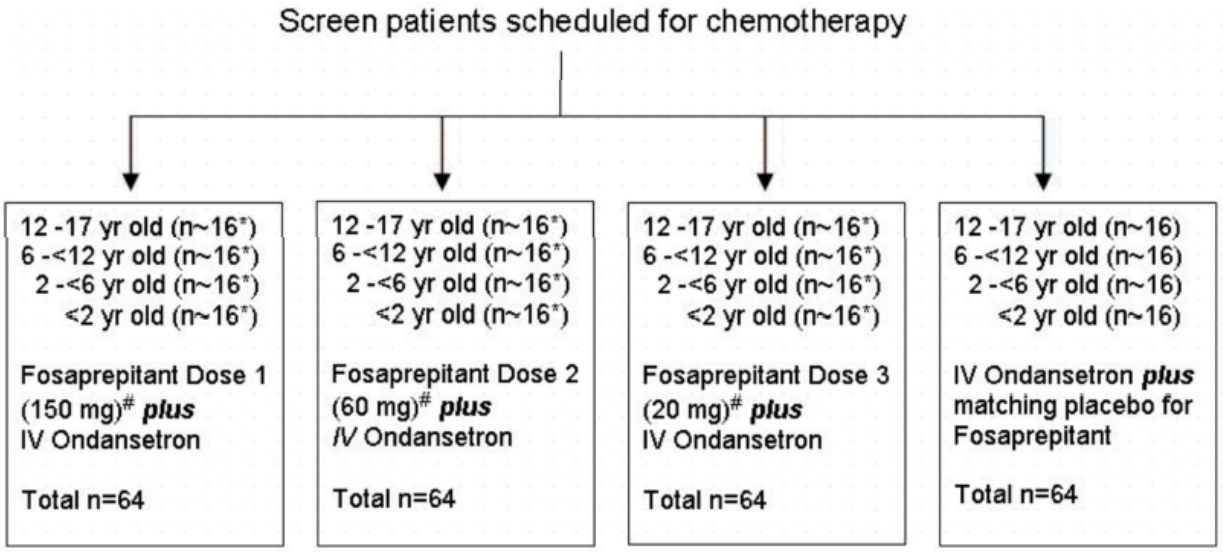
Study Design: This study was a Phase 2b, worldwide, multicenter, partially-blinded, randomized, parallel-group, pharmacokinetic (PK)/pharmacodynamics (PD), dose-ranging study, to evaluate the PK, PD, safety and tolerability of aprepitant, after administration of a single dose of fosaprepitant concomitantly with intravenous (IV) ondansetron, with or without

dexamethasone. Eligible subjects were male or female, birth to 17 years of age, with a documented malignancy and scheduled to receive chemotherapeutic agent(s) associated with moderate, high, or very high risk of emetogenicity.

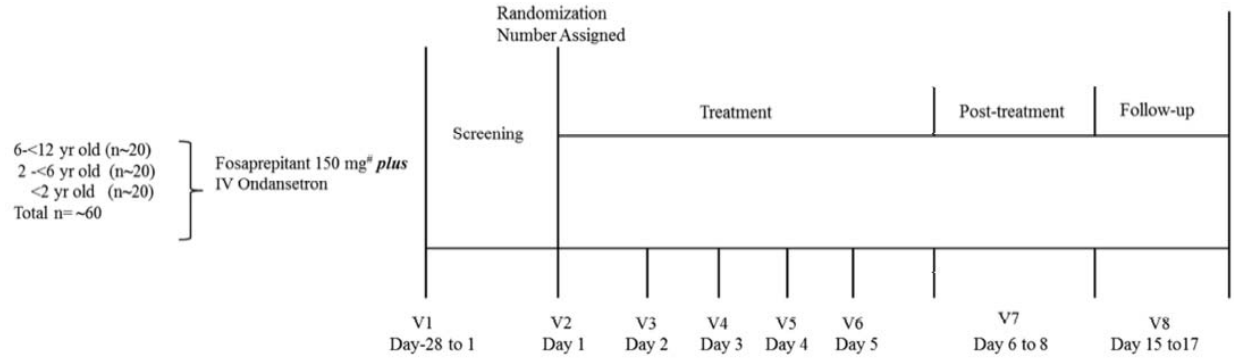
A cohort to evaluate the impact of aprepitant on the PK of dexamethasone in the pediatric age group birth to 1 year old was also implemented.

Reviewer's comment: Only one patient was studied. Thus, the results are not included in this review.

Figure 8. Study Design and Treatment Group. Top panel: Dose Ranging Study Part; Bottom Panel: Study of 5 mg/kg (Up to 150 mg) in < 12 years



* Note: PK only drawn on 12 patients/age group (fosaprepitant dose groups only)
#Dose used for adolescents; children below 12 years of age received a corresponding weight-adjusted dose, described in Section 1.6 of the protocol [16.1.1]



Note: PK samples drawn from all subjects.
#All subjects received a corresponding age-specific weight-adjusted dose.

Pharmacokinetic analysis: Plasma for aprepitant PK assessment was obtained at the end of the fosaprepitant infusion, and 2 to 4 hours, 5 to 7 hours, 8 to 10 hours, and 23 to 25 hours after completion of fosaprepitant infusion. An additional optional plasma sample was collected 46 to 50 hours after completion of fosaprepitant infusion in the 5 mg/kg dose cohort. PK assessment was done in Cycle 1.

Pharmacokinetic Results

Demographics

	Fosaprepitant 3mg/kg Regimen		Fosaprepitant 1.2mg/kg Regimen		Fosaprepitant 0.4mg/kg Regimen		Control Regimen		Fosaprepitant 5mg/kg Regimen		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	42		43		40		35		74		234	
Gender												
Male	24	(57.1)	20	(46.5)	21	(52.5)	18	(51.4)	42	(56.8)	125	(53.4)
Female	18	(42.9)	23	(53.5)	19	(47.5)	17	(48.6)	32	(43.2)	109	(46.6)
Age (Months)												
birth to <2 years	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	23	(31.1)	23	(9.8)
2 to <6 years	8	(19.0)	10	(23.3)	10	(25.0)	9	(25.7)	26	(35.1)	63	(26.9)
6 to <12 years	17	(40.5)	16	(37.2)	13	(32.5)	9	(25.7)	25	(33.8)	80	(34.2)
12 to 17 years	17	(40.5)	17	(39.5)	17	(42.5)	17	(48.6)	0	(0.0)	68	(29.1)
Mean	124.5		121.6		120.7		124.3		60.2		103.0	
SD	51.8		51.3		54.0		55.7		42.3		57.4	
Median	123.5		127.0		129.0		140.0		54.0		102.0	
Range	29 to 210		38 to 202		27 to 209		28 to 206		4 to 142		4 to 210	
Race												
Asian	3	(7.1)	2	(4.7)	2	(5.0)	3	(8.6)	13	(17.6)	23	(9.8)
Black Or African American	1	(2.4)	1	(2.3)	4	(10.0)	2	(5.7)	1	(1.4)	9	(3.8)
Multiple	0	(0.0)	1	(2.3)	1	(2.5)	2	(5.7)	9	(12.2)	13	(5.6)
White	38	(90.5)	39	(90.7)	33	(82.5)	28	(80.0)	51	(68.9)	189	(80.8)
Ethnicity												
Hispanic Or Latino	6	(14.3)	8	(18.6)	10	(25.0)	3	(8.6)	17	(23.0)	44	(18.8)
Not Hispanic Or Latino	27	(64.3)	29	(67.4)	26	(65.0)	24	(68.6)	53	(71.6)	159	(67.9)

Subjects by Age Category and Gender

	Fosaprepitant 3mg/kg Regimen			Fosaprepitant 1.2mg/kg Regimen			Fosaprepitant 0.4mg/kg Regimen		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Subjects in population	24	18	42	20	23	43	21	19	40
Age (Months)									
birth to <2 years	0	0	0	0	0	0	0	0	0
2 to <6 years	4	4	8	5	5	10	5	5	10
6 to <12 years	10	7	17	5	11	16	5	8	13
12 to 17 years	10	7	17	10	7	17	11	6	17
Mean	128.3	119.3	124.5	131.6	113.0	121.6	126.5	114.3	120.7
SD	54.3	49.2	51.8	54.1	48.2	51.3	55.4	53.2	54.0
Median	119.5	125.0	123.5	147.0	118.0	127.0	148.0	113.0	129.0
Range	29 to 210	39 to 196	29 to 210	48 to 202	38 to 200	38 to 202	27 to 205	34 to 209	27 to 209

	Control Regimen			Fosaprepitant 5mg/kg Regimen			Total		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Subjects in population	18	17	35	42	32	74	125	109	234
Age (Months)									
birth to <2 years	0	0	0	12	11	23	12	11	23
2 to <6 years	3	6	9	14	12	26	31	32	63
6 to <12 years	6	3	9	16	9	25	42	38	80
12 to 17 years	9	8	17	0	0	0	40	28	68
Mean	128.6	119.8	124.3	65.5	53.3	60.2	107.5	97.8	103.0
SD	53.4	59.3	55.7	44.7	38.4	42.3	58.7	55.8	57.4
Median	142.0	136.0	140.0	60.5	48.5	54.0	109.0	101.0	102.0
Range	28 to 206	35 to 204	28 to 206	4 to 142	7 to 142	4 to 142	4 to 210	7 to 209	4 to 210

For Fosaprepitant 3mg/kg Regimen, subjects 12-17 years of age received a fixed 150 mg fosaprepitant dose.
For Fosaprepitant 1.2mg/kg Regimen, subjects 12-17 years of age received a fixed 60 mg fosaprepitant dose.
For Fosaprepitant 0.4mg/kg Regimen, subjects 12-17 years of age received a fixed 20 mg fosaprepitant dose.

Source: [P029MK0517: analysis-adsl]

4.2.1.1 Summary of PK parameters

Descriptive Summary of the PK parameters estimated by non-compartmental analysis is shown below:

Table 30. Descriptive Statistics of PK parameters After Single dose of 150 mg or 3 mg/kg by Age Cohorts

Table 11-1

Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant Following Administration of 150 mg Single Dose IV Fosaprepitant Regimen in Subjects Aged 12 to 17 Years (LOQ Values – 10.0 ng/mL)

12 to 17 Years	Summary of Aprepitant Plasma Pharmacokinetic Parameters							
	AUC0-∞† (hr*ng/mL)	AUC0-24hr (hr*ng/mL)	Cmax (ng/mL)	C24hr (ng/mL)	C48hr (ng/mL)	Tmax (hr)	Apparent Terminal t1/2† (hr)	CL/F† (mL/min)
N	3	12	12	12	0	12	3	3
AM	33800	30400	3500	735	NC	0.546	10.5	76.2
SD	7180	8290	972	310	NC	0.144	1.00	16.2
ACV (%)	21.3	27.3	27.7	42.2	NC	26.3	9.6	21.2
Med	33200	29400	3730	714	NC	0.500	10.7	75.2
Min	26900	21300	1800	343	NC	0.500	9.39	60.6
Max	41200	48100	4600	1240	NC	1.00	11.4	92.9
GM	33300	29400	3360	675	NC	0.534	10.5	75.1
GCV (%)	21.6	26.1	32.7	46.0	NC	20.1	9.8	21.6

N:Number of observations; AM: Arithmetic mean; SD: Standard deviation; ACV%: Arithmetic Coefficient of Variation, where ACV%= (SD/AM)*100; Med: Median; Min: Minimum; Max: Maximum; GM: Geometric mean; GCV%: Geometric Coefficient of Variation, where GCV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale; NC: Not Calculated;

†Three out of 12 subjects have sufficient data in terminal phase for apparent terminal t1/2 estimation, therefore t1/2 and related PK parameters (AUC0-∞ and CL/F) were only reported for these 3 subjects.

Table 11-2

Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant Following Administration of 3 mg/kg (up to 150 mg) Single Dose IV Fosaprepitant Regimen in Subjects Aged 6 to <12 Years (LOQ Values – 10.0 ng/mL)

6 to <12 Years	Summary of Aprepitant Plasma Pharmacokinetic Parameters[†]							
	AUC0-∞[‡] (hr*ng/mL)	AUC0-24hr (hr*ng/mL)	Cmax (ng/mL)	C24hr (ng/mL)	C48hr (ng/mL)	Tmax (hr)	Apparent Terminal t1/2[‡] (hr)	CL/F[‡] (mL/min)
N	8	14	14	14	0	14	8	8
AM	34300	29200	3550	589	NC	1.99	7.69	69.2
SD	20300	14300	2460	433	NC	1.62	2.09	66.4
ACV (%)	59.1	48.8	69.2	73.5	NC	81.6	27.2	95.9
Med	28400	29500	2700	550	NC	1.14	7.64	46.6
Min	10900	9650	1210	81.0	NC	0.533	4.39	34.0
Max	69000	60700	9190	1260	NC	6.00	11.9	231
GM	29200	26000	2930	419	NC	1.55	7.45	55.0
GCV (%)	69.0	54.9	69.5	119.9	NC	79.6	28.1	68.8

N:Number of observations; AM: Arithmetic mean; SD: Standard deviation; ACV%: Arithmetic Coefficient of Variation, where ACV%= (SD/AM)*100; Med: Median; Min: Minimum; Max: Maximum; GM: Geometric mean; GCV%: Geometric Coefficient of Variation, where GCV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale; NC: Not Calculated;

[†]AN # 201770 was excluded from PK parameter summary statistics due to dosing deviation.

[‡]Eight out of 14 subjects have sufficient data in terminal phase for apparent terminal t1/2 estimation, therefore t1/2 and related PK parameters (AUC0-∞ and CL/F) were only reported for these 8 subjects.

Table 11-3

Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant Following Administration of 3 mg/kg (up to 150 mg) Single Dose IV Fosaprepitant Regimen in Subjects Aged 2 to <6 Years (LOQ Values – 10.0 ng/mL)

2 to <6 Years	Summary of Aprepitant Plasma Pharmacokinetic Parameters							
	AUC0-∞[†] (hr*ng/mL)	AUC0-24hr (hr*ng/mL)	Cmax (ng/mL)	C24hr (ng/mL)	C48hr (ng/mL)	Tmax (hr)	Apparent Terminal t1/2[†] (hr)	CL/F[†] (mL/min)
N	5	6	6	6	0	6	5	5
AM	15300	21800	2320	278	NC	2.29	6.55	66.2
SD	11100	22200	1540	398	NC	2.14	3.62	25.5
ACV (%)	72.9	101.8	66.1	142.9	NC	93.5	55.3	38.5
Med	9830	10600	1590	63.2	NC	1.00	4.96	63.6
Min	9530	9140	1020	33.5	NC	1.00	4.29	31.9
Max	35100	65100	4550	1020	NC	6.08	12.9	101
GM	13100	15900	1960	115	NC	1.68	5.95	61.8
GCV (%)	60.6	94.7	69.8	255.1	NC	97.5	48.2	45.0

N:Number of observations; AM: Arithmetic mean; SD: Standard deviation; ACV%: Arithmetic Coefficient of Variation, where ACV%= (SD/AM)*100; Med: Median; Min: Minimum; Max: Maximum; GM: Geometric mean; GCV%: Geometric Coefficient of Variation, where GCV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale; NC: Not Calculated;

[†]Five out of 6 subjects have sufficient data in terminal phase for apparent terminal t1/2 estimation, therefore t1/2 and related PK parameters (AUC0-∞ and CL/F) were only reported for these 5 subjects.

Table 31. Descriptive Statistics of PK parameters After Single dose of 60 mg or 1.2 mg/kg by Age Cohorts

Table 11-4

Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant Following Administration of 60 mg Single Dose IV Fosaprepitant Regimen in Subjects Aged 12 to 17 Years (LOQ Values – 10.0 ng/mL)

12 to 17 Years	Summary of Aprepitant Plasma Pharmacokinetic Parameters							
	AUC0-∞† (hr*ng/mL)	AUC0-24hr (hr*ng/mL)	Cmax (ng/mL)	C24hr (ng/mL)	C48hr (ng/mL)	Tmax (hr)	Apparent Terminal t1/2† (hr)	CL/F† (mL/min)
N	8	12	12	12	0	12	8	8
AM	12300	9700	1180	142	NC	0.722	7.92	91.7
SD	4660	4200	408	86.4	NC	0.608	1.38	32.5
ACV (%)	37.8	43.3	34.6	61.0	NC	84.2	17.4	35.5
Med	10400	8590	1200	121	NC	0.500	7.97	96.8
Min	7090	3980	487	63.0	NC	0.500	5.74	52.9
Max	18900	17300	1910	372	NC	2.60	9.88	141
GM	11600	8860	1110	124	NC	0.614	7.81	86.4
GCV (%)	38.9	47.5	39.9	55.5	NC	52.7	18.0	38.9

N:Number of observations; AM: Arithmetic mean; SD: Standard deviation; ACV%: Arithmetic Coefficient of Variation, where ACV%= (SD/AM)*100; Med: Median; Min: Minimum; Max: Maximum; GM: Geometric mean; GCV%: Geometric Coefficient of Variation, where GCV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale; NC: Not Calculated;

†Eight out of 12 subjects have sufficient data in terminal phase for apparent terminal t1/2 estimation, therefore t1/2 and related PK parameters (AUC0-∞ and CL/F) were only reported for these 8 subjects.

Table 11-5

Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant Following Administration of 1.2 mg/kg (up to 60 mg) Single Dose IV Fosaprepitant Regimen in Subjects Aged 6 to <12 Years (LOQ Values – 10.0 ng/mL)

6 to <12 Years	Summary of Aprepitant Plasma Pharmacokinetic Parameters							
	AUC0-∞† (hr*ng/mL)	AUC0-24hr (hr*ng/mL)	Cmax (ng/mL)	C24hr (ng/mL)	C48hr (ng/mL)	Tmax (hr)	Apparent Terminal t1/2† (hr)	CL/F† (mL/min)
N	9	13	13	13	0	13	9	9
AM	10700	12000	1360	219	NC	2.14	8.23	78.8
SD	5440	11000	903	379	NC	1.96	1.83	39.1
ACV (%)	51.0	91.9	66.3	172.6	NC	91.5	22.3	49.6
Med	8920	8190	1030	98.6	NC	1.03	8.02	81.9
Min	2860	2670	471	18.7	NC	0.500	6.03	32.5
Max	21300	45600	3070	1440	NC	6.17	12.3	156
GM	9370	9310	1140	110	NC	1.56	8.06	70.3
GCV (%)	62.4	78.1	67.3	153.1	NC	92.8	21.3	55.8

N:Number of observations; AM: Arithmetic mean; SD: Standard deviation; ACV%: Arithmetic Coefficient of Variation, where ACV%= (SD/AM)*100; Med: Median; Min: Minimum; Max: Maximum; GM: Geometric mean; GCV%: Geometric Coefficient of Variation, where GCV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale; NC: Not Calculated;
†Nine out of 13 subjects have sufficient data in terminal phase for apparent terminal t1/2 estimation, therefore t1/2 and related PK parameters (AUC0-∞ and CL/F) were only reported for these 9 subjects.

Table 11-6

Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant Following Administration of 1.2 mg/kg (up to 60 mg) Single Dose IV Fosaprepitant Regimen in Subjects Aged 2 to <6 Years (LOQ Values – 10.0 ng/mL)

2 to <6 Years	Summary of Aprepitant Plasma Pharmacokinetic Parameters							
	AUC0-∞† (hr*ng/mL)	AUC0-24hr (hr*ng/mL)	Cmax (ng/mL)	C24hr (ng/mL)	C48hr (ng/mL)	Tmax (hr)	Apparent Terminal t1/2† (hr)	CL/F† (mL/min)
N	5	8	8	8	0	8	5	5
AM	16000	19700	2030	332	NC	1.36	7.27	29.6
SD	9680	18500	1780	430	NC	0.868	3.47	22.1
ACV (%)	60.4	93.6	87.5	129.7	NC	63.6	47.7	74.4
Med	12400	14200	1480	222	NC	1.00	5.51	22.0
Min	4820	4600	716	26.6	NC	1.00	3.73	12.1
Max	27700	62300	6180	1350	NC	3.50	11.6	65.7
GM	13400	14700	1600	170	NC	1.23	6.63	24.2
GCV (%)	80.3	93.8	77.0	216.5	NC	45.4	51.3	79.1

N:Number of observations; AM: Arithmetic mean; SD: Standard deviation; ACV%: Arithmetic Coefficient of Variation, where ACV%= (SD/AM)*100; Med: Median; Min: Minimum; Max: Maximum; GM: Geometric mean; GCV%: Geometric Coefficient of Variation, where GCV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale; NC: Not Calculated;
†Five out of 8 subjects have sufficient data in terminal phase for apparent terminal t1/2 estimation, therefore t1/2 and related PK parameters (AUC0-∞ and CL/F) were only reported for these 5 subjects.

Table 32. Descriptive Statistics of PK parameters After Single dose of 20 mg or 0.4 mg/kg by Age Cohorts

Table 11-7

Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant Following Administration of 20 mg Single Dose IV Fosaprepitant Regimen in Subjects Aged 12 to 17 Years (LOQ Values – 10.0 ng/mL)

12 to 17 Years	Summary of Aprepitant Plasma Pharmacokinetic Parameters							
	AUC0-∞† (hr*ng/mL)	AUC0-24hr (hr*ng/mL)	Cmax (ng/mL)	C24hr (ng/mL)	C48hr (ng/mL)	Tmax (hr)	Apparent Terminal t1/2† (hr)	CL/F† (mL/min)
N	9	13	13	13	0	13	9	9
AM	3500	4820	582	101	NC	0.736	8.27	105
SD	1430	7240	437	247	NC	0.561	1.20	29.0
ACV (%)	40.9	150.3	75.1	244.8	NC	76.2	14.6	27.6
Med	2940	2400	437	34.3	NC	0.500	8.29	113
Min	2360	1010	173	0.00	NC	0.500	6.27	47.4
Max	7030	28500	1710	920	NC	2.50	10.4	141
GM	3310	3110	467	NC	NC	0.636	8.19	101
GCV (%)	34.3	94.0	76.2	NC	NC	51.3	14.9	34.3

N:Number of observations; AM: Arithmetic mean; SD: Standard deviation; ACV%: Arithmetic Coefficient of Variation, where ACV%= (SD/AM)*100; Med: Median; Min: Minimum; Max: Maximum; GM: Geometric mean; GCV%: Geometric Coefficient of Variation, where GCV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale; NC: Not Calculated;
†Nine out of 13 subjects have sufficient data in terminal phase for apparent terminal t1/2 estimation, therefore t1/2 and related PK parameters (AUC0-∞ and CL/F) were only reported for these 9 subjects.

Table 11-8

Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant Following Administration of 0.4 mg/kg (up to 20 mg) Single Dose IV Fosaprepitant Regimen in Subjects Aged 6 to <12 Years (LOQ Values – 10.0 ng/mL)

6 to <12 Years	Summary of Aprepitant Plasma Pharmacokinetic Parameters							
	AUC0-∞† (hr*ng/mL)	AUC0-24hr (hr*ng/mL)	Cmax (ng/mL)	C24hr (ng/mL)	C48hr (ng/mL)	Tmax (hr)	Apparent Terminal t1/2† (hr)	CL/F† (mL/min)
N	8	12	12	12	0	12	8	8
AM	2860	4260	507	70.4	NC	1.68	6.58	89.6
SD	1120	5040	443	136	NC	2.46	2.36	40.9
ACV (%)	39.0	118.4	87.3	193.2	NC	146.3	35.9	45.6
Med	2950	2710	375	25.4	NC	1.00	6.76	84.0
Min	1270	1480	173	0.00	NC	0.667	3.85	30.8
Max	4180	19800	1820	485	NC	9.50	10.5	164
GM	2650	3090	407	NC	NC	1.17	6.21	80.9
GCV (%)	45.7	81.5	70.5	NC	NC	75.3	38.4	54.1

N:Number of observations; AM: Arithmetic mean; SD: Standard deviation; ACV%: Arithmetic Coefficient of Variation, where ACV%= (SD/AM)*100; Med: Median; Min: Minimum; Max: Maximum; GM: Geometric mean; GCV%: Geometric Coefficient of Variation, where GCV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale; NC: Not Calculated;
†Eight out of 12 subjects have sufficient data in terminal phase for apparent terminal t1/2 estimation, therefore t1/2 and related PK parameters (AUC0-∞ and CL/F) were only reported for these 8 subjects.

Table 11-9

Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant Following Administration of 0.4 mg/kg (up to 20 mg) Single Dose IV Fosaprepitant Regimen in Subjects Aged 2 to <6 Years (LOQ Values – 10.0 ng/mL)

2 to <6 Years	Summary of Aprepitant Plasma Pharmacokinetic Parameters[†‡]							
	AUC0-∞[%] (hr*ng/mL)	AUC0-24hr[§] (hr*ng/mL)	Cmax (ng/mL)	C24hr (ng/mL)	C48hr (ng/mL)	Tmax (hr)	Apparent Terminal t1/2[%] (hr)	CL/F[%] (mL/min)
N	4	5	6	6	0	6	4	4
AM	2070	1840	323	9.23	NC	1.34	6.18	48.5
SD	992	742	103	14.8	NC	0.771	3.51	28.4
ACV (%)	47.9	40.4	32.0	160.1	NC	57.4	56.8	58.5
Med	1930	1570	330	0.00	NC	1.03	4.88	42.3
Min	1230	1170	201	0.00	NC	1.00	3.67	23.6
Max	3190	3020	479	33.6	NC	2.92	11.3	85.6
GM	1890	1730	309	NC	NC	1.22	5.57	42.6
GCV (%)	53.0	39.0	33.6	NC	NC	44.7	53.7	64.5

N:Number of observations; AM: Arithmetic mean; SD: Standard deviation; ACV%: Arithmetic Coefficient of Variation, where ACV%= (SD/AM)*100; Med: Median; Min: Minimum; Max: Maximum; GM: Geometric mean; GCV%: Geometric Coefficient of Variation, where GCV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale; NC: Not Calculated;

[†]AN # 201127 was excluded from PK parameter summary statistics due to dosing deviation.

[‡]For AN # 104463, the 0hr (End of Infusion) and 48hr samples were missing and other post dose samples are BLOQ. So PK parameters were not estimated for this subject.

[§]For AN # 104099 the AUC0-24 was not estimated due to insufficient data.

[%]Four out of 6 subjects have sufficient data in terminal phase for apparent terminal t1/2 estimation, therefore t1/2 and related PK parameters (AUC0-∞ and CL/F) were only reported for these 4 subjects.

Table 33. Descriptive Statistics of PK parameters After Single dose of 5 mg/kg by Age Cohorts (< 12 years)

Table 11-10

Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant Following Administration of 5 mg/kg (up to 150 mg) Single Dose IV Fosaprepitant Regimen in Subjects Aged 6 - < 12 Years (LOQ Values – 10.0 ng/mL)

6 to <12 Years	Summary of Aprepitant Plasma Pharmacokinetic Parameters							
	AUC0-∞‡ (hr*ng/mL)	AUC0-24hr† (hr*ng/mL)	Cmax (ng/mL)	C24hr (ng/mL)	C48hr (ng/mL)	Tmax (hr)	Apparent Terminal t1/2‡ (hr)	CL/F‡ (mL/min)
N	13	23	24	24	11	24	13	13
AM	55300	47400	4400	1210	164	2.92	9.77	42.1
SD	11900	17300	1910	1000	124	5.09	2.49	12.7
ACV (%)	21.5	36.5	43.5	83.0	75.9	174.7	25.5	30.3
Med	54000	45200	4390	867	99.6	1.00	9.33	38.0
Min	36200	21800	1960	452	18.5	0.917	5.99	22.4
Max	73200	89300	10500	4950	391	24.5	14.5	62.8
GM	54100	44700	4090	992	120	1.57	9.47	40.3
GCV (%)	22.6	36.2	39.8	61.9	112.7	114.7	26.4	31.7

N:Number of observations; AM: Arithmetic mean; SD: Standard deviation; ACV%: Arithmetic Coefficient of Variation, where ACV%= (SD/AM)*100; Med: Median; Min: Minimum; Max: Maximum; GM: Geometric mean; GCV%: Geometric Coefficient of Variation, where GCV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale;

†For AN # 104816 the 0hr (End of Infusion) and 48hr samples were missing and AUC0-24hr parameter value was excluded from summary statistics.

‡Thirteen out of 24 subjects have sufficient data in terminal phase for apparent terminal t1/2 estimation, therefore t1/2 and related PK parameters (AUC0-∞ and CL/F) were only reported for these 13 subjects.

Table 11-11

Plasma Pharmacokinetic Parameters With Descriptive Statistics for Aprepitant Following Administration of 5 mg/kg (up to 150 mg) Single Dose IV Fosaprepitant Regimen in Subjects Aged 2 to <6 Years (LOQ Values – 10.0 ng/mL)

2 to <6 Years	Summary of Aprepitant Plasma Pharmacokinetic Parameters							
	AUC0-∞† (hr*ng/mL)	AUC0-24hr (hr*ng/mL)	Cmax (ng/mL)	C24hr (ng/mL)	C48hr (ng/mL)	Tmax (hr)	Apparent Terminal t1/2† (hr)	CL/F† (mL/min)
N	20	25	25	25	20	25	20	20
AM	46400	45000	4270	1060	232	1.90	9.27	31.8
SD	18600	23800	2370	1020	471	2.16	4.17	13.8
ACV (%)	40.1	52.9	55.4	96.3	202.6	114.1	45.0	43.5
Med	42800	36100	3950	577	50.8	1.00	8.21	27.7
Min	18600	16300	1500	194	0.00	0.917	5.61	12.8
Max	100000	131000	11300	4040	1970	9.33	22.9	72.0
GM	43300	40500	3800	738	NC	1.39	8.64	29.3
GCV (%)	39.0	47.2	51.0	99.9	NC	75.3	37.2	42.6

N:Number of observations; AM: Arithmetic mean; SD: Standard deviation; ACV%: Arithmetic Coefficient of Variation, where ACV%= (SD/AM)*100; Med: Median; Min: Minimum; Max: Maximum; GM: Geometric mean; GCV%: Geometric Coefficient of Variation, where GCV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale; NC: Not Calculated;

†Twenty out of 25 subjects have sufficient data in terminal phase for apparent terminal t1/2 estimation, therefore t1/2 and related PK parameters (AUC0-∞ and CL/F) were only reported for these 20 subjects.

Table 11-12

Plasma Pharmacokinetic Parameters With Descriptive Statistics for Aprepitant Following Administration of 5 mg/kg (up to 150 mg) Single Dose IV Fosaprepitant Regimen in Subjects Aged Birth to <2 Years (LOQ Values – 10.0 ng/mL)

Birth to <2 Years	Summary of Aprepitant Plasma Pharmacokinetic Parameters							
	AUC0-∞† (hr*ng/mL)	AUC0-24hr‡ (hr*ng/mL)	Cmax (ng/mL)	C24hr‡ (ng/mL)	C48hr (ng/mL)	Tmax (hr)	Apparent Terminal t1/2† (hr)	CL/F† (mL/min)
N	16	21	22	21	10	22	16	16
AM	37200	36800	3550	691	352	2.01	7.94	24.2
SD	15800	21800	1500	852	929	2.10	2.86	11.9
ACV (%)	42.5	59.2	42.2	123.3	264.1	104.3	36.0	49.3
Med	35700	32500	3260	535	30.8	1.08	7.02	21.6
Min	12500	10200	1340	78.0	0.00	1.00	4.16	7.81
Max	81100	118000	7040	3970	2990	9.00	12.4	50.4
GM	34200	32700	3280	436	NC	1.50	7.46	21.6
GCV (%)	45.8	50.9	43.0	123.7	NC	76.5	38.0	53.8

N:Number of observations; AM: Arithmetic mean; SD: Standard deviation; ACV%: Arithmetic Coefficient of Variation, where ACV%= (SD/AM)*100; Med: Median; Min: Minimum; Max: Maximum; GM: Geometric mean; GCV%: Geometric Coefficient of Variation, where GCV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale; NC: Not Calculated;

† Sixteen out of 22 subjects have sufficient data in terminal phase for apparent terminal t1/2 estimation, therefore t1/2 and related PK parameters (AUC0-∞ and CL/F) were only reported for these 16 subjects.

‡ For AN # 103687, only 0hr (End of Infusion) sample is available and for this subject only Cmax and Tmax were reported with an assumption that Cmax was reached at the end of infusion.

Reviewer's comment: All patients enrolled in 5 mg/kg dose cohort were age > 6 months.

Concentration-time profiles of aprepitant are shown below.

Figure 11-1

Arithmetic Mean Plasma Concentration (SD) vs. Time Profiles for Aprepitant Following Administration a Single IV Fosaprepitant Dose of 150 mg, 60 mg and 20 mg in Subjects Aged 12 to 17 Years (Top = Linear Scales; Bottom = Semi-Log Scale)

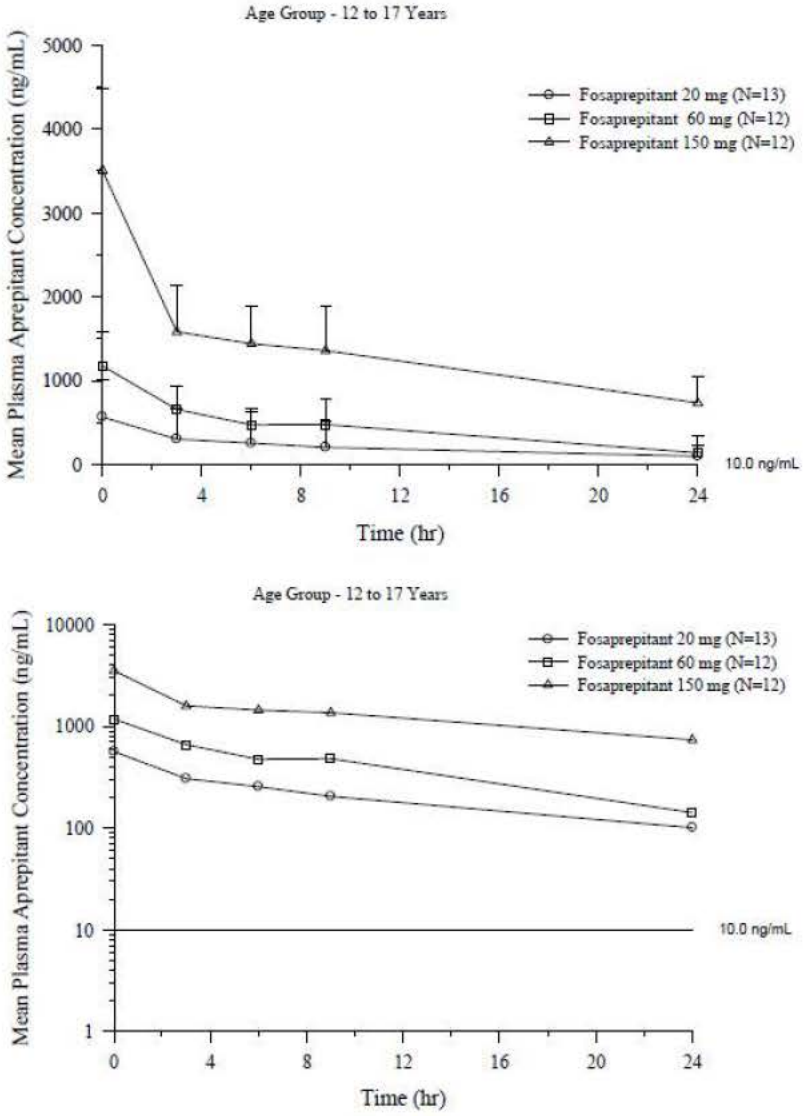


Figure 11-2

Arithmetic Mean Plasma Concentration (SD) vs. Time Profiles for Aprepitant Following Administration of a Single IV Fosaprepitant Dose of 5 mg/kg (up to 150 mg), 3 mg/kg (up to 150 mg), 1.2 mg/kg (up to 60 mg) and 0.4 mg/kg (up to10 mg) in Subjects Aged 6 to <12 Years (Top = Linear Scales; Bottom = Semi-Log Scale)

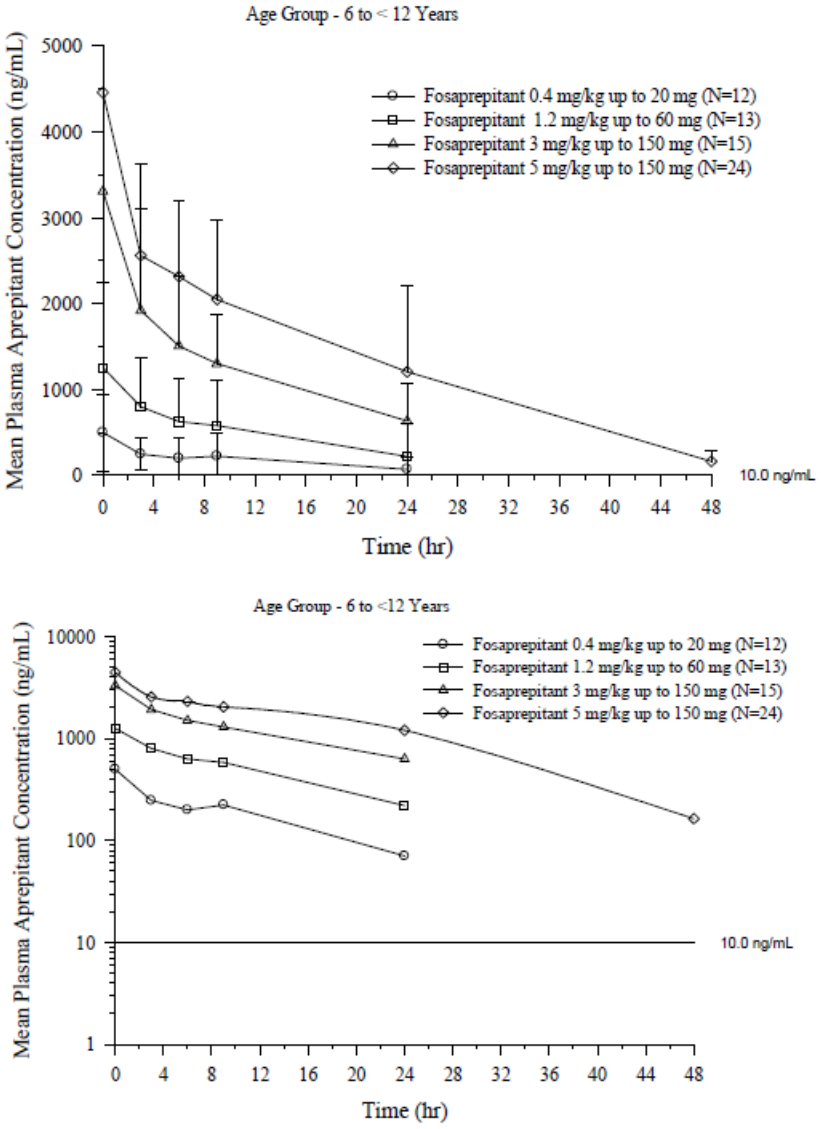


Figure 11-3

Arithmetic Mean Plasma Concentration (SD) vs. Time Profiles for Aprepitant Following Administration of a Single IV Fosaprepitant Dose of 5 mg/kg (up to 150 mg), 3 mg/kg (up to 150 mg), 1.2 mg/kg (up to 60 mg) and 0.4 mg/kg (up to10 mg) in Subjects Aged 2 to <6 Years (Top = Linear Scales; Bottom = Semi-Log Scale)

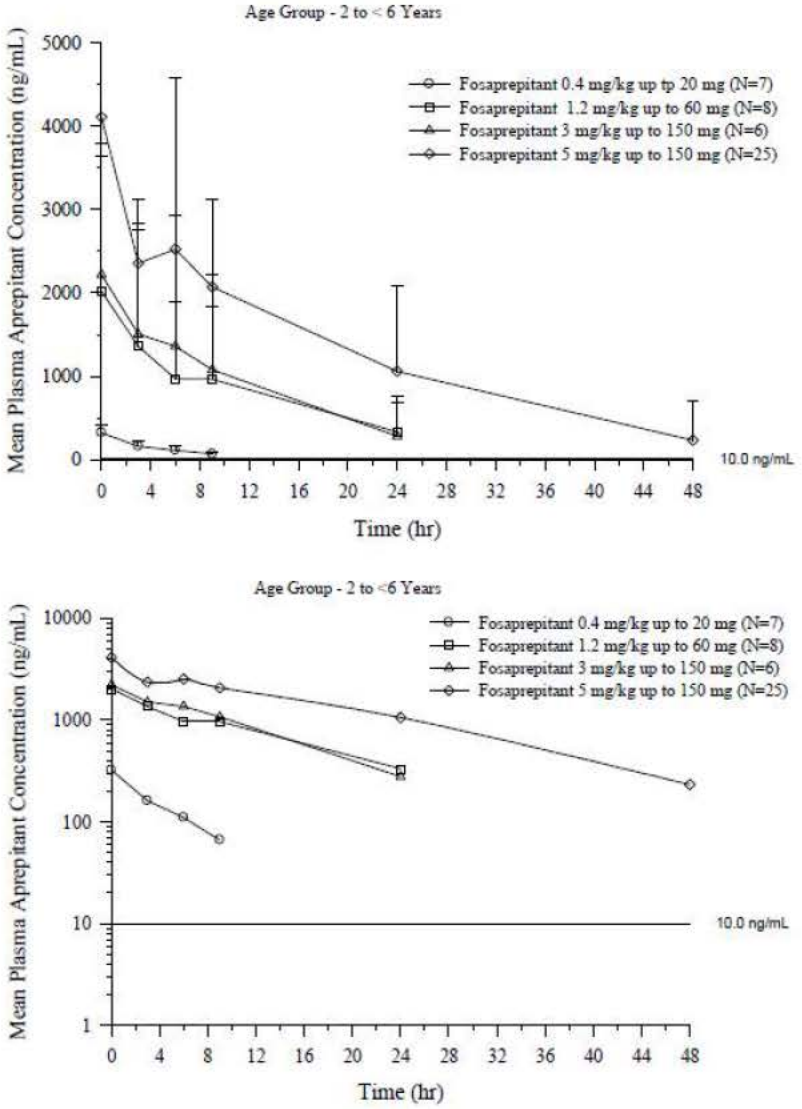
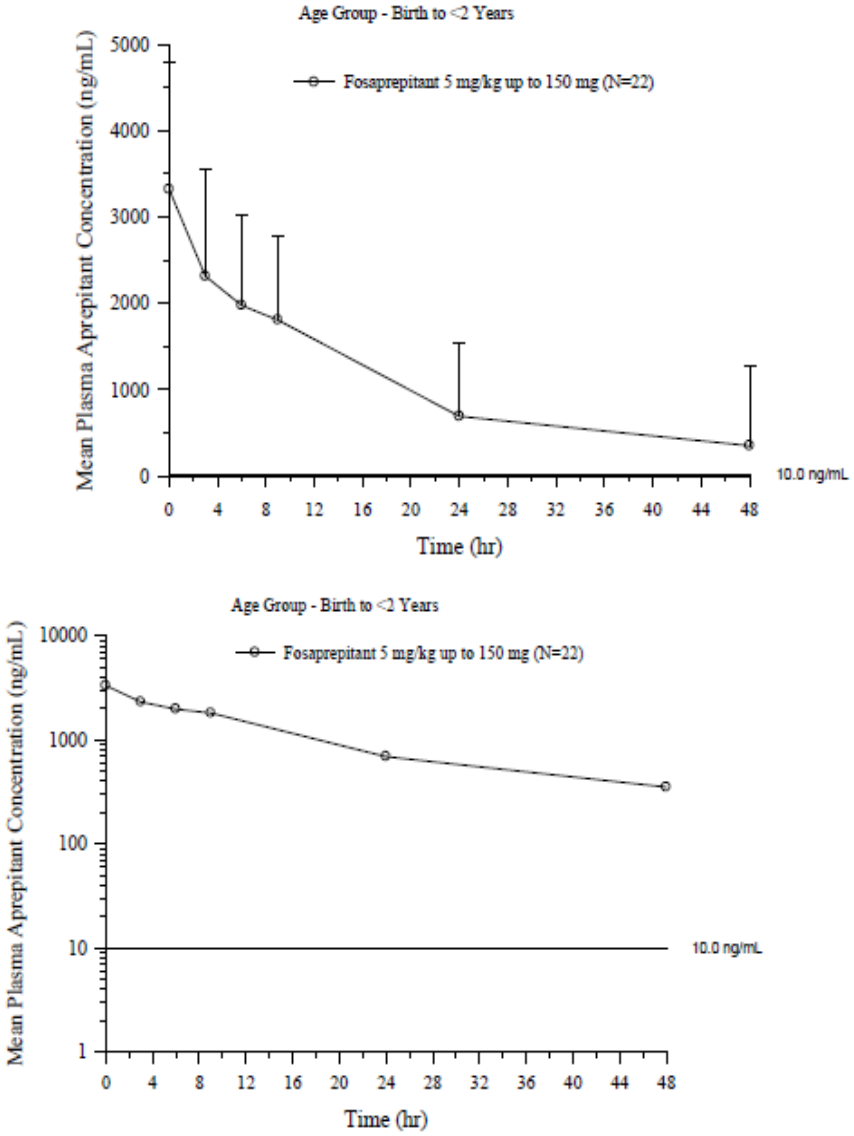


Figure 11-4

Arithmetic Mean Plasma Concentration (SD) vs. Time Profiles for Aprepitant Following Administration of a Single IV Fosaprepitant Dose of 5 mg/kg (up to 150 mg), 3 mg/kg (up to 150 mg), 1.2 mg/kg (up to 60 mg) and 0.4 mg/kg (up to10 mg) in Subjects Aged Birth to <2 Years (Top = Linear Scales; Bottom = Semi-Log Scale)

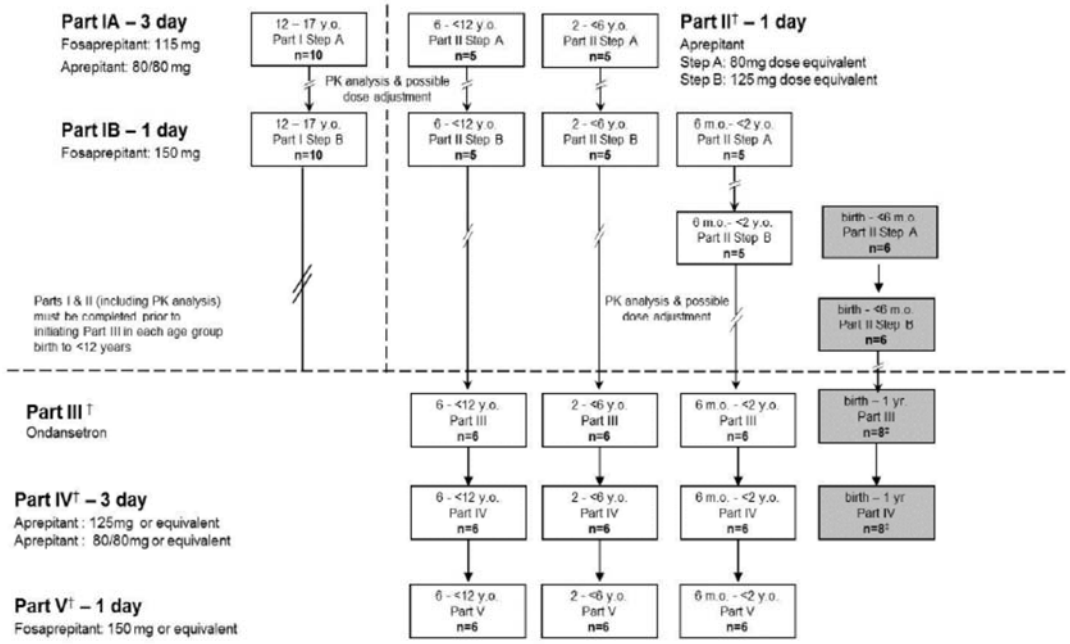


4.2.2 Study P134

Title: A Multi-center, Open-label, 5-Part Study to Evaluate the Pharmocokinetics, Safety, and Tolerability of Aprepitant and Fosaprepitant Dimeglumine in Pediatric Patients Receiving Emetogenic Chemotherapy

Study Design: This is a multi-center, open-label, 5-part study to evaluate pharmacokinetics, safety, and tolerability of oral aprepitant and intravenous fosaprepitant dimeglumine. Eligible patients were male and female, birth to 17 years of age and scheduled to receive moderately or highly emetogenic chemotherapy or a chemotherapy regimen not previously tolerated due to nausea and/or vomiting for a documented malignancy.

Study Schematic



† Patients in Part II Steps A and B >6 months old were expected to be unique patients. Patients in Parts III, IV, and V were expected to be the same patients undergoing subsequent rounds of chemotherapy.

‡ Enrollment in the birth to 1-year cohort into Parts III and IV for dexamethasone evaluation were expected to include approximately 2 patients each from the following age groups: birth to 2 months, 2 to 4 months, 4 to 8 months, and 8 to 12 months.

Note: Patients <1 year in the 6-month to 2-year cohort may have had dexamethasone PK samples obtained (as applicable) but they were not required to do so; none were collected. Shaded cohorts were not enrolled.

Reviewer's comment: No PK data were collected from patients < 6 months old.

Treatment groups using fosaprepitant are summarized below by the reviewer:

						Age range (yr)			
Part	**Step**	**Route**	**Dose on Day 1**	**Regimen**	**Oral dose‡ on Days 2 and 3**	**12 to 17**	**6 to 12**	**2 to 6**	**0.5 to 2**
I	A	IV	115 mg	3-day	80	√			
I	B	IV	150 mg	1-day	--	√			
V	--	IV	3mg/kg	1-day	--		√	√	√
‡: Emend oral suspension was used; √: age group dosed									

Reviewer's comment: PK data from PO aprepitant regimens (Part II and IV) and the analytical methods for aprepitant were reviewed when they were submitted to NDA 207865 for the approval of oral suspension for pediatric patients. Refer to Clinical Pharmacology Review of NDA 207865.

Pharmacokinetic analysis

Aprepitant: The blood sampling schemes for aprepitant PK are as follows:

Part I, Step A: Predose, -45, -30, -15, 0 minutes (start of chemotherapy), 1.5, 3, 4, 6, 8, 24, 48, 72 hours post start of chemotherapy on Day 1 for aprepitant and/or fosaprepitant PK.

Part I, Step B: Predose, -45 minutes, -30 minutes, 0 minutes (start of chemotherapy), 30 minutes, and 1.5, 3, 4, 6, 8, 24, 48, 72 hours post start of chemotherapy on Day 1 for aprepitant and/or fosaprepitant PK.

Part V: Predose, -45, -30, 0 minutes (start of chemotherapy) and 30 minutes, 1.5, 3, 4, 6, 8, 24, 48, 72 hours post start of chemotherapy on Day 1.

Fosaprepitant: The blood sampling for fosaprepitant PK were collected in Part I Step A and Part V:

Part I, Step B: pre-dose, -45 min (immediately after the 30 min infusion of fosaprepitant), 30 min prior to the start of chemotherapy, 0 min (at start of chemotherapy) and at 30 minutes from the start of chemotherapy.

Part V: pre-dose, -45 min (immediately after the 60 min fosaprepitant infusion), -30 min (prior to chemotherapy), 0 min (start of chemotherapy).

Pharmacokinetic Results

Demographics:

Table 34. The Demographic Data of Patients Enrolled in the Fosaprepitant Cohorts

<Part I>

	Fosaprepitant (115 mg) Regimen (Step A)		Fosaprepitant (150 mg) Regimen (Step B)	
	n	(%)	n	(%)
Subjects in population	12		11	
Gender				
Male	5	(41.7)	4	(36.4)
Female	7	(58.3)	7	(63.6)
Age (Months)				
12 to 17 years	12	(100.0)	11	(100.0)
Mean	164.9		185.7	
SD	14.9		19.9	
Median	160.0		183.0	
Range	150 to 190		148 to 215	
Race				
Asian	0	(0.0)	1	(9.1)
Black Or African American	1	(8.3)	1	(9.1)
Multi-Racial	2	(16.7)	2	(18.2)
White	9	(75.0)	7	(63.6)
Ethnicity				
Hispanic Or Latino	6	(50.0)	9	(81.8)
Not Hispanic Or Latino	6	(50.0)	2	(18.2)
History of Motion Sickness				
No	6	(50.0)	11	(100.0)
Yes	5	(41.7)	0	(0.0)
Unknown	1	(8.3)	0	(0.0)

<Part V>

	Fosaprepitant Regimen (Part V)	
	n	(%)
Subjects in population	23	
Gender		
Male	7	(30.4)
Female	16	(69.6)
Age (Months)		
6 months to <2 years	7	(30.4)
2 to <6 years	8	(34.8)
6 to <12 years	8	(34.8)
Mean	57.8	
SD	39.6	
Median	49.0	
Range	11 to 123	
Race		
Asian	1	(4.3)
Black Or African American	1	(4.3)
Multi-Racial	10	(43.5)
White	11	(47.8)
Ethnicity		
Hispanic Or Latino	9	(39.1)
Not Hispanic Or Latino	14	(60.9)
History of Motion Sickness		
No	23	(100.0)
Yes	0	(0.0)
Unknown	0	(0.0)
History of Vomiting Post Chemotherapy		
No	6	(26.1)
Yes	17	(73.9)

4.2.2.1 Summary of PK parameters of aprepitant – Part I, Step A (Adolescents)

Patients received single IV dose of 115 mg fosaprepitant on Day 1 followed by 80 mg oral aprepitant on Days 2 and 3.

The descriptive statistics of the PK parameters estimated by non-compartmental analysis are provided in the table below.

Table 35. Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant (MK-0869) Following Administration of a 3-Day Regimen that includes 115 mg IV Fosaprepitant on Day 1 Followed by 80 mg Oral Aprepitant on Days 2 and 3 to 12- to 17-Year-Old Patients Undergoing Chemotherapy

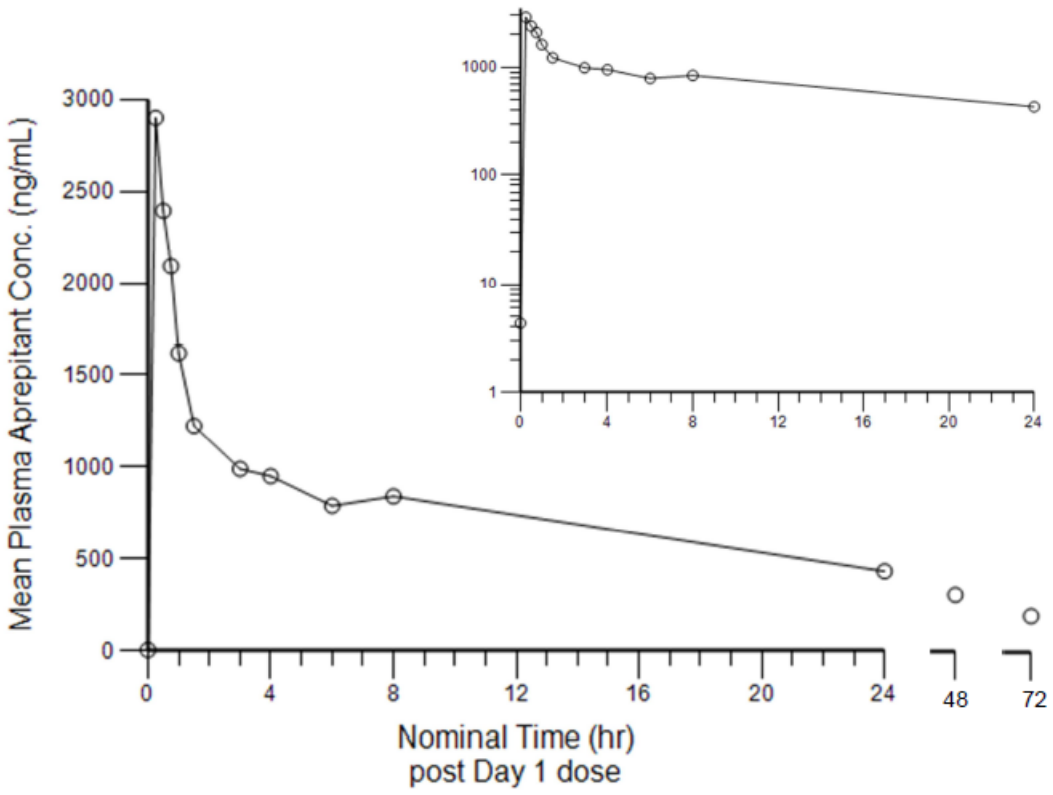
12- to 17-Year-Olds	Cmax (ng/ml)	Tmax (hr)	C_{24hr} (ng/mL)	$t_{½}^{\#}$ (hr)	CL (ml/hr)	AUC_{0-24hr} (hr*ng/ml)	C_{48hr} (ng/mL)	C_{72hr} (ng/mL)
N	12	12	8	6	5	8	10	11
AM	3240	0.41	433	11.0	6310	19500	310	199
SD	1280	0.27	318	4.42	2750	8010	288	281
Min	1650	0.25	133	6.87	3140	9940	66.2	BLQ
Median	3080	0.25	407	10.2	7210	19300	171	84.9
Max	6210	1.00	1120	19.2	8880	33100	904	796
"CV%	39.4	65.9	73.6	40.2	43.6	41.1	93.1	141
HM	2840	0.31	284	9.84	5210	16700	151	--
Pseudo SD	1060	0.12	200	3.25	2830	7200	118	--
GM	3030	0.35	348	10.4	5760	18000	210	--
*CV%	39.4	57.81	80.0	37.7	52.9	44.4	117	--
Adults (Protocol 012L1)						$AUC_{0-\infty}$		
AM	3267					31724		
SD	1159					14287		
GM	3095					29611		

Pseudo SD = Jackknife estimate of the standard deviation of the harmonic mean.
N: Number of observations; AM: Arithmetic Mean; SD: Standard Deviation.
BLQ = Below limit of quantitation (<10.0 ng/mL); BLQ values have been considered as zero for calculation of descriptive statistics.
Min: Minimum; Max: Maximum; GM: Geometric Mean; HM: Harmonic Mean.
"CV%: Arithmetic Coefficient of Variation, where "CV% = SD/AM*100.
*CV%: Geometric Coefficient of Variation, where *CV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale.
#: (Apparent) terminal half-life.
= Not evaluable since λz could not be estimated from the available data.
† excluded from descriptive statistics since samples were taken after next day dose.
§ excluded from descriptive statistics since AUC%extrap >25% of total AUC (AUC0-∞).
ß excluded from descriptive statistics since t1/2 > tlast.

Source data: Study P134 CSR, Table 11-1

The mean concentration-time profile in linear and semi-log scales is show in the figure below.

Figure 9. The Mean Concentration-Time Profile of Aprepitant. Inset Represents the Profile in Semi-Log Scale.



Source data: Study P134 CSR, Figure 11-1

4.2.2.2 Summary of PK parameters of aprepitant – Part I, Step B (Adolescents)

Patients received single IV dose of 150 mg fosaprepitant on Day 1 only.

The descriptive statistics of the PK parameters estimated by non-compartmental is shown in the table below.

Table 36. Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant (MK-0869) Following Administration of a Single Day IV Regimen at a Dose of 150 mg Fosaprepitant (MK-0517) to 12- to 17-Year-Old Patients Undergoing Chemotherapy

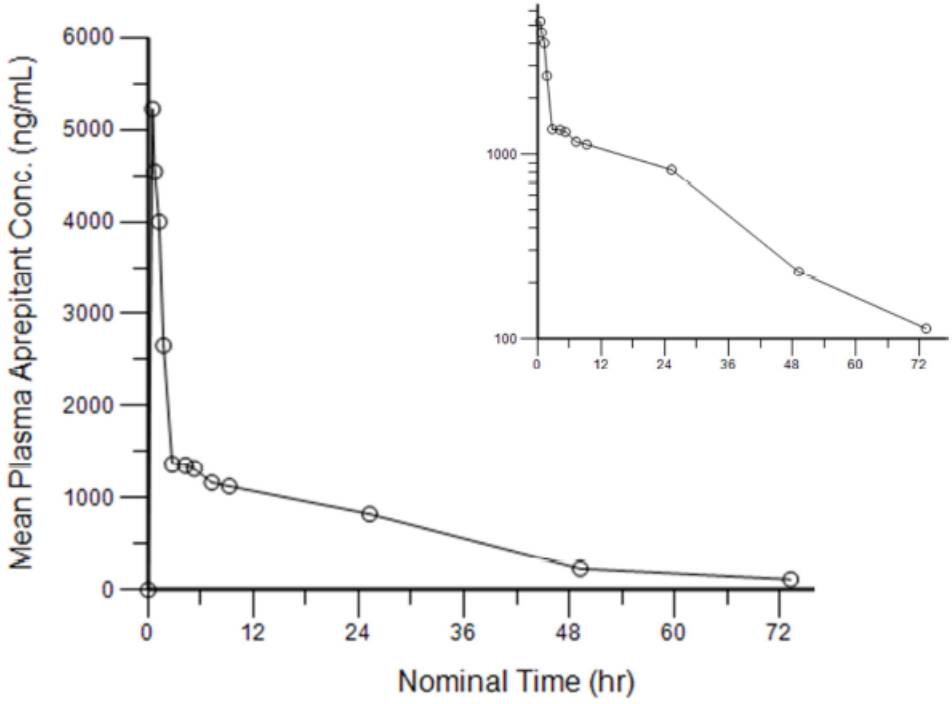
	Cmax (ng/mL)	Tmax (hr)	C_{24hr} (ng/mL)	C_{48hr} (ng/mL)	C_{72hr} (ng/mL)	$t_{½}^{\#}$ (hr)	CL (mL/hr)	AUC_{0-24hr} (hr*ng/mL)	AUC_{0-48hr} (hr*ng/mL)	AUC_{0-72hr} (hr*ng/mL)	$AUC_{0-\infty}$ (hr*ng/mL)
12- to 17-Year-Olds											
N	11	11	11	10	11	11	8	11	11	11	8
AM	5870	0.64	825	230	114	22.2	3750	30800	42300	46900	43600
SD	2770	0.30	321	324	186	19.8	1390	7020	11600	15900	11700
Min	2880	0.50	413	BLQ	BLQ	7.91	2630	17800	21300	21500	21700
Median	4960	0.50	742	112	14.5	12.1	3450	31000	42200	43700	43500
Max	12300	1.50	1360	1080	498	67.8	6920	42200	64200	83000	57000
"CV%	47.1	46.7	38.9	141	164	89.3	37.1	22.8	27.5	34.0	26.8
HM	4980	0.58	718	--	--	13.8	3440	29100	39100	42100	40000
Pseudo SD	1980	0.14	284	--	--	7.49	907	8250	13500	16700	16200
GM	5380	0.60	769	--	--	16.8	3570	30000	40800	44500	42000
*CV%	44.8	35.27	40.9	--	--	84.7	32.2	25.3	30.2	35.5	32.2
Adults (Protocol 165)											
AM	4145							25105			
SD	1152							5778			

Pseudo SD = Jackknife estimate of the standard deviation of the harmonic mean.
N: Number of observations; AM: Arithmetic Mean; SD: Standard Deviation.
BLQ = Below limit of quantitation (<10.0 ng/mL); BLQ values have been considered as zero for calculation of descriptive statistics;
Min: Minimum; Max: Maximum; GM: Geometric Mean; HM: Harmonic Mean.
"CV%: Arithmetic Coefficient of Variation, where "CV% = SD/AM*100.
*CV%: Geometric Coefficient of Variation, where *CV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale.
#: (Apparent) terminal half-life.
* excluded from descriptive statistics since AUC% extrap >25% of total AUC (AUC0-∞).
† excluded from descriptive statistics since sample result > 2 times higher than the predicted concentration by the best fitted terminal slope without this value.

Source data: Study P134 CSR, Table 11-2

The mean concentration-time profile in linear and semi-log scales is show in the figure below.

Figure 10. The Mean Concentration-Time Profile of Aprepitant. Inset Represents the Profile in Semi-Log Scale.



Source data: Study P134 CSR, Figure 11-2

4.2.2.3 Summary of PK parameters of fosaprepitant – Part I, Step B (Adolecents)

Table 37. Summary Plasma Fosaprepitant Cmax and Tmax Values Following IV Administration of 150 mg Fosaprepitant in 12- to 17-Year-Old Patients Undergoing Chemotherapy

	Tmax (hr)	Cmax (ng/ml)
N	11	11
Mean	0.614	1310
SD	0.251	964
Min	0.500	26.6
Median	0.500	1020
Max	1.33	3300
CV%"	40.9	73.9
Geometric Mean	0.583	851
CV%* Geometric Mean	30.9	207

Although individual parameters and descriptive statistics are reported to three significant digits, descriptive statistics are calculated from the un-rounded parameters;

AN: Allocation Number; N: Number of observations; AM: Arithmetic Mean; SD: Standard Deviation;

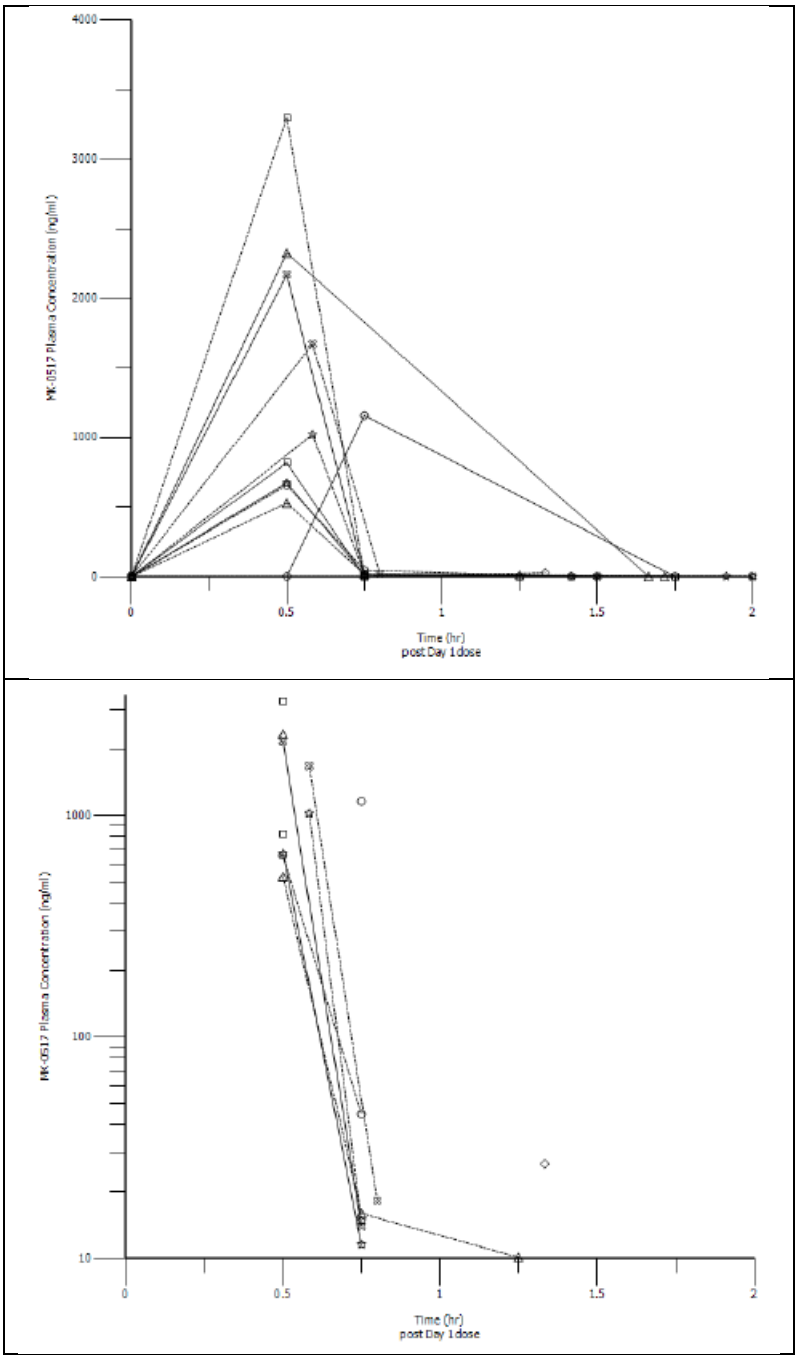
"CV%: Arithmetic Coefficient of Variation, where "CV% = SD/AM*100;

*CV%: Geometric Coefficient of Variation, where *CV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale;

Min: Minimum; Max: Maximum; GM: Geometric Mean

Source data: Study P134 CSR, Table 11-3

Figure 11. The Individual Concentration-Time Profile of Fosaprepitant. Top panel: Linear Scale; Bottom Panel: Semi-log Scale.



Source data: Study P134 CSR, Figures 14-3 and 14-4

4.2.2.4 Summary of PK parameters of aprepitant – Part V

Patients age 6 months to < 12 years received single IV dose of 3 mg/kg fosaprepitant.

The descriptive statistics of the PK parameters estimated by non-compartmental analysis in different age groups (6mon - 2yr, 2-6 years, 6 to < 12 years) were provided in the tables below.

Table 38. Plasma Pharmacokinetic Parameters with Descriptive Statistics for Aprepitant (MK-0869) Following Administration of a Single Day IV Regimen at a Dose of 3 mg/kg Fosaprepitant (MK-0517) to 6-Month- to <12-Year-Old Patients Undergoing Chemotherapy

	Cmax (ng/ml)	Tmax (hr)	C_{24hr} (ng/mL)	C_{48hr} (ng/mL)	C_{72hr} (ng/mL)	$t_{½}^{\#}$ (hr)	CL (ml/hr)	AUC_{0-24hr} (hr*ng/ml)	AUC_{0-48hr} (hr*ng/ml)	AUC_{0-72hr} (hr*ng/ml)	$AUC_{0-\infty}$ (hr*ng/ml)
6-Month- to <2-Year-Olds											
N	7	7	6	6	6	6	6	6	6	6	6
AM	1700	1.13	150	--$^{\downarrow}$	--$^{\downarrow}$	7.71	5010	11700	13300	13800	13800
SD	636	0.17	103	--$^{\downarrow}$	--$^{\downarrow}$	3.10	6270	6980	7770	7940	7980
Min	838	1.00	BLQ	BLQ	BLQ	2.76	1580	1810	1890	1890	1760
Median	1730	1.00	169	BLQ	BLQ	7.74	2280	11300	13900	14600	14800
Max	2470	1.42	282	50.8	19.8	12.4	17600	19800	21900	22100	22100
"CV%	37.4	15.4	69.0	--$^{\downarrow}$	--$^{\downarrow}$	40.3	125	59.7	58.3	57.7	57.8
HM	1460	1.11	--	--	--	6.24	2560	6120	6640	6750	6470
Pseudo SD	723	0.16	--	--	--	4.96	1370	12500	15100	15900	16600
GM	1580	1.12	--	--	--	7.05	3250	9170	10400	10700	10600
*CV%	44.8	15.01	--	--	--	53.6	113	110	116	118	123

	Cmax (ng/ml)	Tmax (hr)	C_{24hr} (ng/mL)	C_{48hr} (ng/mL)	C_{72hr} (ng/mL)	$t_{½}^{\#}$ (hr)	CL (ml/hr)	AUC_{0-24hr} (hr*ng/ml)	AUC_{0-48hr} (hr*ng/ml)	AUC_{0-72hr} (hr*ng/ml)	$AUC_{0-\infty}$ (hr*ng/ml)
2- to <6-Year-Olds											
N	7	7	7	7	7	7	6	7	7	7	6
AM	2430	1.41	184	--$^{\downarrow}$	--$^{\downarrow}$	6.44	3460	18300	20600	21100	23400
SD	1100	0.83	189	--$^{\downarrow}$	--$^{\downarrow}$	2.35	2680	11100	12900	13200	12800
Min	1260	1.00	BLQ	BLQ	BLQ	3.69	1370	6190	6890	6890	7350
Median	2570	1.03	182	BLQ	BLQ	5.94	1990	20600	22400	23200	25400
Max	3880	3.27	462	114	22.1	10.9	7000	36000	40000	40200	40200
"CV%	45.3	58.8	102	--$^{\downarrow}$	--$^{\downarrow}$	36.4	77.3	60.6	62.5	62.5	54.7
HM	1990	1.20	--	--	--	5.81	2270	12400	13400	13600	16100
Pseudo SD	972	0.34	--	--	--	2.00	1250	8950	9900	10200	13700
GM	2200	1.28	--	--	--	6.11	2730	15200	16800	17100	19800
*CV%	51.6	44.84	--	--	--	35.7	84.3	78.2	83.4	84.7	77.2

	Cmax (ng/ml)	Tmax (hr)	C_{24hr} (ng/mL)	C_{48hr} (ng/mL)	C_{72hr} (ng/mL)	$t_{½}^{\#}$ (hr)	CL (ml/hr)	AUC_{0-24hr} (hr*ng/ml)	AUC_{0-48hr} (hr*ng/ml)	AUC_{0-72hr} (hr*ng/ml)	AUC(0-∞) (hr*ng/ml)
6- to <12-Year-Olds											
N	8	8	8	8	8	8	8	8	8	8	8
AM	2850	1.07	308	37.5	--$^{\downarrow}$	8.76	3590	19500	23100	24000	24100
SD	641	0.11	240	56.5	--$^{\downarrow}$	3.34	1880	6720	9660	10500	11100
Min	1800	1.00	100	BLQ	BLQ	5.73	1460	14000	15200	15300	15400
Median	2830	1.00	210	16.2	BLQ	7.49	3360	16300	19700	20500	20800
Max	3630	1.25	751	159	92.5	14.4	7670	34000	44700	47800	49500
"CV%	22.5	10.5	77.8	151	--$^{\downarrow}$	38.1	52.3	34.4	41.8	43.9	46.0
HM	2710	1.06	192	--	--	7.89	2900	18000	20700	21300	21300
Pseudo SD	730	0.10	128	--	--	2.40	1570	4580	6100	6450	6560
GM	2780	1.07	239	--	--	8.28	3220	18700	21700	22400	22500
*CV%	24.5	10.11	87.5	--	--	35.8	52.6	30.7	36.5	38.0	39.3
Adults (Protocol 165)											
AM	4145							25105			
SD	1152							5778			

Pseudo SD = Jackknife estimate of the standard deviation of the harmonic mean.

N: Number of observations; AM: Arithmetic Mean; SD: Standard Deviation; HM: Harmonic Mean; Min: Minimum; Max: Maximum; GM: Geometric Mean..

BLQ = Below limit of quantitation (<10.0 ng/mL); BLQ values have been considered as zero for calculation of descriptive statistics.

"CV%: Arithmetic Coefficient of Variation, where "CV% = SD/AM*100.

*CV%: Geometric Coefficient of Variation, where *CV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale.

#: (Apparent) terminal half-life.

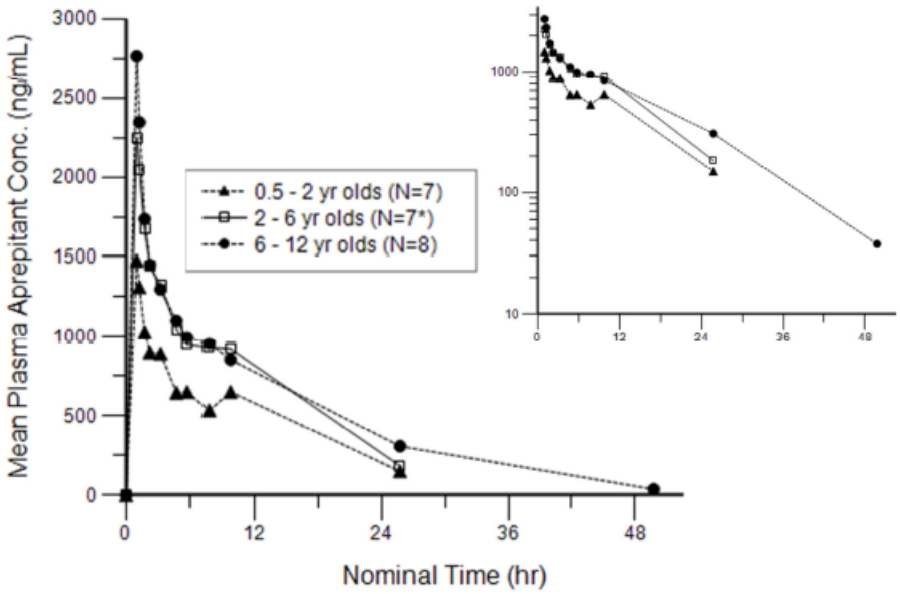
C24, C48 and C72 refer to concentrations 24hr, 48hr and 72hr after start chemotherapy, resp. (i.e. 25.75hr, 49.75hr and 73.75hr after start fosaprepitant infusion, resp.).

$^{\downarrow}$ Not reportable since <50% of the concentration results ≥ Lower Limit of Quantitation (LLOQ).

In some cases AUC0-∞ results are < AUC0-72 results. This can be explained by the fact that AUC0-∞ is calculated based on the last predicted concentration, i.e., concentration at the final observation time estimated using the linear regression performed to estimate λz. Whereas AUC0-72 is calculated based on interpolation only.

Source data: Study P134 CSR, Tables 11-13, 11-14, and 11-15

Figure 12. Mean Plasma Concentration vs. Time Profiles for Aprepitant (MK-0869) Following Administration of a Single Day IV Regimen at a Dose of 3 mg/kg Fosaprepitant (MK-0517) to 6-Month- to <12-Year-Old Patients Undergoing Chemotherapy. The profiles in semi-log scale are in the inlet.



Source data: Study P134 CSR, Figure 11-5

4.2.2.5 Summary of PK parameters of fosaprepitant – Part V

Table 39. Summary of Plasma Fosaprepitant Cmax and Tmax Values Following IV Administration of 3 mg/kg Fosaprepitant by Age Group

Age Range		Tmax (hr)	Cmax (ng/mL)
6 Months to <2 Years Old	N	7	7
	Mean	1.13	2756
	SD	0.175	3364
	Min	1.00	20.2
	Median	1.00	159
	Max	1.42	7260
	CV%	15.4	122
	Geometric Mean	1.12	494
	CV% Geometric Mean	15.0	2138
2 to <6 Years Old	N	7	8
	Mean	1.05	3034
	SD	0.089	1718
	Min	1.00	BLQ
	Median	1.02	3292
	Max	1.25	5237
	CV%	8.5	56.6
	Geometric Mean	1.05	NR
	CV% Geometric Mean	7.92	NR
6 to <12 Years Old	N	8	8
	Mean	1.04	1654
	SD	0.088	1995
	Min	1.00	357
	Median	1.00	910
	Max	1.25	6202
	CV%	8.50	121
	Geometric Mean	1.04	1009
	CV% Geometric Mean	7.91	133

Although individual parameters and descriptive statistics are reported to three significant digits, descriptive statistics are calculated from the un-rounded parameters.

N: Number of observations; AM: Arithmetic Mean; SD: Standard Deviation.

BLQ = Below limit of quantitation (<10.0 ng/mL); BLQ values have been considered as zero for calculation of descriptive statistics.

Min: Minimum; Max: Maximum; GM: Geometric Mean.

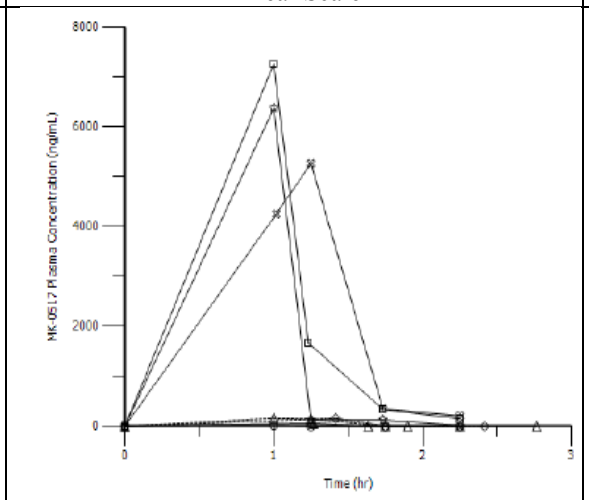
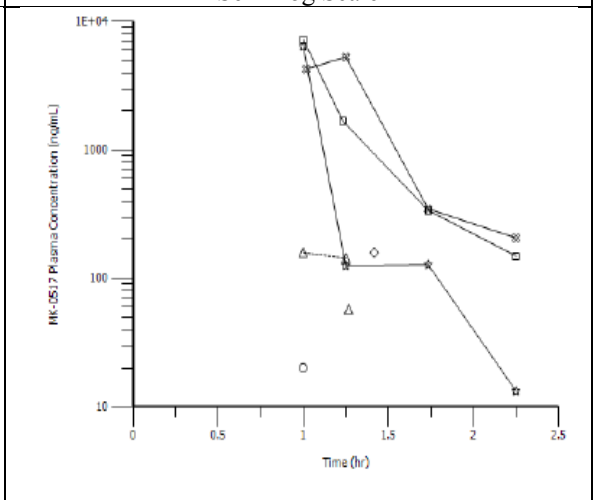
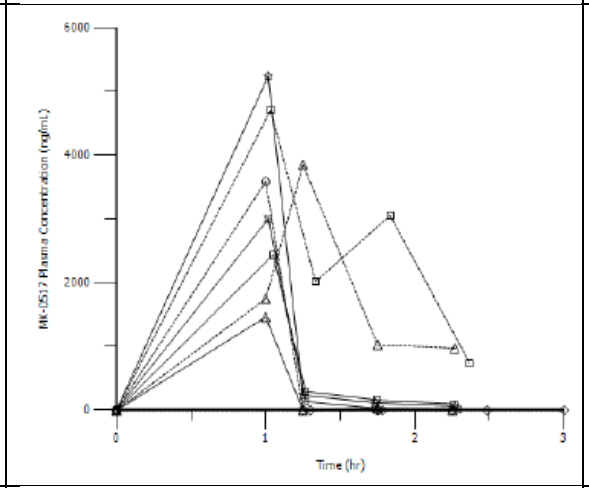
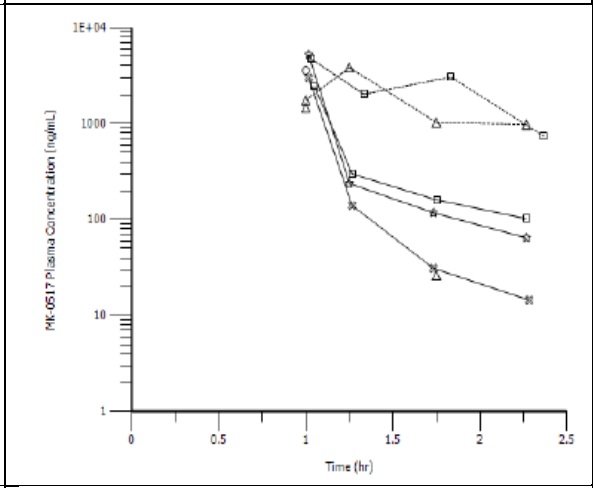
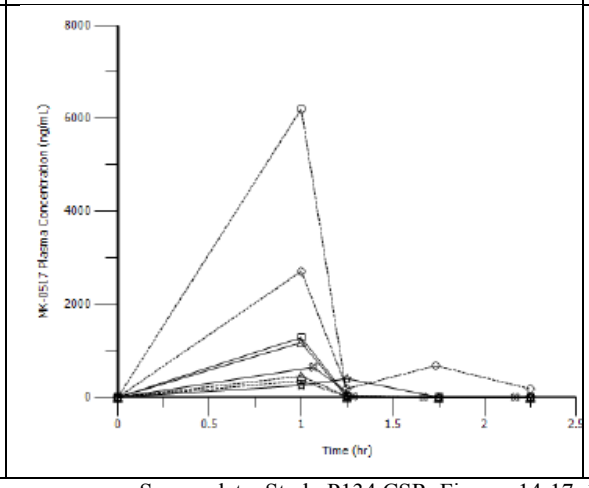
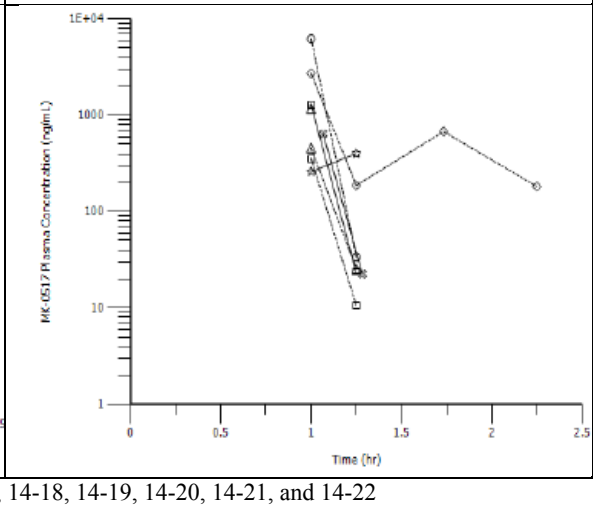
"CV%: Arithmetic Coefficient of Variation, where "CV% = SD/AM*100.

*CV%: Geometric Coefficient of Variation, where *CV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale.

NR: Not reportable since <50% of the concentration results > Lower Limit of Quantitation (LLOQ).

Source data: Study P134 CSR, Table 11-16

Figure 13. The Individual Concentration-Time Profile of Fosaprepitant by Age Groups

	Linear Scale	Semi-log Scale
0.5 to < 2 years		
2 to < 6 years		
6 to < 12 years		

Source data: Study P134 CSR, Figures 14-17, 14-18, 14-19, 14-20, 14-21, and 14-22

4.3. Pharmacometrics Review

4.3.1 Sponsor's Analysis

In this section, the sponsor's verbatim text and figures are in normal font. The reviewer's comments are in Italic.

4.3.1.1 Objectives

- Update the existing population PK model of aprepitant after aprepitant/fosaprepitant administration using final clinical data from studies P097, P134, P148 and P029 and assess the impact of key covariates (including demographics, oral and IV formulations) in CINV / PONV patients;
- Evaluate / validate the updated population PK model to insure its accuracy, precision and robustness;
- Perform model-based simulations to determine the appropriate single-(1) day and 3-day dosing regimens of fosaprepitant by assessing PK exposure of aprepitant in targeted age groups of pediatric patients (i.e., <2 years old, 2 to <6 years old, 6 to <12 years old, 12 to <18 years old).

4.3.1.2 Datasets

Concentration-time data of aprepitant collected from 316 pediatric subjects with PONV and CINV from clinical studies P097, P148, P134 and P029 were used to construct the population PK model.

- Protocol P097 CINV, a PK/PD study in adolescents aged 12 – 17 years receiving the adult 3-day oral dosing regimen (final market capsules, 125 mg on Day 1, 80 mg on Days 2-3).
- Protocol P134 CINV, a study in adolescents aged 12 – 17 years receiving the adult 3-day IV EMEND regimen (115 mg IV EMEND on Day 1, 80 mg oral suspension EMEND on Days 2-3), and single doses of aprepitant as oral suspension to pediatric patients aged 6 months – 12 years (doses adjusted by body size);
- Protocol P148 Post-operative induced nausea and vomiting (PONV), a study in adolescents aged 12 – 17 years receiving the adult 40 mg capsule single dose, and pediatrics aged 2 – 12 years receiving single doses of aprepitant as oral suspension (doses adjusted by body size).

Table 40. Summary of Continuous Demographic Data at Baseline (Summarized by Age Groups)

Continuous Covariates	Continuous Covariates Mean (CV%) Median [Minimum-Maximum]			
	<2 years N=52	2 to <6 years N=81	6 to <12 years N=96	12 to ≤19 years N=87
Age (years)	1.20 (35.7) 1.17 [0.500-1.92]	4.05 (29.0) 4.08 [2.00-5.92]	9.17 (18.4) 9.33 [6.00-11.9]	14.7 (11.4) 14.5 [12.0-19.0]
Body mass index (kg/m^2)	16.9 (11.3) 16.8 [12.3-21.0]	15.4 (12.9) 15.2 [11.8-24.4]	17.0 (20.3) 16.2 [11.6-28.3]	20.2 (22.0) 19.6 [12.5-34.3]
Height (cm)	76.4 (8.7) 77.6 [63.5-88.0]	101 (9.5) 101 [83.0-125]	136 (8.9) 135 [112-165]	165 (5.3) 163 [146-185]
Weight (kg)	9.94 (18.1) 9.95 [6.80-14.3]	15.8 (23.0) 15.4 [9.20-33.8]	32.0 (31.8) 29.7 [15.9-68.4]	55.3 (26.4) 54.4 [32.0-104]

CV= Coefficient of variation; N= Number of subjects
Note 1: Interim data of Study P029 was used to derive the descriptive statistics. Note 2: SUBJID=# (b) (6) (Study P029, 8.3 years old, female) was included in the interim data but was excluded from the final data since the dose was not adequately captured. The patient characteristics of this subject are included in the descriptive statistics.

Source data: Population PK and Simulation Report, Table 4

Table 41. Summary of Categorical Demographic Data (Summarized by Age Groups)

Categorical Covariates		Count (%) of Subjects in Sub-Population			
		<2 years N=52	2 to <6 years N=81	6 to <12 years N=96	12 to ≤19 years N=87
Race	White	34(65.4%)	66(81.5%)	84(87.5%)	68(78.2%)
	Black	1(1.92%)	3(3.70%)	3(3.13%)	5(5.75%)
	Asian	7(13.5%)	4(4.94%)	5(5.21%)	2(2.30%)
	American Indian/native	1(1.92%)	0	0	1(1.15%)
	Multi/Other	9(17.3%)	8(9.88%)	4(4.17%)	11(12.6%)
Sex	Male	28(53.8%)	36(44.4%)	49(51.0%)	53(60.9%)
	Female	24(46.2%)	45(55.6%)	47(49.0%)	34(39.1%)

N= Number of subjects
Note 1: Interim data of Study P029 was used to derive the descriptive statistics. Note 2: SUBJID=# (b) (6) Study P029, 8.3 years old, female) was included in the interim data but was excluded from the final data since the dose was not adequately captured. The patient characteristics of this subject are included in the descriptive statistics.

Source data: Population PK and Simulation Report, Table 5

4.3.1.3 Model

All PK data were evaluated using nonlinear mixed-effects modeling implemented in NONMEN v7.3 with first order conditional estimation (FOCE) interaction and Perl speaks NONMEM (PsN) v4.4.8 software. Dataset preparation, exploration and visualization of the data were performed using R® V3.3.1 with comprehensive R archive network (CRAN) and Certara Strategic Consulting (CSC) packages.

The population pharmacokinetic model previously developed based on final locked data of studies P097 P134 and P148 with was used as a starting point.

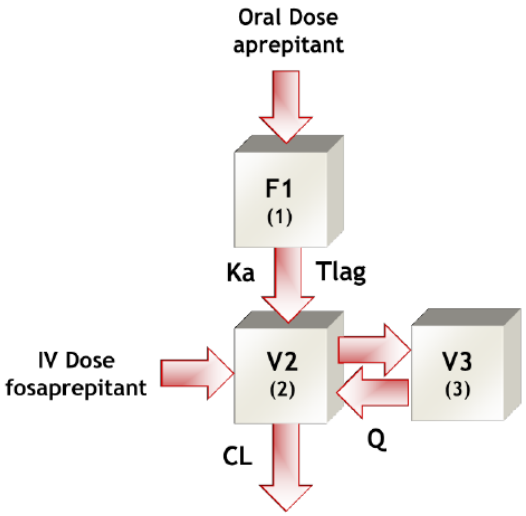
Reviewer's comment: This model was used to support the approval of oral Emend in pediatric patients. Refer to Clinical Pharmacology Review of NDA21549/S-025 (Efficacy Supplement of Emend oral capsules) and original NDA 207865 (Emend oral suspension) for details.

The structural model was a 2-compartment linear model with first-order rate of absorption and lag-time of absorption. The structural model included 1) effect of formulation on Tlag to adequately capture the delay caused by the degradation of the capsule administrated to adolescents (Study P097); 2) an allometric component accounting for body size (i.e. parameters were scaled to WT/70 using a power of 0.75 for clearances and a power of 1 for volumes).

Fosaprepitant with molecular weight of 614.4 g/mol is rapidly converted to the active drug, aprepitant (molecular weight of 534.44 g/mol), following IV administration. In NONMEM control files, the doses of fosaprepitant were scaled using a conversion factor of 534.44 / 614.4.

ADVAN4 and TRANS4 NONMEM subroutines were used to allow for a closed-form solution and simultaneous fit of oral (aprepitant) and IV (fosaprepitant) data, as well as relative bioavailability estimation. Log10-transformed concentration data and actual observation time were used as the model input. Log-additive model for the residual error allowed using FOCE estimation method without INTERACTION term.

Table 42. The Schematic Drawing of the Structure Model



CL = Systemic clearance; F1 = Relative bioavailability for oral administration; Ka = First-order constant of absorption; Tlag = Lag-time of absorption; Q = Inter-compartmental clearance; V2 = Central volume of distribution; V3 = Peripheral volume of distribution
Note: Compartment (1) represents the depot compartment (2) represents central compartment and compartment (3) – peripheral compartment.

Source data: Population PK and Simulation Report, Figure 2

The final population PK model included the following covariate effects:

- Age on V2: × (Age/8)-0.205 with 95CI%= (-0.288, -0.122),
- Dose on CL: × (Dose/80)-0.253 with 95CI%= (-0.333, -0.172)
- Formulation on Ka with capsule (P097) for reference: × exp(0.369) for suspension (P134) with 95%CI=(-0.363, 1.10) and × exp(0.821) for suspension for excipients (P148) with 95CI%= (0.0228, 1.62)
- Reduced level of EDTA (P029) on CL: × exp(-0.295) for Study P029 with 95%CI=(-0.421, -0.168)

4.3.1.4 Results

4.3.1.4.1 Base model

Table 43. Typical Values for the Structure (Base) Population PK Model of Aprepitant/Fosaprepitant

Parameter	Units	Estimate	SE	RSE	Shrinkage	Equation
OFV		-4037.3347				
CL	L/h	5.25	0.228	4.4%		$CL = tvCL \times (Weight/70)^{0.75} \times \exp(\eta_{CL})$
V2	L	46.3	5.96	12.9%		$V2 = tvV2 \times (Weight/70) \times \exp(\eta_{V2})$
Q	L/h	45.3	12.1	26.6%		$Q = tvQ \times (Weight/70)^{0.75} \times \exp(\eta_{Q})$
V3	L	41.5	6.53	15.7%		$V3 = tvV3 \times (Weight/70) \times \exp(\eta_{V3})$
Ka	1/h	0.588	0.0887	15.1%		$Ka = tvKa \times \exp(\eta_{Ka})$
Tlag – suspension	h	0	fixed	.		Tlag = 0
Tlag - capsule	h	0.947	0.0216	2.3%		Tlag = Caps_Tlag
F1		0.839	0.0606	7.2%		$F1 = tvF1 \times \exp(\eta_{F1})$
IIV CL		64.7%	0.0619	14.8%	10.2%	ω^2_{CL}
IIV V2		65.5%	0.0782	18.2%	22.7%	ω^2_{V2}
IIV Q		84.0%	0.273	38.6%	59.6%	ω^2_{Q}
IIV V3		54.4%	0.0849	28.7%	35.9%	ω^2_{V3}
IIV Ka		108.4%	0.253	21.5%	51.0%	ω^2_{Ka}
IIV F1		56.4%	0.101	31.9%	51.2%	ω^2_{F1}
Log10ResErr		0.161	.		17.6%	$\log_{10}(C_{obs}) = \log_{10}(C_{pred}) + Log10ResErr$

CL = Systemic clearance; F1 = Relative bioavailability for oral administration; IIV = Inter-individual variability; Ka = First-order rate constant of absorption; Log10ResErr= Log-Additive Residual Error; OFV = Objective function value; Q = Inter-compartmental clearance; RSE= Relative standard error; SE= Standard error; Tlag = Lag-time of absorption; tvF1 = Typical value of relative bioavailability for oral administration; tvCL = Typical value of systemic clearance; tvKa = Typical value of first-order rate constant of absorption; tvQ = Typical value of inter-compartmental clearance; tvV2= Typical value of central volume of distribution; tvV3= Typical value of peripheral volume of distribution; V2 = Central volume of distribution; V3 = Peripheral volume of distribution.
Note: IIV CV% were calculated as $100\% \times (\omega^2)^{0.5}$.

Source data: Population PK and Simulation Report (04lvbw), Table I-1

4.3.1.4.2 Final model

Table 44. Typical Values for the Final Population PK Model of Aprepitant/Fosaprepitant

Parameter	Units	Estimate	SE	RSE	Shrink	Equation
OFV		-4123.2978				
CL	L/h	5.38	0.363	6.7%		$CL = tvCL \times (WT/70)^{0.75} \times Effect_{Dose} \times \exp(\eta CL)$
V2	L	47.8	4.94	10.3%		$V2 = tvV2 \times (WT/70) \times Effect_{AGE} \times \exp(\eta V2)$
Q	L/h	35.6	8.52	23.9%		$Q = tvQ \times (WT/70)^{0.75} \times \exp(\eta Q)$
V3	L	37.9	4.48	11.8%		$V3 = tvV3 \times (WT/70) \times \exp(\eta V3)$
Ka	1/h	0.319	0.118	37.2%		$Ka = tvKa \times Effect_{Form} \times \exp(\eta Ka)$
Tlag - Capsule	h	0.938	0.0272	2.9%		Tlag = Caps_Tlag
Tlag - Suspension	h	0 fix				
F1		0.918	0.0803	8.7%		$F1 = tvF1 \times \exp(\eta F1)$
Dose_CL		-0.253	0.0410	16.2%		$Effect_{Dose} = (Dose/80)^{Dose\_CL}$
AGE_V2		-0.205	0.0424	20.7%		$Effect_{AGE} = (Age/8)^{AGE\_V2}$
Form_Ka (suspension, study 134)		0.369	0.374	101.3%		Ka=Ka×exp(Form_Ka)
Form_Ka (Excipients, study 148)		0.821	0.407	49.6%		Ka=Ka×exp(Form_Ka)
EDTA_CL (study 029)		-0.295	0.0645	21.9%		CL=CL× exp(EDTA_CL for low – P029)
IIV CL		0.369(60.7%)	.0564	15.3%	11.0%	ω^2_{CL}
IIV V2		0.346(58.8%)	0.0641	18.5%	21.4%	ω^2_{V2}
IIV Q		0.521(72.2%)	0.257	49.4%	64.5%	ω^2_{Q}
IIV V3		0.380(61.6%)	0.0934	24.6%	34.1%	ω^2_{V3}
IIV Ka		1.07(103.6%)	0.231	21.6%	50.2%	ω^2_{Ka}
IIV Tlag		0.00	fixed;			ω^2_{Tlag}
IIV F1		0.304(55.1%)	0.0969	31.9%	51.3%	ω^2_{F1}
Log10ResErr		0.159		.	17.2%	log10(Cobs) = log10(Cpred)+Log10ResErr

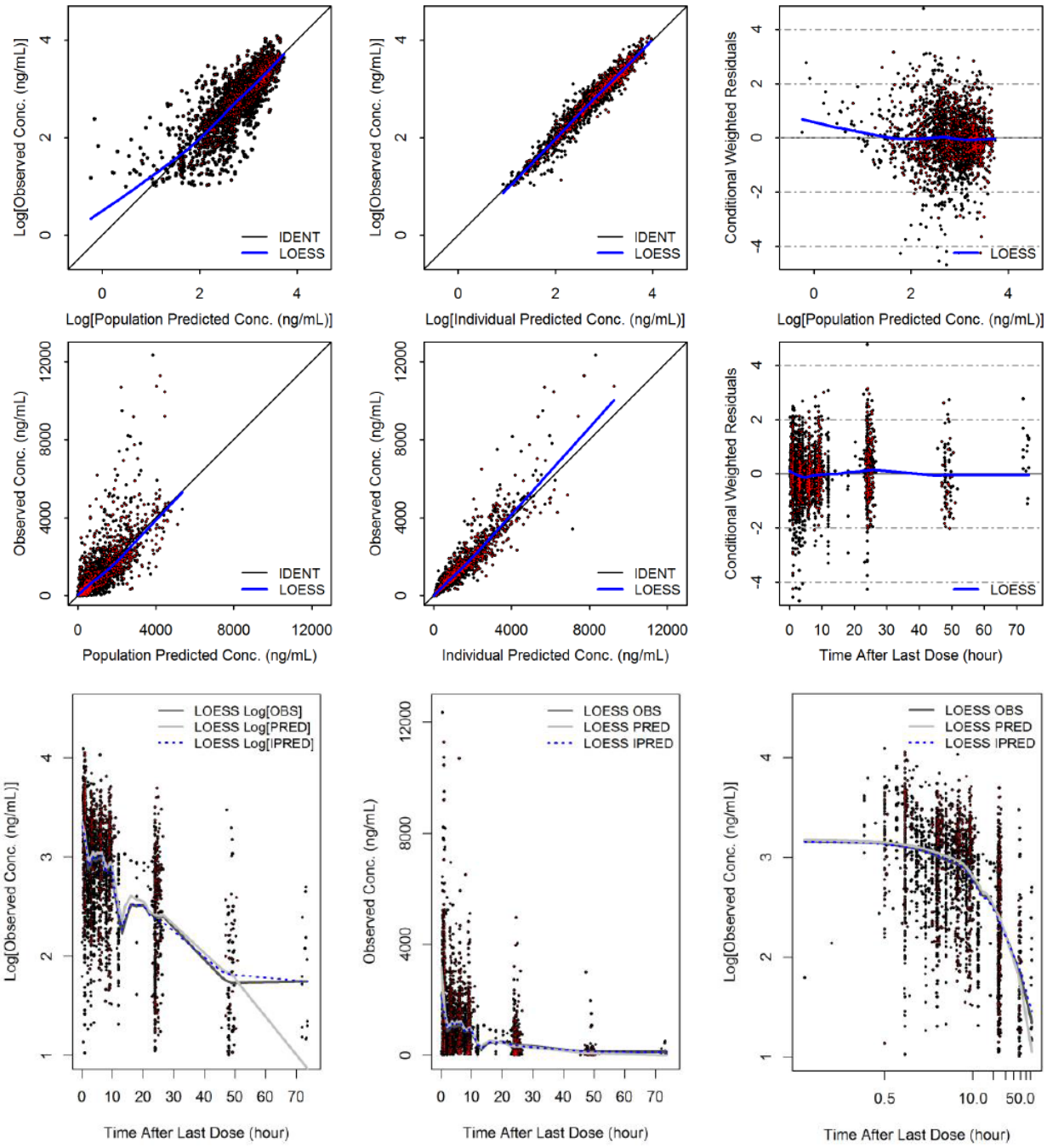
AGE_V2= Effect of age on central volume of distribution; CL = Systemic clearance; Dose_CL= Effect of dose on systemic clearance; EDTA_CL= Effect of ethylenediaminetetraacetic acid on systemic clearance; F1 = Relative bioavailability for oral administration; Form_Ka= Effect of formulation on the first-order rate constant of absorption; IIV = Inter-individual variability; Ka = First-order rate constant of absorption; Log10ResErr= Log-Additive Residual Error; OFV = Objective function value; Q = Inter-compartmental clearance; RSE= Relative standard error; SE= Standard error; Tlag = Lag-time of absorption; tvF1 = Typical value of relative bioavailability for oral administration; tvCL = Typical value of systemic clearance; tvKa = Typical value of first-order rate constant of absorption; tvQ = Typical value of inter-compartmental clearance; tvV2= Typical value of central volume of distribution; tvV3= Typical value of peripheral volume of distribution; V2 = Central volume of distribution; V3 = Peripheral volume of distribution.

Note: IIV CV% were calculated as $100\% \times (\omega^2)^{0.5}$.

Source data: Population PK and Simulation Report, Table I- 5

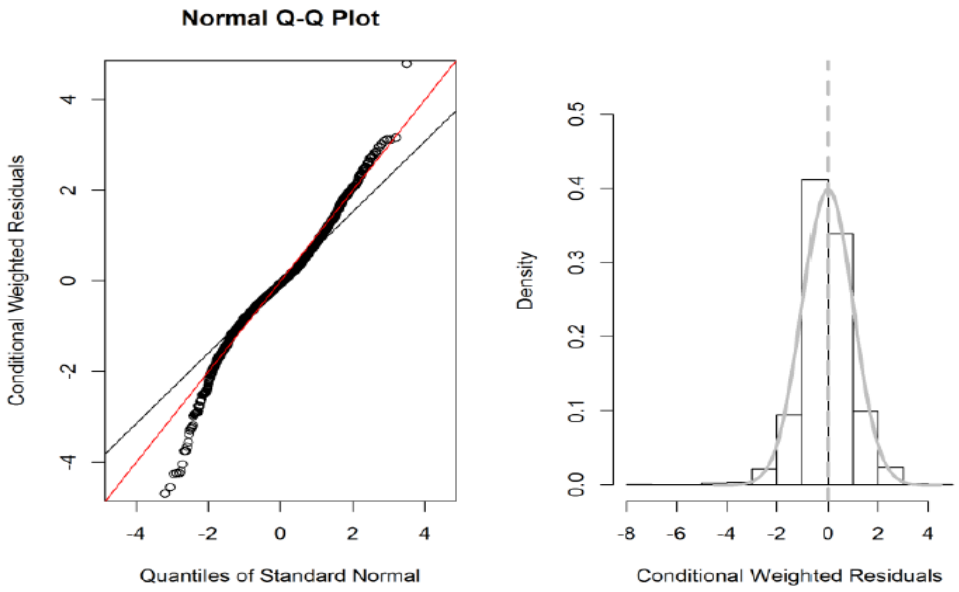
4.3.1.4.3 Model Evaluation

Figure 14. Diagnostic Plots for Final Population Pharmacokinetic Model of Aprepitant in Pediatric Population: Goodness-of-Fit



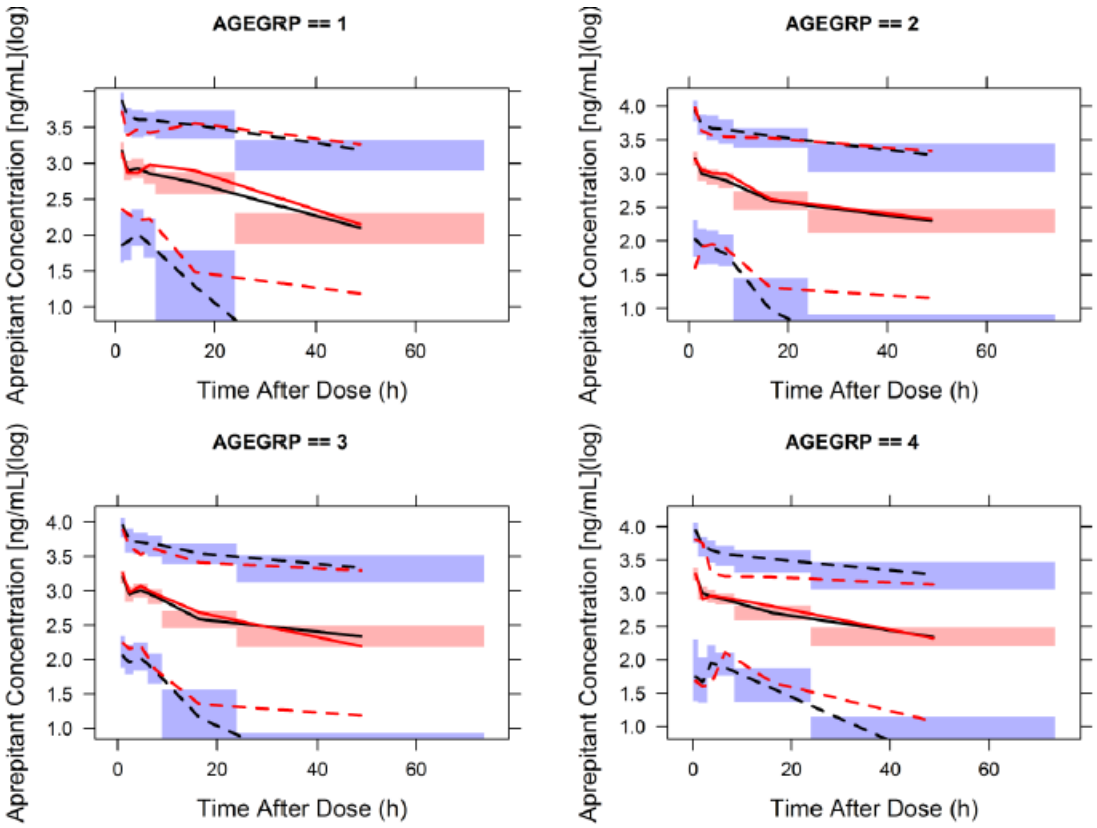
Source data: Table I-42, Table I-43

Figure 15. Diagnostic Plots for Final Population Pharmacokinetic Model of Aprepitant in Pediatric Population: Goodness-of-Fit



Source data: Table I-44

Figure 16. Visual Predictive Check – Final Population PK Model (Linear Scale, Locked Data P029)



AGEGRP = Age group.
Note 1: AGEGRP=1: subjects with <2 years; AGEGRP=2: subjects with 2 to <6 years; AGEGRP=3: subjects with 6 to <12 years; AGEGRP=4: subjects with 12 to ≤19 years.

Note 2: Full and dashed red lines represent 2.5th, 50th and 95th percentiles of observed aprepitant concentrations within each bin; shaded area represent 95% percentile interval of percentiles of predicted concentrations (50th percentiles are in red and 2.5th and 97.5th percentiles in blue).

The visual predictive check (VPC) plot showed that the observed 2.5th, 50th and 97.5th percentiles of concentrations in each age bin were almost all within the 95%CI of the corresponding simulated percentiles. However, the 2.5th percentile of the observed concentration 24 hour after the dose was higher than the 95%CI of the simulated 2.5th percentiles and the simulated concentrations after 24 h under-estimated the observed concentrations. Due to the limited number of PK samples in this time range (*Reviewer's note: only Cmin at Hour 24, 48, and 72 were measured in all the pediatric studies*).

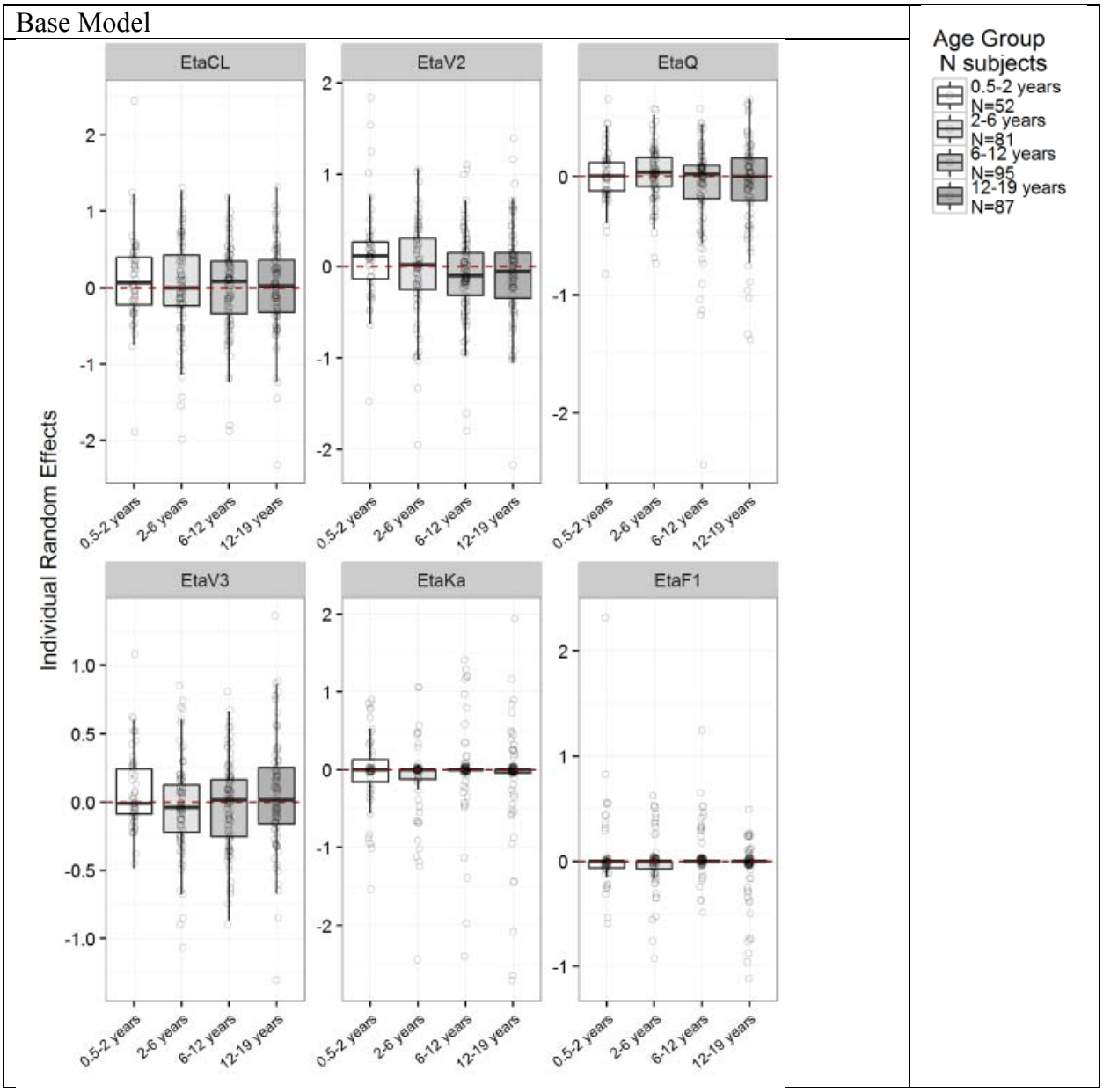
Reviewer's comment: The VPC was conducted following single dose of IV fosaprepitant and compared to the observed data from Study P029, a single-dose dose ranging study. This is acceptable as P029 enrolled all age groups. For all the pediatric studies, only single IV doses of fosaprepitant were used.

4.3.1.4.4 Covariates Effect

The final population PK model included the following covariate effects:

- Age on V2: × (Age/8)-0.205 with 95CI%= (-0.288, -0.122),
- Dose on CL: × (Dose/80)-0.253 with 95CI%= (-0.333, -0.172)
- Formulation on Ka with capsule (P097) for reference: × exp(0.369) for suspension (P134) with 95%CI=(-0.363, 1.10) and × exp(0.821) for suspension for excipients (P148) with 95CI%= (0.0228, 1.62)
- Reduced level of EDTA (P029) on CL: × exp(-0.295) for Study P029 with 95%CI=(-0.421, -0.168)

Figure 17. Relationship between Age and Individual Random Effect – Base vs. Final Population PK Model



Final Model

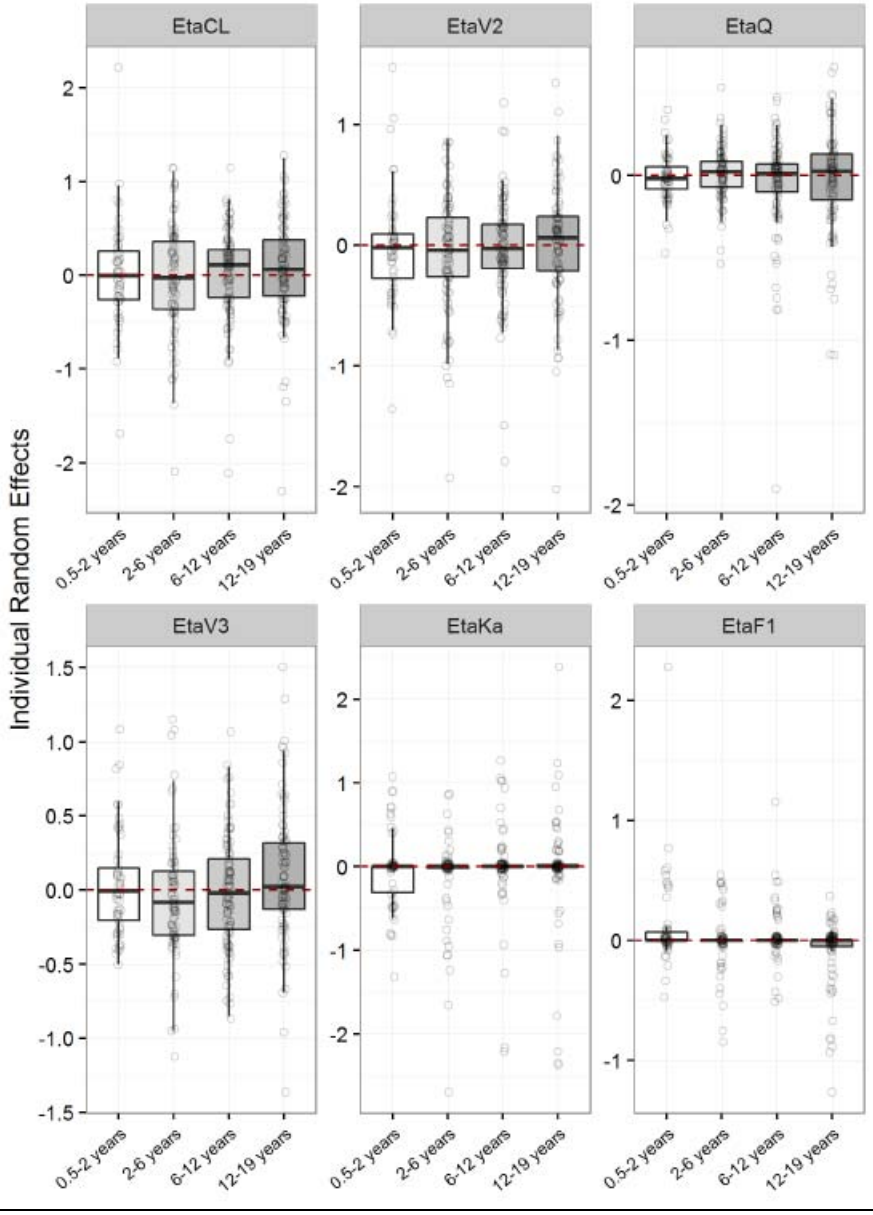
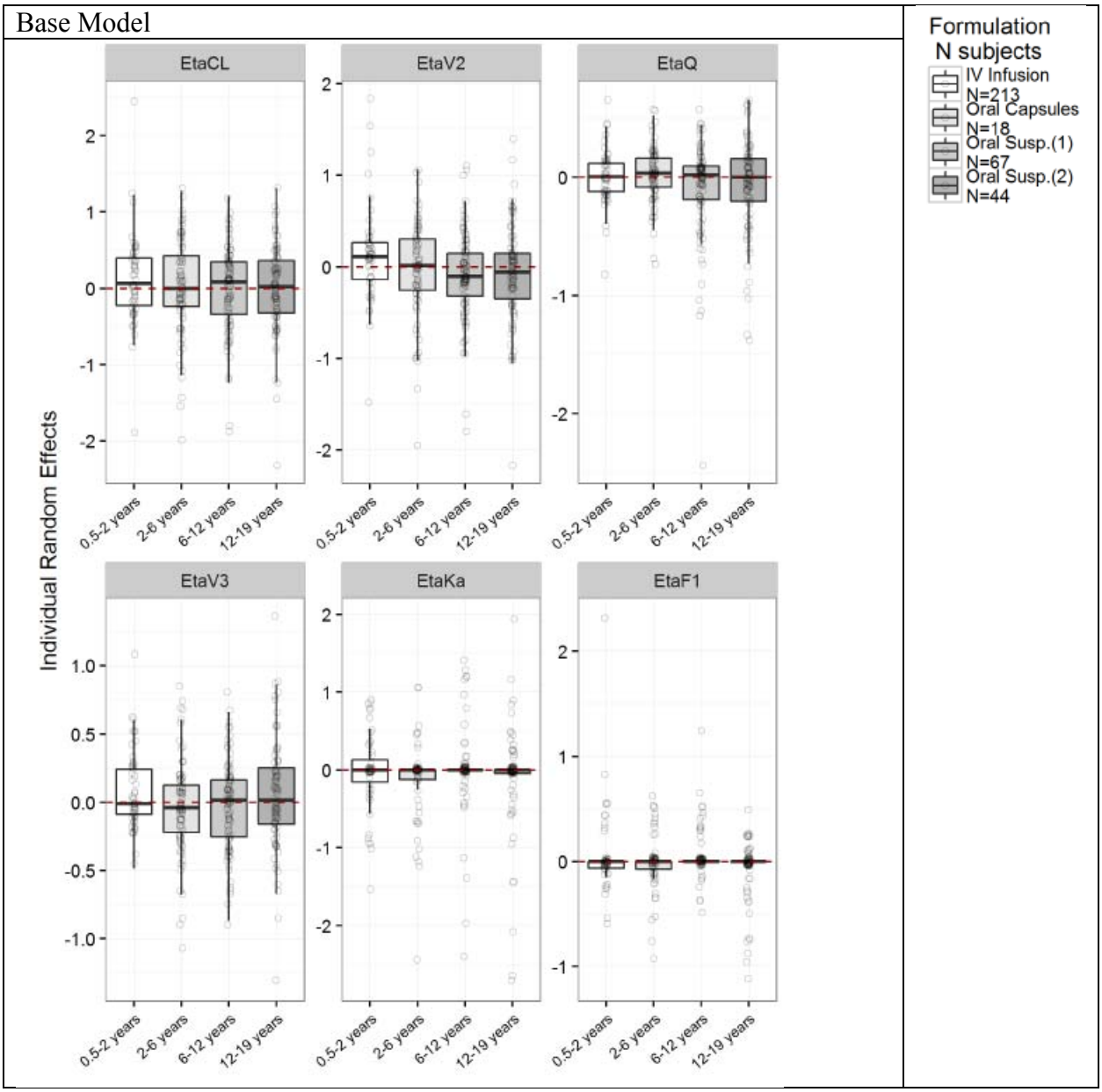

EtaCL
EtaV2
EtaQ
EtaV3
EtaKa
EtaF1
Individual Random Effects
0.5-2 years
2-6 years
6-12 years
12-19 years

Figure 18. Relationship between Formulation and Individual Random Effect – Base vs. Final Population PK Model



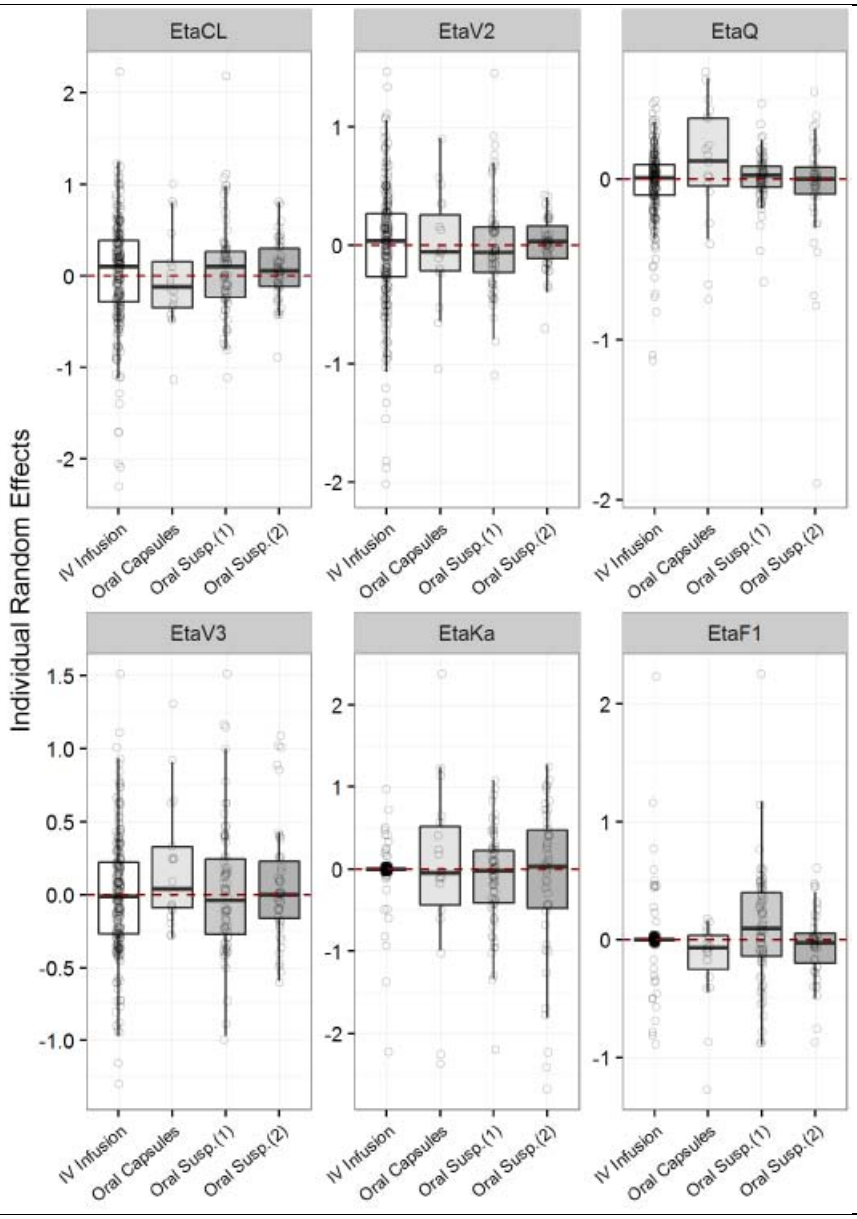
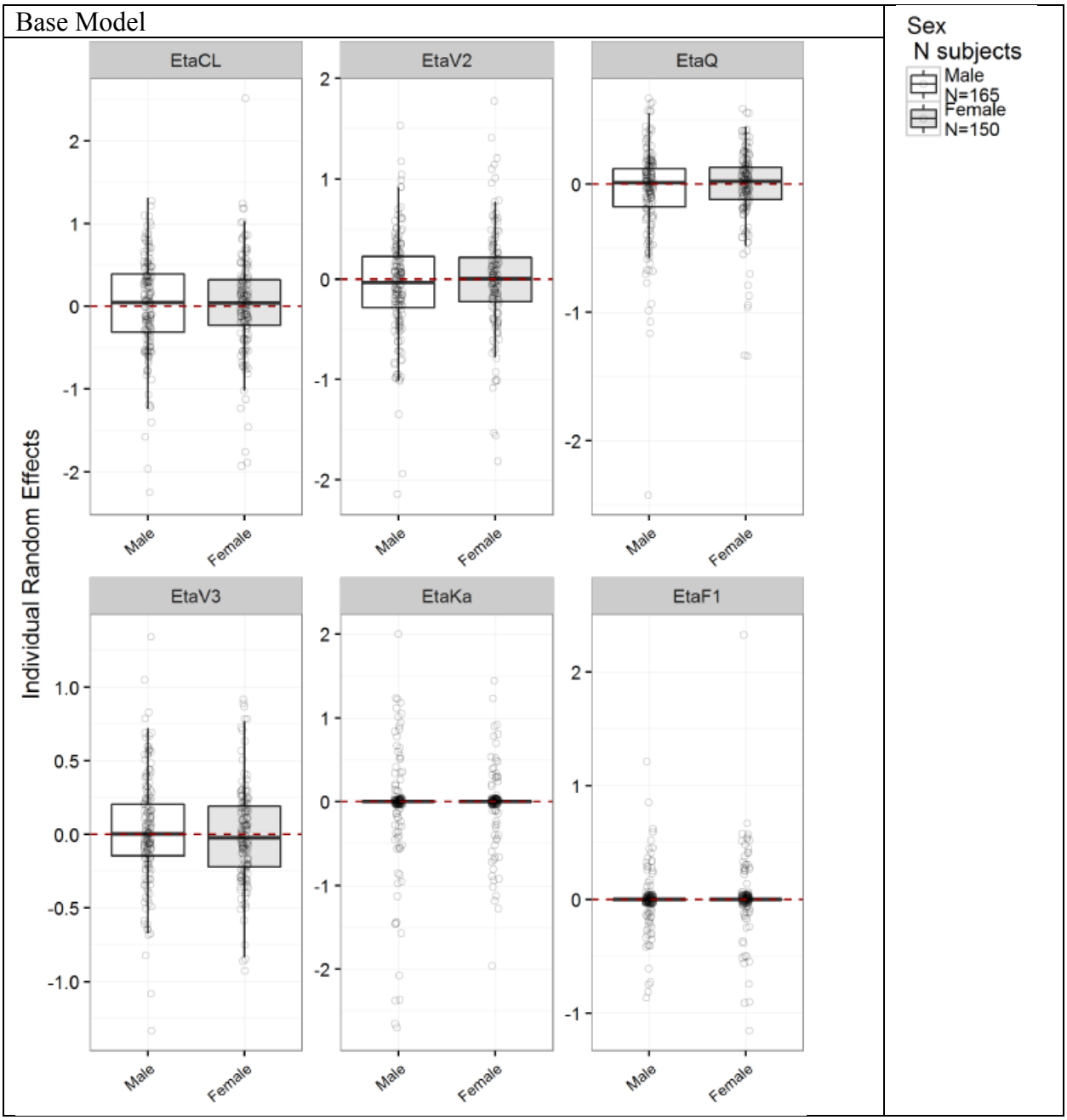
Final Model	
 EtaCL EtaV2 EtaQ EtaV3 EtaKa EtaF1 Individual Random Effects IV Infusion Oral Capsules Oral Susp.(1) Oral Susp.(2)	

Figure 19. Relationship between Sex and Individual Random Effect – Base vs. Final Population PK Model



Final Model

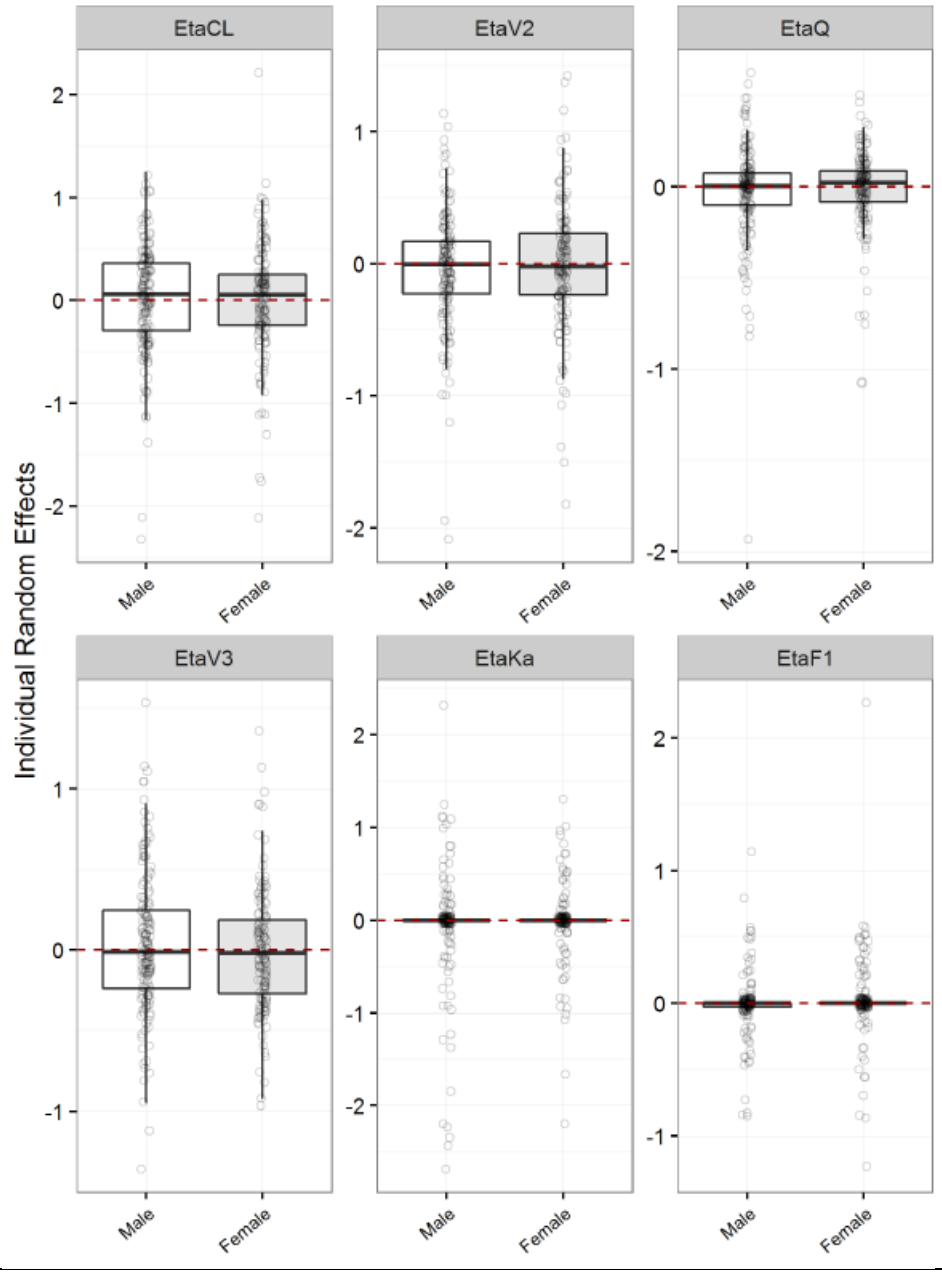
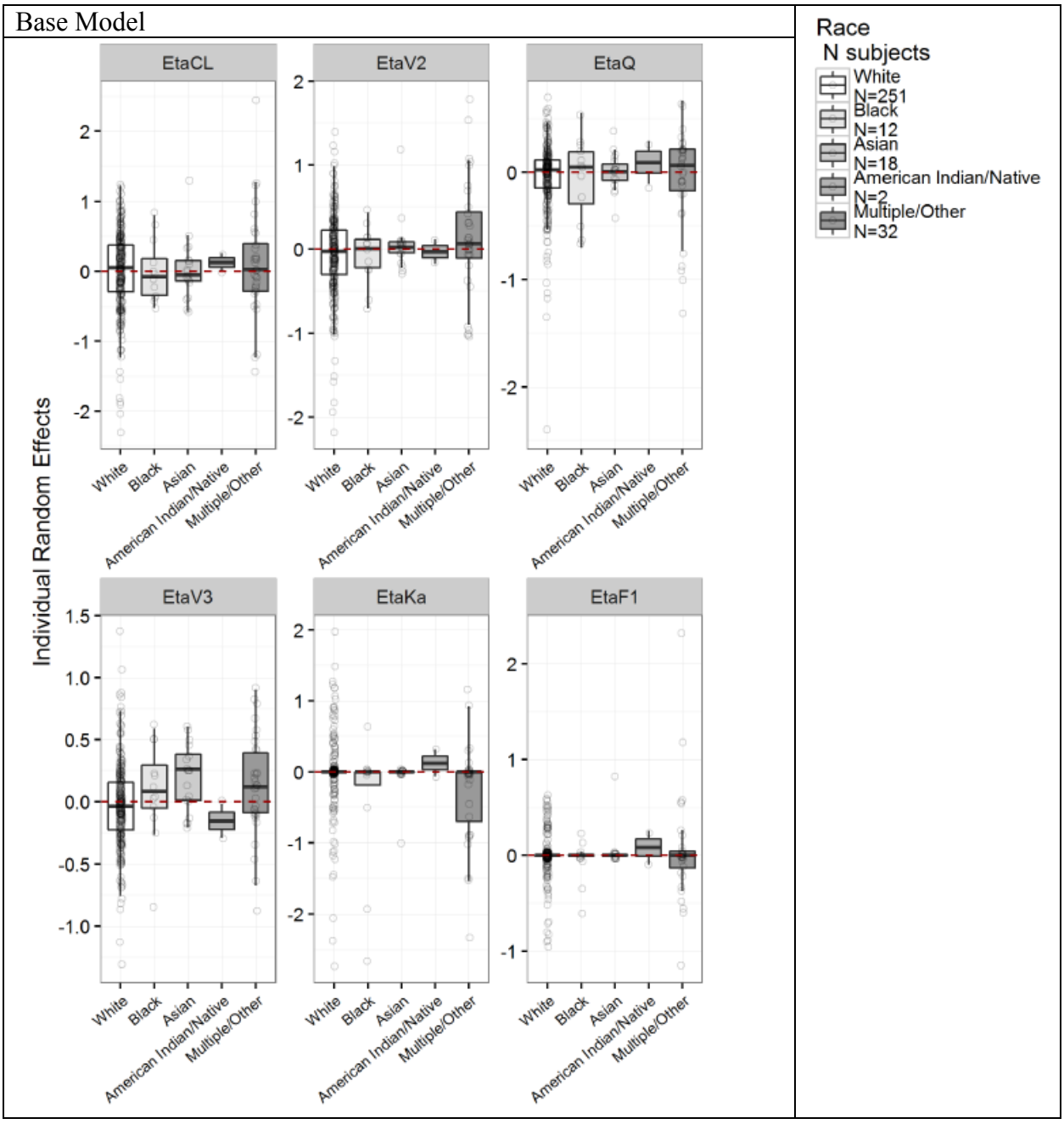


Figure 20. Relationship between Race and Individual Random Effect – Base vs. Final Population PK Model



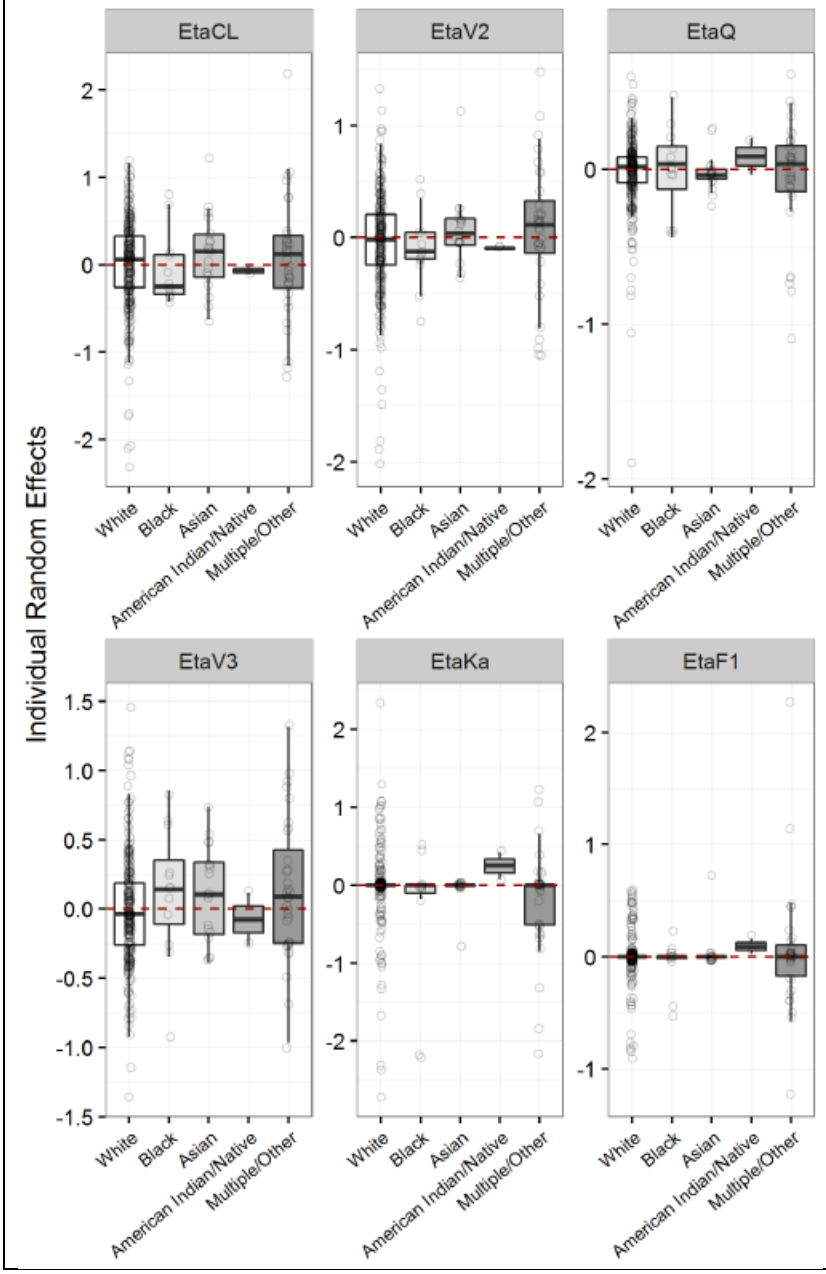
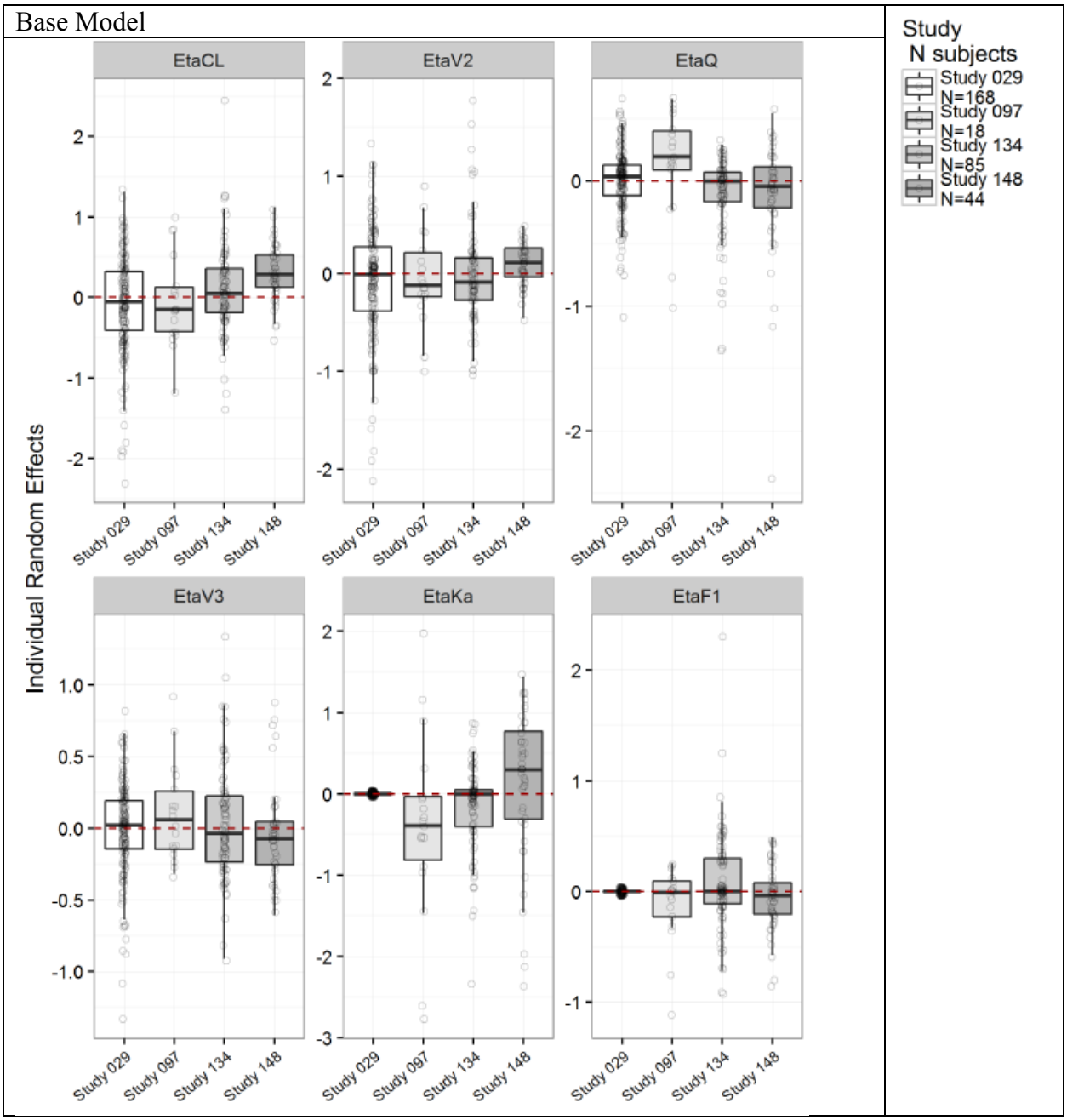
Final Model	
	

Figure 21. Relationship between Study and Individual Random Effect – Base vs. Final Population PK Model



Final Model

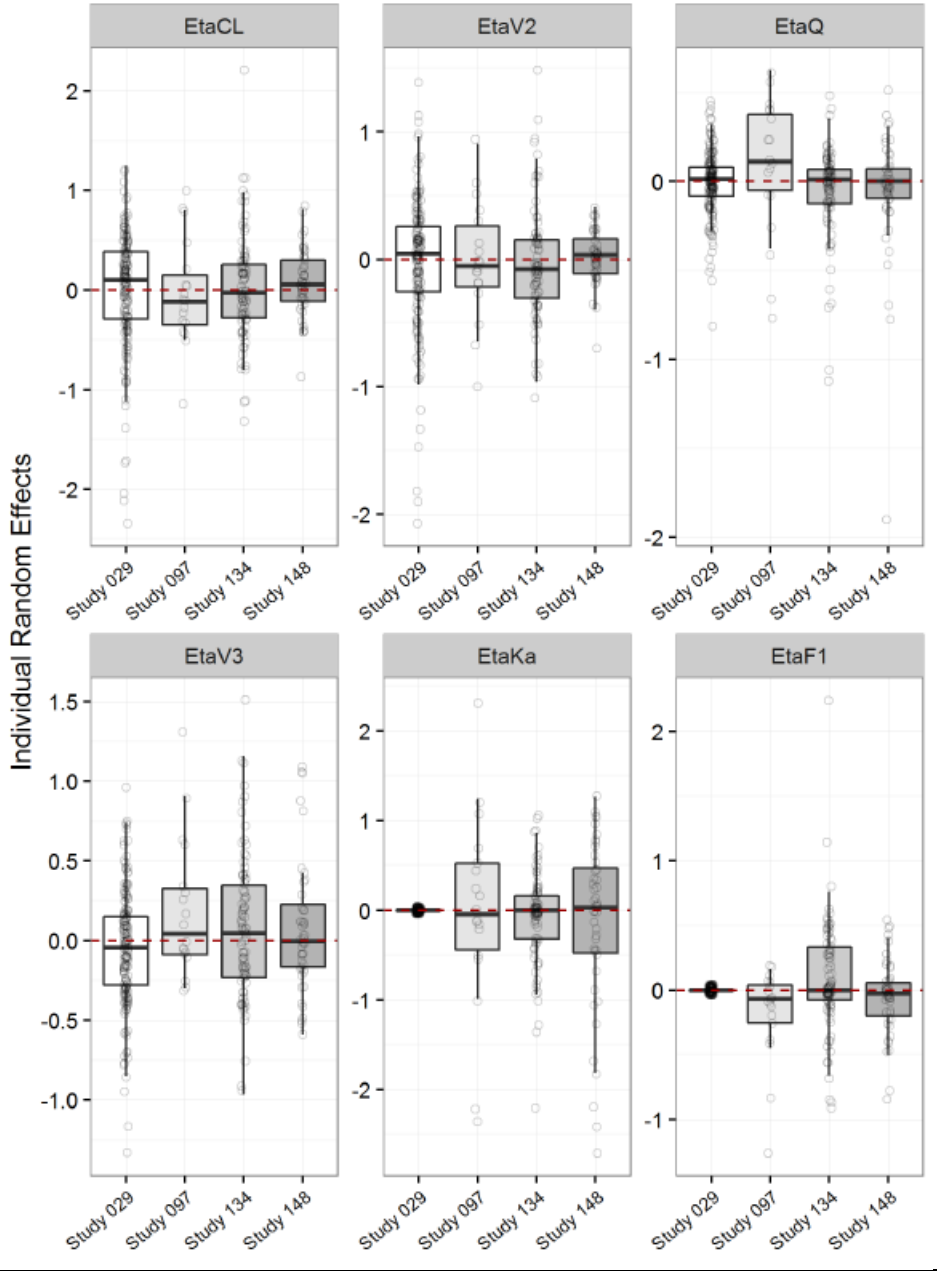
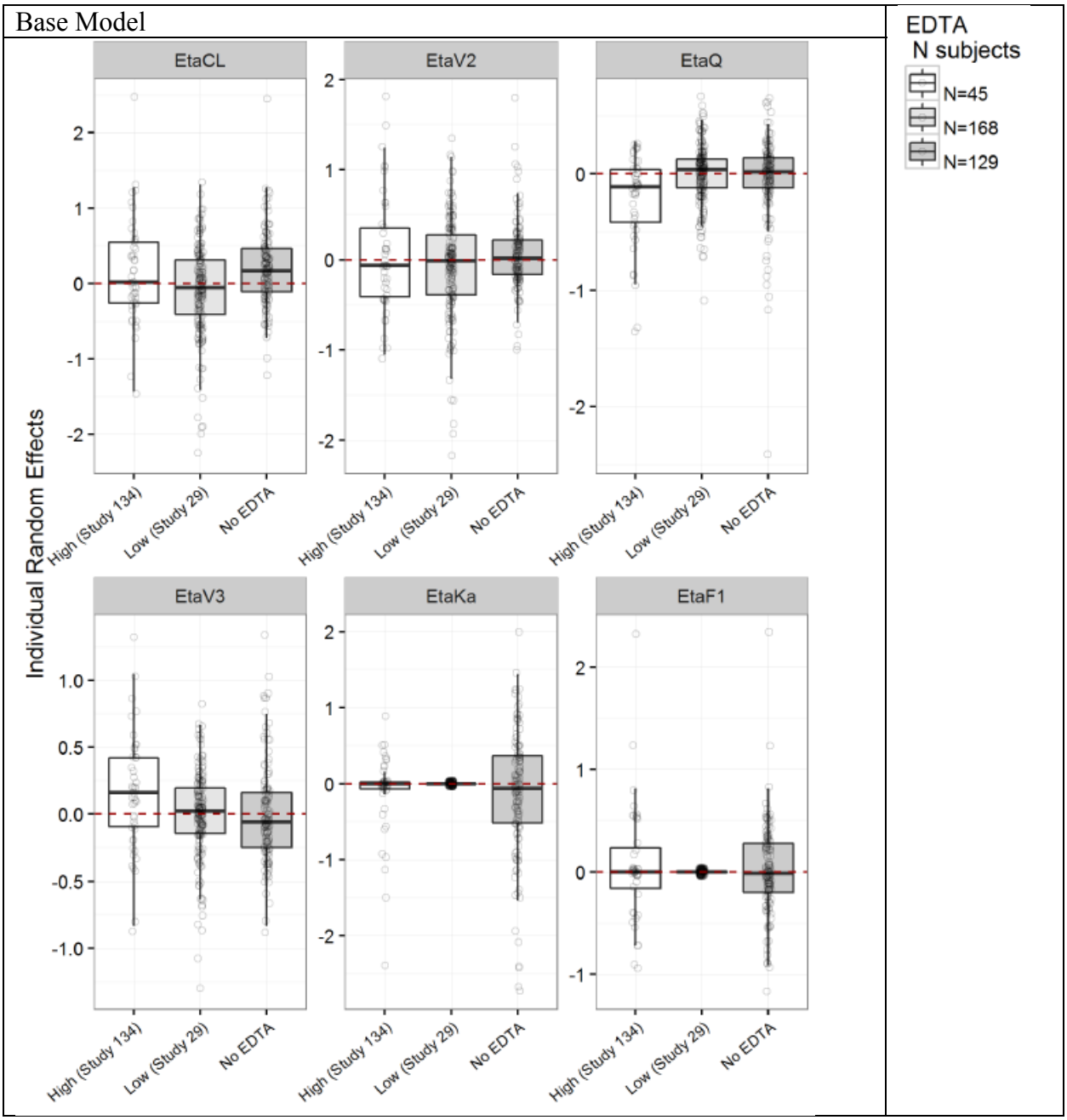
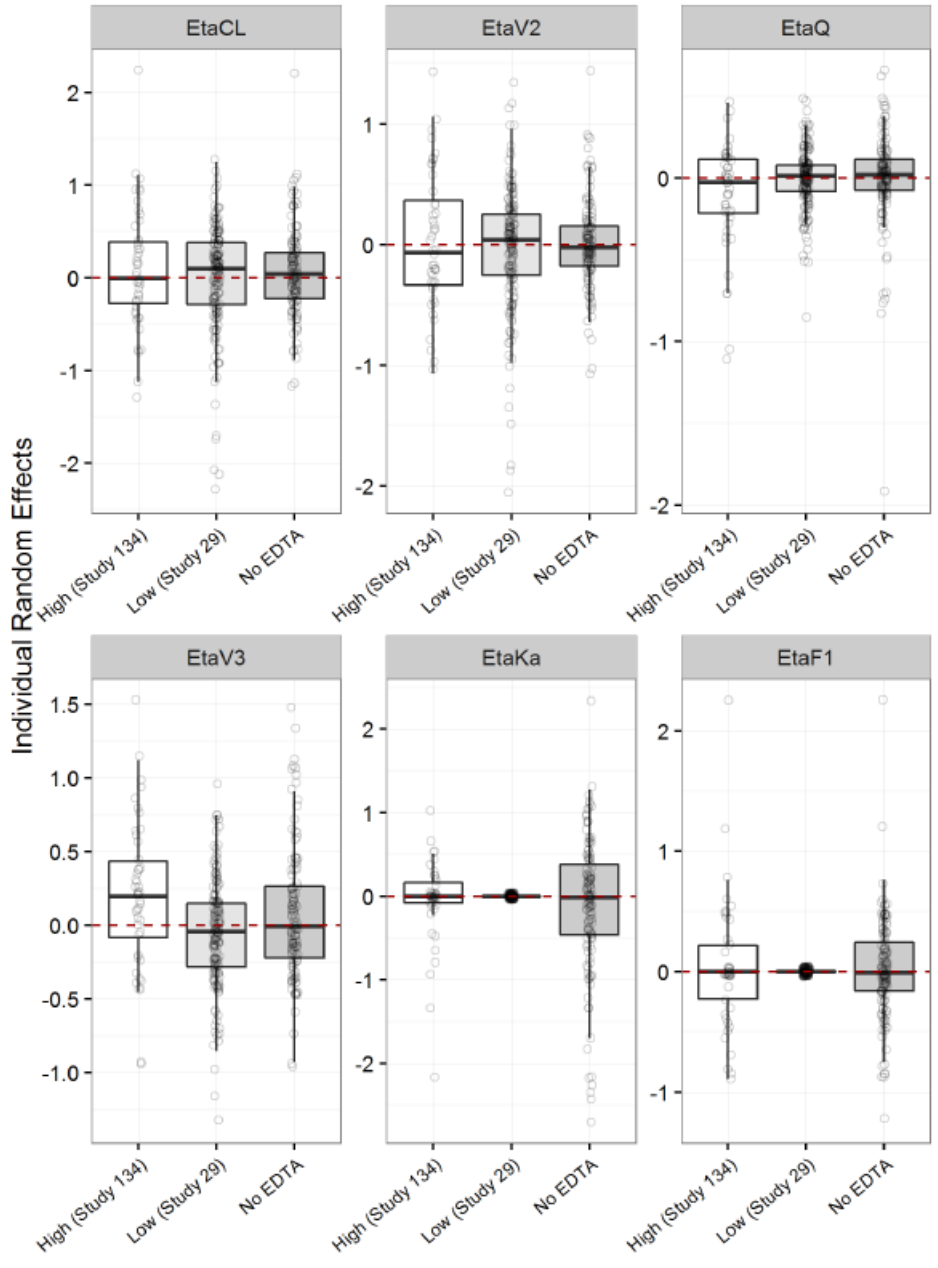


Figure 22. Relationship between Amount of EDTA and Individual Random Effect – Base vs. Final Population PK Model



Final Model



Reviewer's overall assessment: the population PK model was acceptable for the description of aprepitant PK in the product label and simulations for the exposure matching of aprepitant. No additional model development by the reviewer was required.

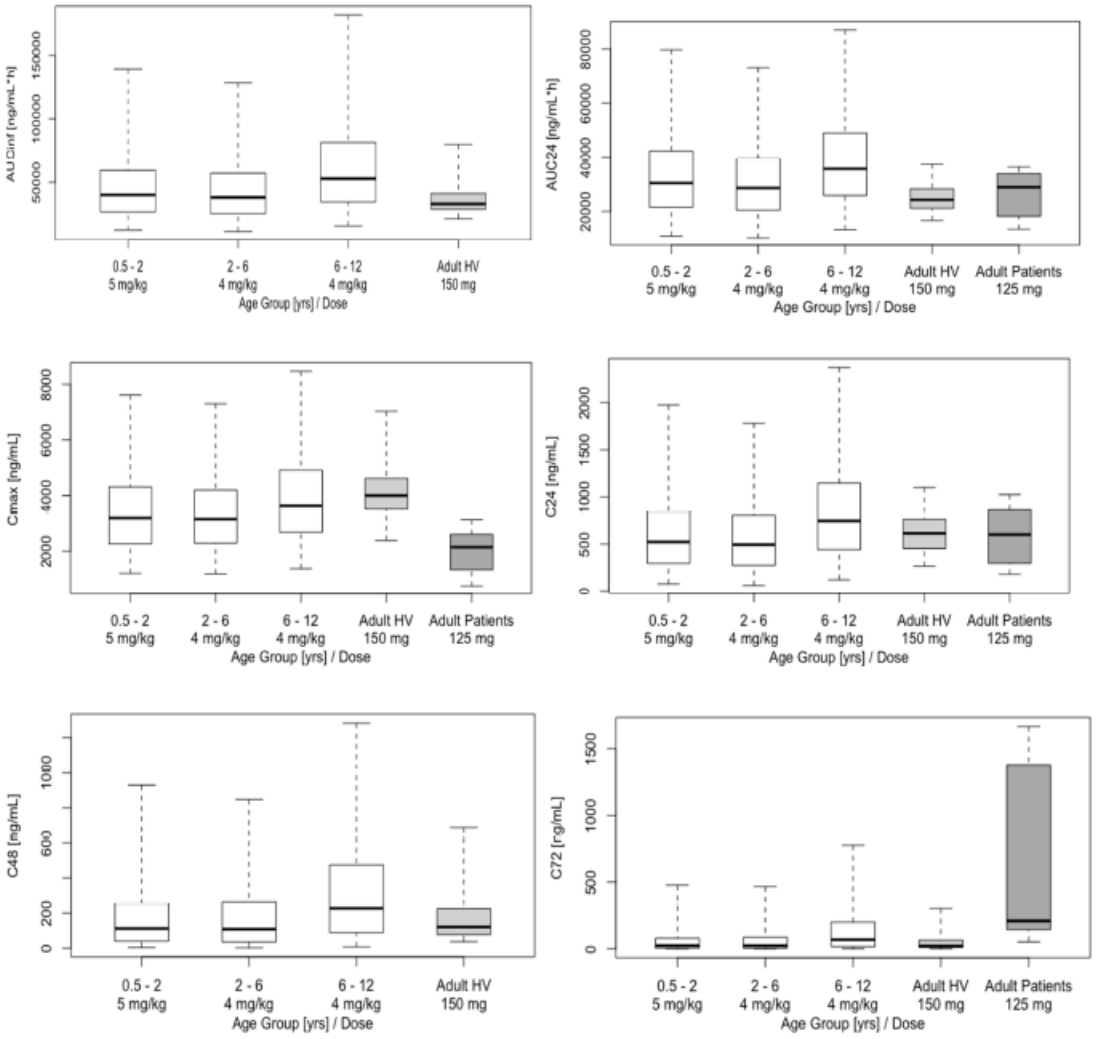
4.3.1.5 Simulation to Support Dose Selection

The final population PK model of aprepitant/fosaprepitant in pediatric population was used to simulate the PK of aprepitant to support single dose of fosaprepitant and 3-day dosing regimens fosaprepitant and aprepitant in CINV/PONV pediatric patients

The results of simulation support the dosing recommendation. Summary plots for the exposure comparisons are presented in Figure 23 and Figure 24.

Single-day regimen

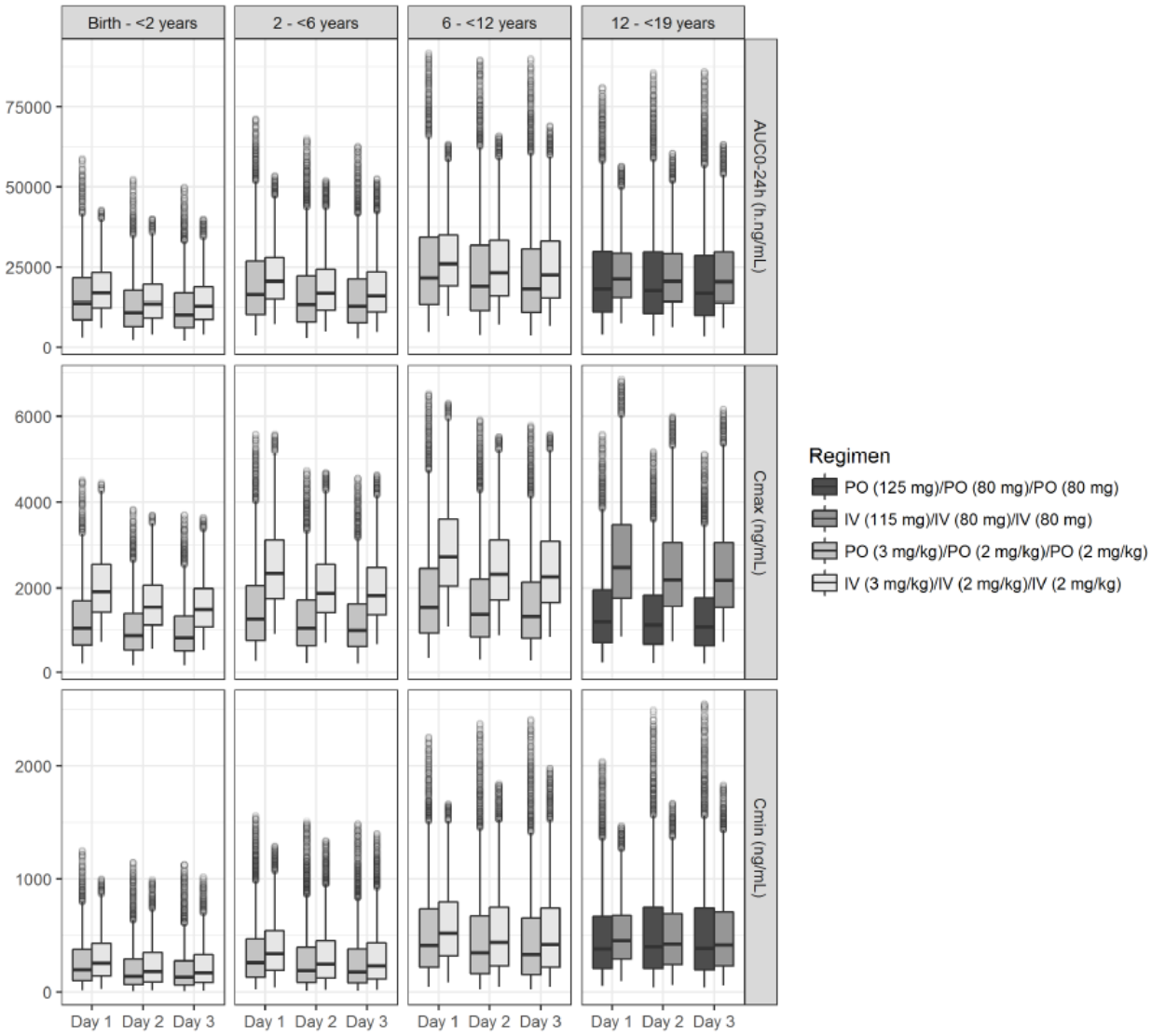
Figure 23. Comparison of Observed 1-day 150 mg IV Fosaprepitant Regimen in Adult Healthy Volunteers, Single Dose 125 mg Oral Aprepitant in Adult Cancer Patients with Model- Simulated Aprepitant PK Parameters (AUCinf, AUC24, Cmax, C24, C48, C72) After Administration of 4 mg/kg in Pediatric Subjects 2 to 12 Years Old and 5 mg/kg in <2 Years Old Subjects (Revised from the Original Figure 2.7.2: 4 without extremes)



Source data: Response to IR on January 12 2018 (SDN570), Figure 2.7.2:4a

Three-day regimen

Figure 24. Comparison of 3-day Oral Aprepitant Regimens in Adolescent (125 mg on Day 1 and 80 mg on Days 2 and 3) and Pediatric Subjects <12 Years Old (3 mg/kg on Day 1 ad 2 mg/kg on Days 2 and 3) with Simulated 3-day IV Fosaprepitant Regimens, 115 mg on Day 1 and 80 mg on Days 2 and 3 in Adolescents and 3 mg/kg and 2 mg/kg on Days 2 and 3 in Pediatric Subjects < 12 Years Old

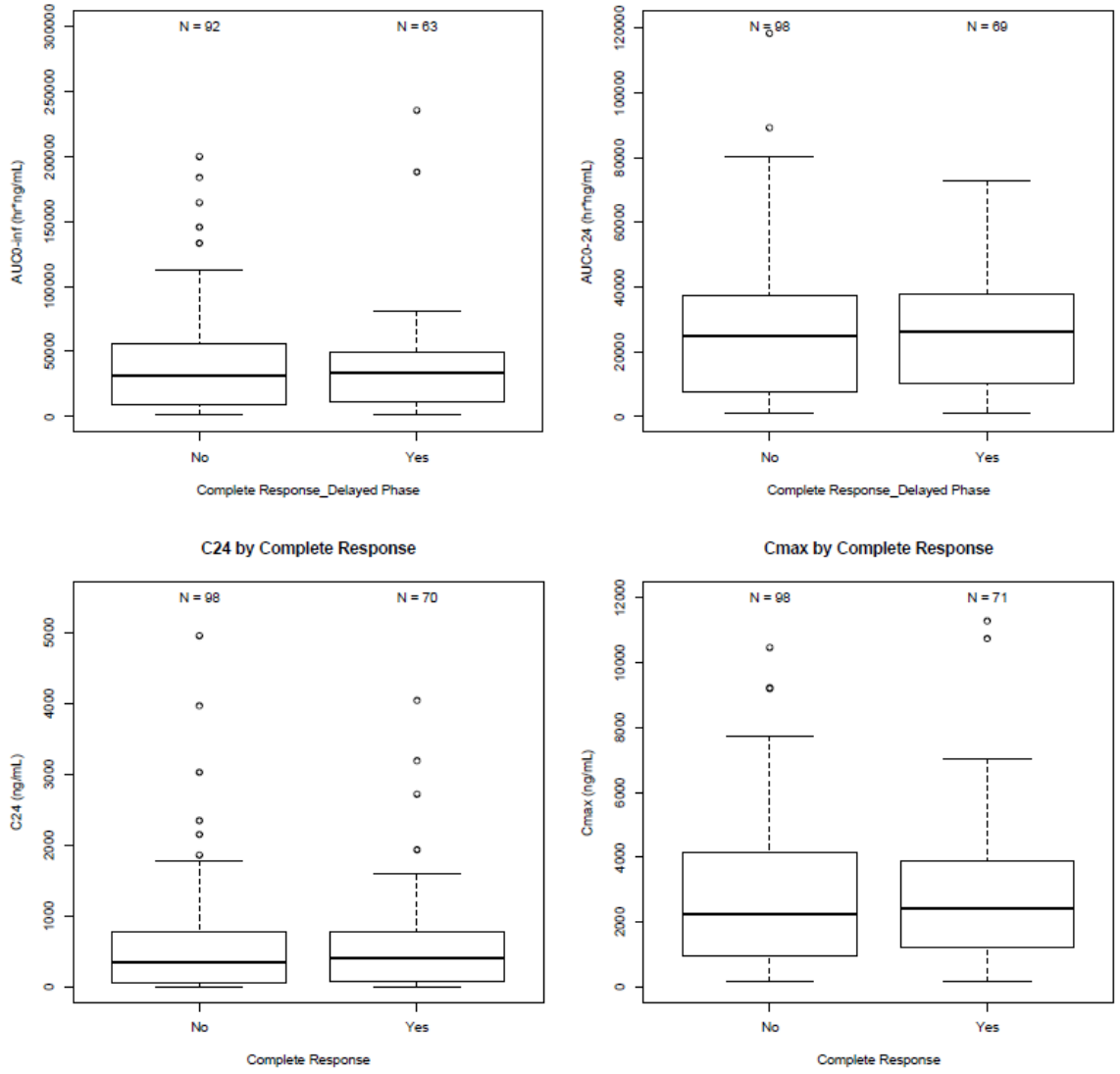


Source data: Section 2.7.2 Summary of Clinical Pharmacology, Figure 2.7.2:5

4.3.1.6 Exposure-Response Analysis for Study P029

Aprepitant exposure (AUC0-inf, AUC0-24, Cmax, and C24) versus the clinical endpoint (yes/no) (**Figure 25**), percent of patients with clinical endpoint (yes only) versus aprepitant exposure (grouped in deciles) (**Figure 26**) and percent of patients with the clinical endpoint (yes/no) by aprepitant exposure (grouped as quartiles) (**Figure 27**) were evaluated.

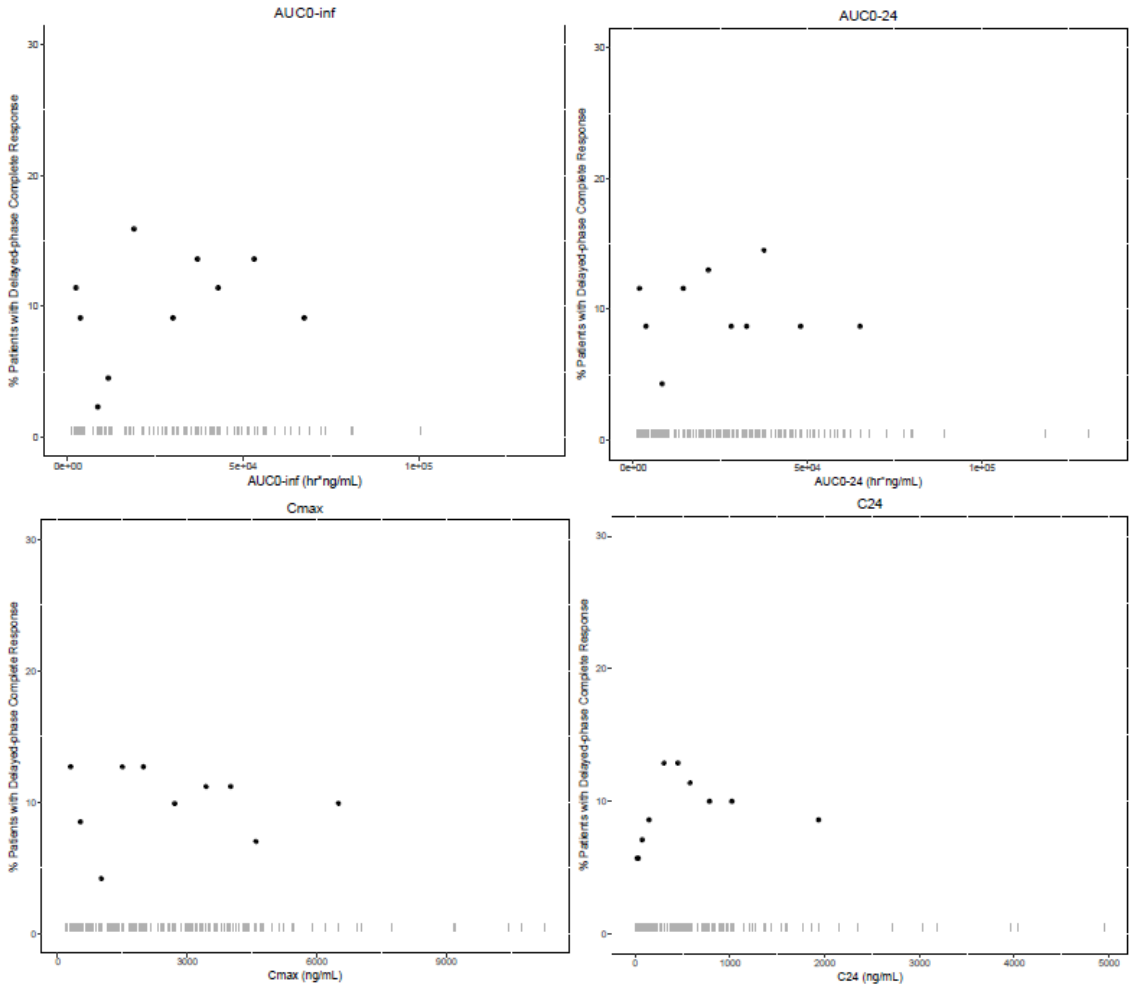
Figure 25. Exploration of Exposure-Response from Protocol 029 Based Upon Aprepitant Exposure (AUC0-inf, AUC0-24, Cmax and C24) versus Complete Response in the Delayed Phase (yes/no)



$AUC_{0\text{-}inf}$= Area under the curve of concentration-time curve from zero to infinity; $AUC_{0\text{-}24}$ =Area under the curve of concentration-time at day 1; C_{max}= Maximum concentration on day 1; C_{24}= Concentration at 24 hours. Boxplots represent interquartile range (box), with the lower whisker denoting values within the first quarter (Q1) - 1.5 * IQR and the upper whisker denoting values within the third quarter (Q3) + 1.5 * IQR and symbols representing values outside of this range of data.

Source data: Response to IR submitted on 2/12/2018, Figure 1

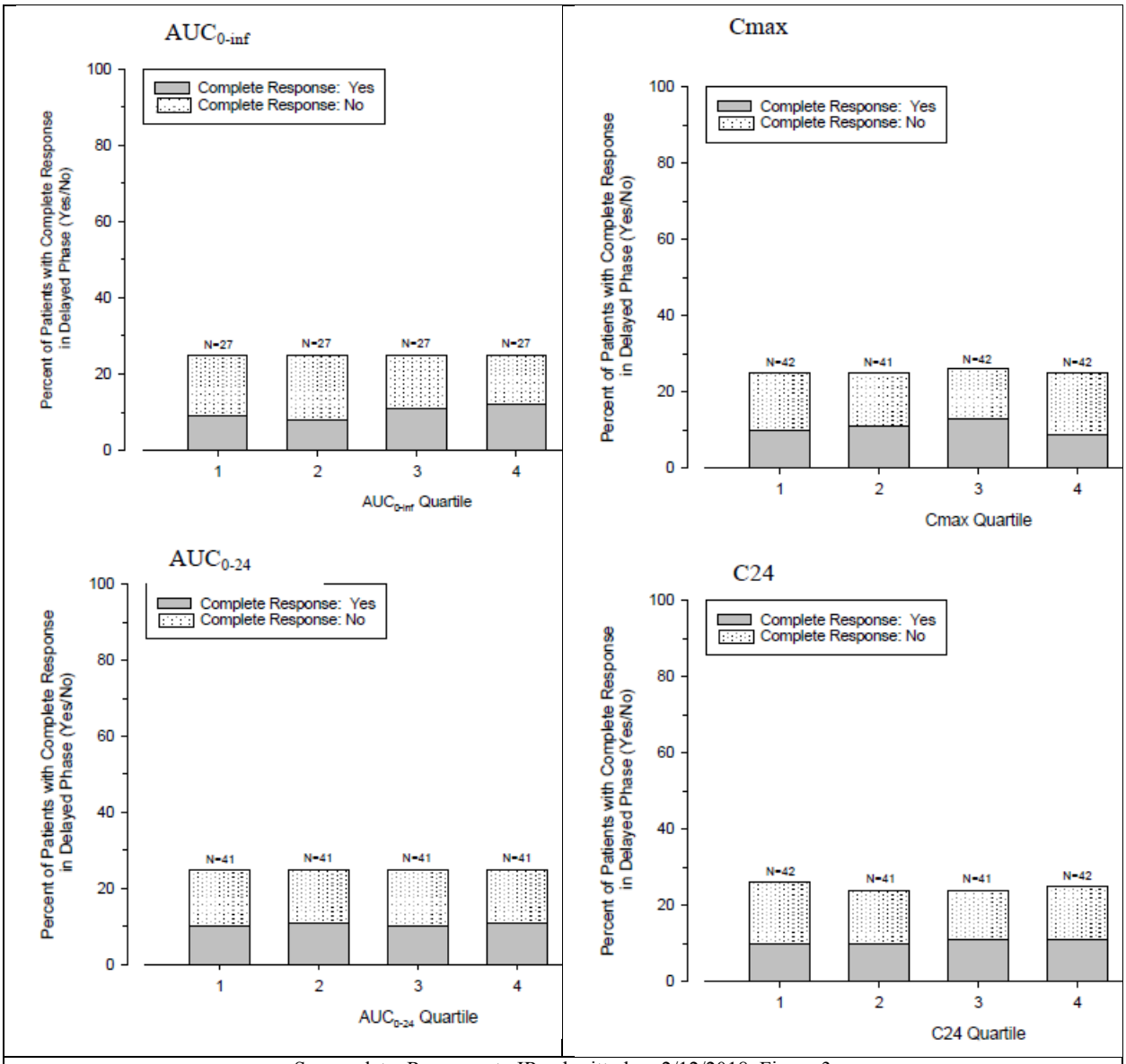
Figure 26. Percent of Patients with Complete Response in the Delayed Phase (yes only) versus Aprepitant Exposure (AUC0-inf, AUC0-24, Cmax and C24, grouped in deciles)



$AUC_{0\text{-}inf}$= Area under the curve of concentration-time curve from zero to infinity; $AUC_{0\text{-}24}$ =Area under the curve of concentration-time at day 1; C_{max}= Maximum concentration on day 1; C_{24}= Concentration at 24 hours. Black dots represent the median of PK parameter values when grouped by deciles. Grey vertical lines denote the entire range of individual PK parameter values.

Source data: Response to IR submitted on 2/12/2018, Figure 2

Figure 27. Percent of Patients with Complete Response in the Delayed Phase (yes/no) versus Aprepitant Exposure (AUC0-inf, AUC0-24, Cmax and C24, grouped in quartiles)



Source data: Response to IR submitted on 2/12/2018, Figure 3

The relationship between Complete Response Rate and single fosaprepitant dose in Cycle 1 from Study P029 are shown in Table 45. It is noteworthy that the study was not powered to measure efficacy, and the open-label amendment (5 mg/kg dose cohort) was not blinded and did not have a control regimen for comparison.

Table 45. Number (%) of Subjects with Complete Response in Cycle 1 by Treatment Regimen Intent to Treat Population

Delayed Phase

Treatment	n/m (%)	Difference (%)†	95% CI for Difference (%)‡
Partially Blinded:			
Fosaprepitant 3mg/kg Regimen	14/42 (33.3)	4.8	(-22.5,25.7)
Fosaprepitant 1.2mg/kg Regimen	11/43 (25.6)	-3.0	(-22.5,24.6)
Fosaprepitant 0.4mg/kg Regimen	17/40 (42.5)	13.9	(-11.7,38.0)
Control Regimen	10/35 (28.6)		
Open-Label:			
Fosaprepitant 5mg/kg Regimen	35/74 (47.3)		

† Fosaprepitant regimen – Control regimen.

‡ Confidence interval (CI) for the difference was calculated using the method proposed by Miettinen and Nurminen, accounting for dose and dexamethasone use (yes/no).

n/m = Number of subjects with desired response/number of subjects included in time point

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

Partially Blinded:

For Fosaprepitant 3mg/kg Regimen, subjects 12-17 years of age received a fixed 150 mg fosaprepitant dose.

For Fosaprepitant 1.2mg/kg Regimen, subjects 12-17 years of age received a fixed 60 mg fosaprepitant dose.

For Fosaprepitant 0.4mg/kg Regimen, subjects 12-17 years of age received a fixed 20 mg fosaprepitant dose.

Acute Phase

Treatment	n/m (%)	Difference (%)†	95% CI for Difference (%)‡
Partially Blinded:			
Fosaprepitant 3mg/kg Regimen	14/42 (33.3)	4.8	(-22.5,25.7)
Fosaprepitant 1.2mg/kg Regimen	11/43 (25.6)	-3.0	(-22.5,24.6)
Fosaprepitant 0.4mg/kg Regimen	17/40 (42.5)	13.9	(-11.7,38.0)
Control Regimen	10/35 (28.6)		
Open-Label:			
Fosaprepitant 5mg/kg Regimen	35/74 (47.3)		

† Fosaprepitant regimen – Control regimen.

‡ Confidence interval (CI) for the difference was calculated using the method proposed by Miettinen and Nurminen, accounting for dose and dexamethasone use (yes/no).

n/m = Number of subjects with desired response/number of subjects included in time point

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

Partially Blinded:

For Fosaprepitant 3mg/kg Regimen, subjects 12-17 years of age received a fixed 150 mg fosaprepitant dose.

For Fosaprepitant 1.2mg/kg Regimen, subjects 12-17 years of age received a fixed 60 mg fosaprepitant dose.

For Fosaprepitant 0.4mg/kg Regimen, subjects 12-17 years of age received a fixed 20 mg fosaprepitant dose.

Overall Phase

Treatment	n/m (%)	Difference (%)[†]	95% CI for Difference (%)[‡]
Partially Blinded:			
Fosaprepitant 3mg/kg Regimen	13/42 (31.0)	11.0	(-18.2,29.3)
Fosaprepitant 1.2mg/kg Regimen	8/43 (18.6)	-1.4	(-23.2,21.9)
Fosaprepitant 0.4mg/kg Regimen	14/40 (35.0)	15.0	(-10.7,38.1)
Control Regimen	7/35 (20.0)		
Open-Label:			
Fosaprepitant 5mg/kg Regimen	33/74 (44.6)		

[†] Fosaprepitant regimen – Control regimen.

[‡] Confidence interval (CI) for the difference was calculated using the method proposed by Miettinen and Nurminen, accounting for dose and dexamethasone use (yes/no).

n/m = Number of subjects with desired response/number of subjects included in time point

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

Partially Blinded:

For Fosaprepitant 3mg/kg Regimen, subjects 12-17 years of age received a fixed 150 mg fosaprepitant dose.

For Fosaprepitant 1.2mg/kg Regimen, subjects 12-17 years of age received a fixed 60 mg fosaprepitant dose.

For Fosaprepitant 0.4mg/kg Regimen, subjects 12-17 years of age received a fixed 20 mg fosaprepitant dose.

Source data: P029 CSR, Tables 11-18, 11-19, and 11-20

The results of subgroup analysis of Complete Response Rate are listed in Table 46. Importantly, pediatric patients in the fosaprepitant treatment groups receiving single-day chemotherapy reported a higher incidence of Complete Response in the delayed phase as compared to children who received multi-day chemotherapy in those same treatment groups. This forms the basis for recommending single-day fosaprepitant regimen to be used in patients receiving single-day chemotherapy.

Table 46. Number (%) of Subjects with Complete Response† in Cycle 1 by Subgroup of Age and Treatment Group Intent to Treat Population

	Fosaprepitant 3mg/kg Regimen n/m (%)	Fosaprepitant 1.2mg/kg Regimen n/m (%)	Fosaprepitant 0.4mg/kg Regimen n/m (%)	Control Regimen n/m (%)	Fosaprepitant 5mg/kg Regimen n/m (%)
Delayed Phase					
Age Group					
birth to <2 years	0/0(-.-)	0/0(-.-)	0/0(-.-)	0/0(-.-)	12/23 (52.2)
2 to <6 years	2/8 (25.0)	3/10 (30.0)	6/10 (60.0)	2/9 (22.2)	16/26 (61.5)
6 to <12 years	5/17 (29.4)	3/16 (18.8)	7/13 (53.8)	4/9 (44.4)	7/25 (28.0)
12 to 17 years	7/17 (41.2)	5/17 (29.4)	4/17 (23.5)	4/17 (23.5)	0/0(-.-)
Chemotherapy Duration in Cycle 1					
One Day of Chemotherapy	2/3 (66.7)	4/6 (66.7)	6/10 (60.0)	1/4 (25.0)	11/18 (61.1)
More Than 1 Day of Chemotherapy	12/39 (30.8)	7/37 (18.9)	11/30 (36.7)	9/31 (29.0)	24/56 (42.9)
Acute Phase					
birth to <2 years	0/0(-.-)	0/0(-.-)	0/0(-.-)	0/0(-.-)	21/23 (91.3)
2 to <6 years	4/8 (50.0)	6/10 (60.0)	10/10 (100.0)	4/9 (44.4)	23/26 (88.5)
6 to <12 years	9/17 (52.9)	9/16 (56.3)	9/13 (69.2)	5/9 (55.6)	16/25 (64.0)
12 to 17 years	14/17 (82.4)	9/17 (52.9)	11/17 (64.7)	5/17 (29.4)	0/0(-.-)
Chemotherapy Duration in Cycle 1					
One Day of Chemotherapy	3/3 (100.0)	2/6 (33.3)	6/10 (60.0)	2/4 (50.0)	14/18 (77.8)
More Than 1 Day of Chemotherapy	24/39 (61.5)	22/37 (59.5)	24/30 (80.0)	12/31 (38.7)	46/56 (82.1)
Overall Phase					
birth to <2 years	0/0(-.-)	0/0(-.-)	0/0(-.-)	0/0(-.-)	12/23 (52.2)
2 to <6 years	2/8 (25.0)	2/10 (20.0)	6/10 (60.0)	1/9 (11.1)	15/26 (57.7)
6 to <12 years	4/17 (23.5)	2/16 (12.5)	5/13 (38.5)	3/9 (33.3)	6/25 (24.0)
12 to 17 years	7/17 (41.2)	4/17 (23.5)	3/17 (17.6)	3/17 (17.6)	0/0(-.-)
Chemotherapy Duration in Cycle 1					
One Day of Chemotherapy	2/3 (66.7)	2/6 (33.3)	3/10 (30.0)	1/4 (25.0)	10/18 (55.6)
More Than 1 Day of Chemotherapy	11/39 (28.2)	6/37 (16.2)	11/30 (36.7)	6/31 (19.4)	23/56 (41.1)

† Complete Response = No vomiting and no rescue therapy.
‡ Overall Phase: 0 to 120 hours following initiation of chemotherapy.
n/m = Number of subjects with desired response/number of subjects included in time point
Partially Blinded:
For Fosaprepitant 3mg/kg Regimen, subjects 12-17 years of age received a fixed 150 mg fosaprepitant dose.
For Fosaprepitant 1.2mg/kg Regimen, subjects 12-17 years of age received a fixed 60 mg fosaprepitant dose.
For Fosaprepitant 0.4mg/kg Regimen, subjects 12-17 years of age received a fixed 20 mg fosaprepitant dose.

Source data: P029 CSR, Tables 11-27, 11-28, and 11-29

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/s/

ELIZABETH Y SHANG
03/30/2018

JUSTIN C EARP
03/30/2018

INSOOK KIM
03/30/2018

GILBERT J BURCKART
03/31/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022023Orig1s017

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs/Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Pediatric Labeling Review

From: Amy M. Taylor, MD, MHS Medical Officer
Division of Pediatric and Maternal Health

Through: Hari Cheryl Sachs, MD, Team Leader
Division of Pediatric and Maternal Health

John J. Alexander, MD, MPH Deputy Director
Division of Pediatric and Maternal Health

NDA Number: 22-023/ Supplement S-017

Sponsor: Merck Sharp & Dohme Corporation

Drug: Emend® (fosaprepitant) for Injection

Dosage form and route of administration: injection, intravenous

Approved Indications:

Adults

In combination with other antiemetic agents for the:

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

Pediatric

- none

Consult request: The Division of Gastroenterology and Inborn Errors Products (DGIEP) requests DPMH's assistance with the

review of the sNDA and proposed labeling for Emend® (fosaprepitant) in the pediatric population.

Background

Emend® for injection (fosaprepitant) was originally approved for the HEC and MEC indications in adults on January 25, 2008. The sponsor submitted a sNDA on October 3, 2017 containing non-clinical and pediatric clinical data along with a pediatric assessment to support changes to the labeling for the use of Emend for injection in the prevention of chemotherapy induced nausea and vomiting in patients treated with highly and moderately emetogenic chemotherapy in pediatric patients. The sponsor's submission is designed to fulfill the PREA postmarketing requirement (PMR) associated with this NDA and to meet the terms of the Written Request (WR) issued for Emend for injection.

The sponsor currently has the following PREA PMR:

> 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. Use modeling and simulation including the results of the above study to identify 1-Day and 3-Day intravenous fosaprepitant doses in pediatric patients 0 to 17 years of age that provide similar aprepitant PK exposures to pediatric aprepitant doses and exposures which have demonstrated acceptable safety and efficacy profiles in patients receiving single and multi-day chemotherapy regimens, respectively.

Reviewer comment: Emend® for injection is not approved for post-operative nausea and vomiting. The product labeling includes a caution stating that 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. The original Emend® for injection formulation (115 mg fosaprepitant) contained 14.4 mg edetated disodium (EDTA). On November 12, 2010, a new formulation with 150 mg fosaprepitant and 18.8 mg EDTA was approved for adults. In the original WR issued on February 2, 2009, a concern that the original Emend® for injection formulation contained a level of EDTA considered too high for pediatric patients was included. The concern was related to a possible association with hypotension and syncope. The development of an age appropriate formulation with a lower level of EDTA was included in the WR. On December 2, 2016, a new formulation of Emend® for injection was approved with a lower EDTA concentration (5.4 mg). The formulation with the higher EDTA concentration is no longer marketed.

Related product

A related product with the same trade name, but a different active ingredient, Emend® capsules (aprepitant) for oral use (NDA 21-549), was approved for pediatric use on August 28, 2015, in combination with other antiemetic agents for acute and delayed nausea and vomiting associated with initial and repeat courses of HEC and MEC in pediatric patients 12 years of age and older. Emend® oral suspension (NDA207-865) was approved for use on December 17, 2015 in combination with other antiemetic agents for

acute and delayed nausea and vomiting associated with initial and repeat courses of HEC and MEC in pediatric patients 6 months of age and older.

The sponsor continues to have a PREA PMR to study PONV in pediatric patients 0 to less than 17 years for oral Emend® (aprepitant). The sponsor received a deferral extension for the submission of the studies until 2020.

Written Request

A WR was issued on February 9, 2009 and amended four times; the last time was February 27, 2017. The current amended WR includes the following studies and additional required analysis:

- A nonclinical 4-week study in juvenile dogs (2-weeks of age) studying at least 3 dose levels.
- A single dose, randomized, PK and dose-ranging study of at least 3 dose levels of fosaprepitant, and placebo, to characterize aprepitant PK parameters and the exposure response relationship following intravenous fosaprepitant (age-appropriate I.V. formulation) in combination with a 5HT3 antagonist and dexamethasone in patients 0 to 17 years.
- Additional required analysis (Chemotherapy Induced Nausea and Vomiting (CINV) 1-Day and 3-Day (IV/IV/IV) Emend Regimen. Specifically, the sponsor is to use modeling and simulation to identify 1-Day and 3-Day IV fosaprepitant doses in pediatric patients 0 to 17 years of age that provide similar aprepitant PK exposures to the 1- day IV regimen or 3-day oral aprepitant regimens which have demonstrated acceptable safety and efficacy profiles in adults and pediatric cancer patients, respectively.

The objectives of the additional analysis were to:

- To identify a 1-Day IV dosing regimen in pediatric patients that will provide exposures similar to the 1-Day IV regimen which has demonstrated efficacy and safety in adult cancer patients
- To identify a 3-Day IV dosing regimen in pediatric patients that will provide exposures similar to the 3-Day oral aprepitant regimen which has demonstrated efficacy and safety in pediatric cancer patients
- To explore the feasibility of a flexible 3-Day combination IV/oral regimen in pediatric patients that will provide exposures similar to the 3-Day oral aprepitant regimen which has demonstrated efficacy and safety in pediatric cancer patients

Clinical studies and analyses conducted

Single dose study

The sponsor conducted a single-dose PK study of fosaprepitant in combination with a 5HT3 antagonist and dexamethasone in pediatric patients ages 0 to 17 years. Of note, despite the sponsor's efforts, only 1 patient less than 6 months was enrolled in the study.

Age Group	# of patients enrolled	# of patients with PK samples[1]
0 to < 6 months[2]	1	None
6 m to < 2 years	22	22
2 to 6 years	54	45
6 to 12	71	63

years		
12 to 17 years	51	37

[1]Among subjects randomized/allocated to the fosaprepitant treatment group, PK samples were available for a total of 167 subjects who received a single IV dose of fosaprepitant.

[2]For the cohort of patients aged 0 < 6 months, diligent and reasonable efforts have been made to encourage enrollment in this age group. A total of 23 subjects were enrolled across the planned 0 to <2 years age cohort. PK samples were analyzed for 22 subjects who received fosaprepitant and one patient who received dexamethasone. One subject < 6 months of age enrolled, however, no PK was available from this patient.

The study included an assessment of safety of the single-day dosing and complete response as an efficacy endpoint. The study was not powered for efficacy. Efficacy of the single day regimen is supported by extrapolation of efficacy from adequate and well controlled trials in adults.

Reviewer comment: DGIEP agrees that the sponsor made diligent and reasonable efforts to encourage enrollment in this age group. Details of these efforts are included in Attachment 1.

Modeling and Simulation
The sponsor conducted modeling and simulation to identify a single-day and 3-Day fosaprepitant doses in pediatric patients that demonstrate similar aprepitant exposures to oral aprepitant. However, the C_{max} of the IV doses is higher compared to oral administration while the AUC is similar to oral administration AUCs.

In the sponsor's proposed labeling, dosing for pediatric patients 6 months to 17 years was included. The dosing regimen included an IV dose for 6 month to less than 12 years and 12 years to less than 17 years for Day 1 (b) (4) (b) (4)

Reviewer comment: DGIEP's clinical team expressed concern that safety data are not available in either pediatric or adult patients for IV doses on Day 2 and Day 3 or for multi-day IV dosing and requested that the pharmacometric team provide a recommendation for the duration of dosing which would lower the C_{max} on Days 2 and 3 to a C_{max} similar to oral aprepitant. The pharmacometric team's recommendation is to double the infusion time which would lower the C_{max} by 50%.

DGIEP, DPMH, and Clinical Pharmacology participated in a conference call with the sponsor to offer them 2 options for the dosing regimen:

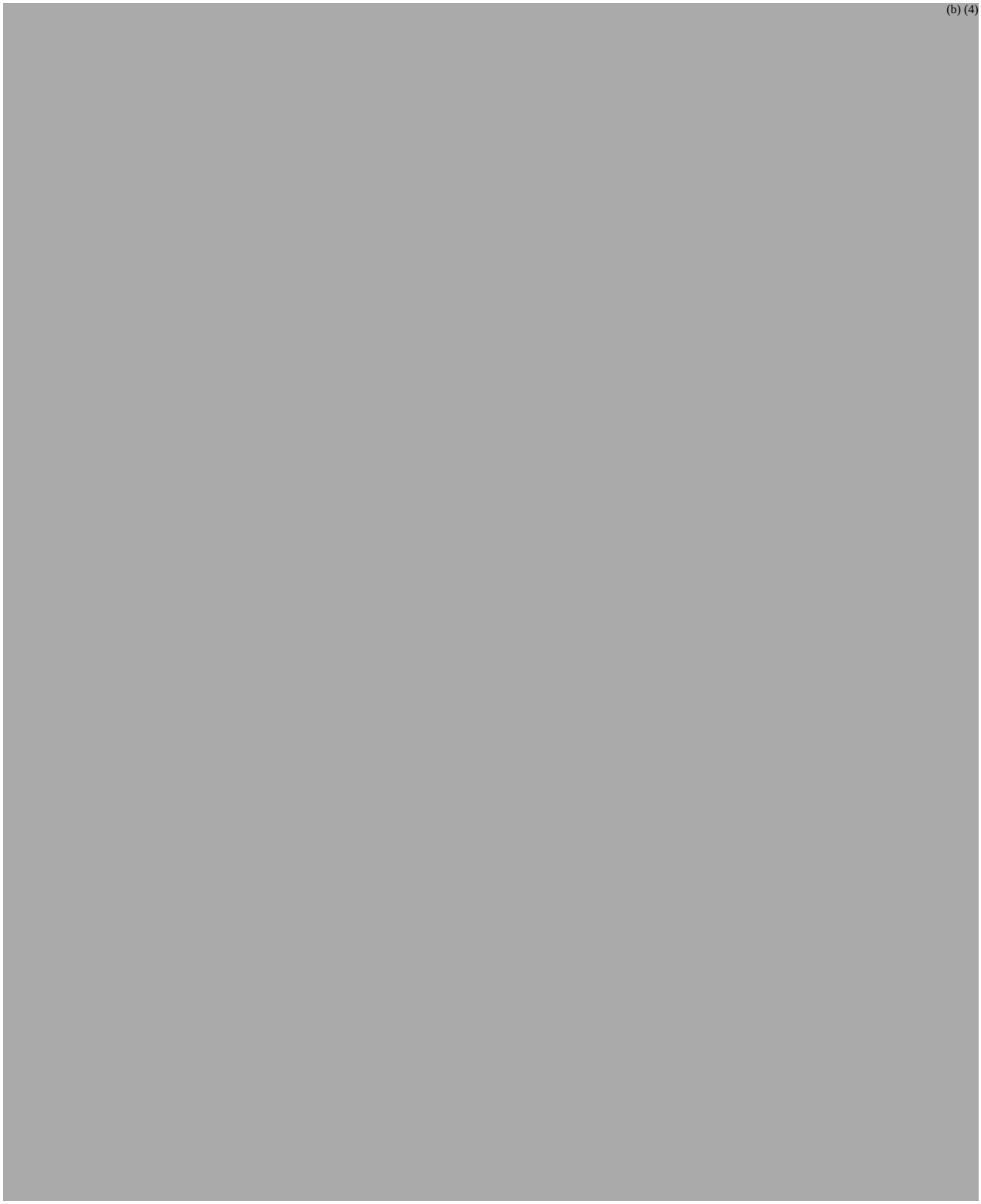
- *An IV/IV/IV dosing regimen in which the infusion rate is doubled, 60 minutes for patients 12 to 17 years and 120 minutes for patients 6 months to less than 12 years.*
- *An IV/PO/PO dosing regimen with no option for IV dosing on Days 2 and 3.*

During the call, the sponsor stated that they would prefer to add only the IV/PO/PO to the labeling. The sponsor cited concerns that the longer infusion time is impractical and the different infusion rates between Day 1 and Days 2 and 3 may be confusing to providers.

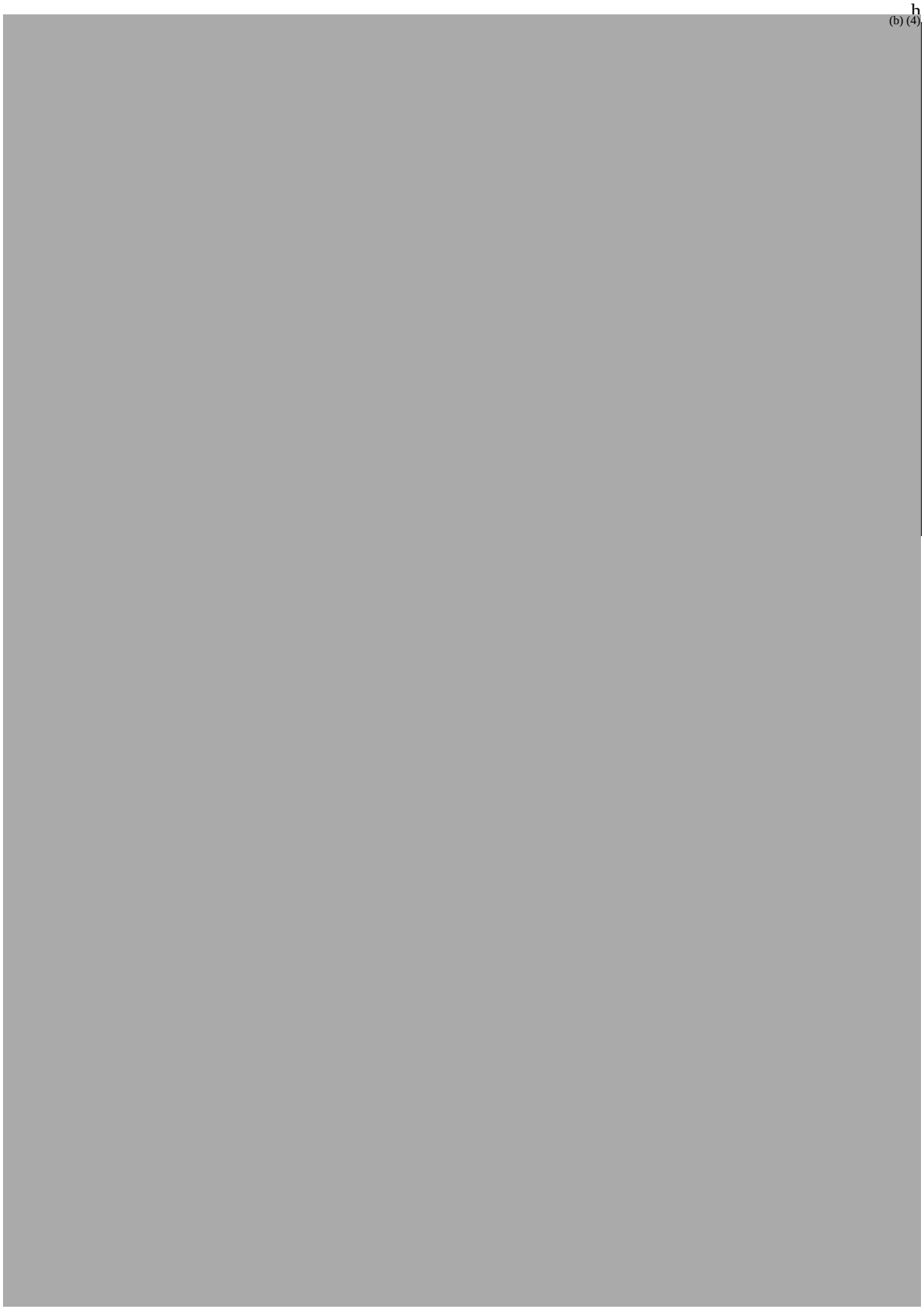
Proposed Revised Labeling for Emend for Injection

The sponsor's most recent FDA-approved labeling is dated October 17, 2017. Recommended information to be added to selected sections of labeling is underlined. Information to be deleted has a strikethrough. DPMH (Pediatric Team) comments and rationale for recommendations to the labeling are in italics.

(b) (4)



(b) (4)



(b) (4)

Reviewer comment: Consider moving Table 4 before Table 3. Move the recommendation that the infusion be given approximately 30 minutes prior to chemotherapy out of the tables and into the text above the tables in order to simplify the tables. (b) (4)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of EMEND (b) (4) in pediatric patients 6 months of age to 17 years of age for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC and MEC. (b) (4)

(b) (4)

(b) (4) Adverse reactions were similar to those reported in adult patients *[see* (b) (4)

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

Juvenile Animal Study

(b) (4)

(b) (4)

Reviewer comment: A summary statement outlining the findings in the juvenile animal studies should be added before the details of the studies are given. The human equivalence to the animal age should be added.

14 CLINICAL STUDIES

(b) (4)

Reviewer comment: Only information related to efficacy studies should be included in Section 14. Since use in pediatric patients is based on PK studies and modeling and simulation, no information on pediatric patients should be included in this section. The information on extrapolation can be moved to subsection 8.4.

Recommendations

- Consider moving Table 4 (single dose regimen) before Table 3 (multiple day regimen).
- Move the recommendation that the infusion be given approximately 30 minutes prior to chemotherapy out of the tables and into the text above the tables in order to simplify the tables.
- Place information related to extrapolation in subsection 8.4.

- Add a summary statement to the information on juvenile animal studies. The human equivalence to the animal age should be added.
- Remove all information related to pediatric patients from Section 14.

These recommendations were communicated to DGIEP during labeling meetings. Labeling negotiations are ongoing. The final labeling may differ as a result of those negotiations (see approval letter).

Attachment 1

The following is from a meeting background package dated November 1, 2016.

During the course of the study the Sponsor worked with investigators and their support staff to understand the specific challenges of enrolling infants and to identify approaches to improve recruitment These efforts on the part of the Sponsor include the following

- Multiple face to face meetings between the Clinical Director and investigators site staff to discuss enrollment challenges and potential strategies to improve recruitment of the infant cohort
- Teleconferences presentations conducted by the Clinical Director with investigators and site staff to address specific questions about the necessity and benefit of CINV prophylaxis in infants
- Reminders to the sites that additional time required for chart review to identify infant patients would be reimbursed according to the site contract
- Motivational letters of appreciation sent to investigators of high enrolling sites encouraging them to continue recruitment efforts in the youngest cohort
- Collection and distribution of best practices for enrollment in the birth to year old cohort from high enrolling sites
- Referral letter templates provided to investigators to encourage referral of patients from colleagues for participation in the study
- Consistent contact of headquarter and country level personnel with the sites via telephone site visits and email to address questions and evaluate patient eligibility in real time
- Site questionnaires administered by the Sponsor to identify and mitigate, when possible, issues with enrollment as they occurred.

In the above mentioned questionnaires, sites were polled to gather additional information about the challenges of recruiting infants. Based on the feedback provided, the main obstacles articulated by investigators and their support staff are summarized below:

- Infants less than year of age with cancer are very rare
- Repeated PK sampling in this cohort particularly those infants with a single lumen central venous catheter is very burdensome Because peripheral IV insertion is technically challenging parents and investigators are reluctant to subject young infants with cancer to unnecessary additional procedures
- Parental refusal for participation due to worries that investigational drugs could prolong hospitalization or lead to unexpected adverse events
- Infants often do not receive HEC or MEC
- Infants that do require emetogenic chemotherapy generally have advanced disease and are too sick to participate

- For patients with leukemia, one of the most common types of cancers in young infants, treatment involves corticosteroids a class of medications prohibited in Protocol
- Young infants are believed to not be as susceptible to CINV therefore the benefit of prophylaxis in these subjects is questioned by investigators and parents

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/s/

AMY M TAYLOR
03/05/2018

HARI C SACHS
03/05/2018
I agree with these recommendations.

JOHN J ALEXANDER
03/05/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	March 1, 2018
Requesting Office or Division:	Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number:	NDA 22023/S-017
Product Name and Strength:	Emend (fosaprepitant) for Injection 150 mg
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Merck Sharp & Dohme (Merck & Co.)
Submission Date:	October 3, 2017
OSE RCM #:	2017-2335
DMEPA Primary Reviewer:	Sherly Abraham, RPh
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 REASON FOR REVIEW

This review evaluates the label and labeling for Emend for injection prior approval labeling supplement (sNDA 22023/S-017), submitted on October 3, 2017. The Division of Gastroenterology and Inborn Error Products (DGIEP) requested that DMEPA review the proposed prescribing information (PI) for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

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

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Merck & Co. submitted a prior approval labeling supplement (sNDA 22023/S-017) to fulfill their written request and Pediatric Research Equity Act (PREA) for Emend (fosaprepitant) for injection. This supplement proposes to extend the use of Emend for injection to pediatric patients 6 months and older (1-day and 3-day dosing regimen) in the prevention of chemotherapy induced nausea and vomiting with highly and moderately emetogenic chemotherapy.

DMEPA reviewed the proposed PI to determine whether there are any significant concerns in terms of safety related to preventable medication errors. We did not identify any medication error concerns from our search of the previous DMEPA reviews or ISMP Newsletters. We defer to the Division for the appropriateness of the pediatric dosing for this product. We find the proposed changes to the PI acceptable from a medication error perspective. DMEPA communicated our recommendations for the proposed PI to the DGIEP team in the labeling

meeting settings. Additionally, there were no proposed changes to carton labeling and container label.

4 CONCLUSION & RECOMMENDATION

DMEPA concludes that the proposed PI is acceptable. We have no further recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Emend for injection that Merck and Co. submitted on October 3, 2017.

Table 2. Relevant Product Information for Emend for injection

Initial Approval Date	March 27, 2003
Active Ingredient	fosaprepitant
Indication	Indicated in adults and pediatric patients 6 months of age and older,(proposed) in combination with other antiemetic agents, for the prevention of: 1) acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin. 2) delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).
Route of Administration	intravenous
Dosage Form	injection
Strength	150 mg
Dose and Frequency	Adults: 150 mg on Day 1. Single dose regimen for pediatrics below:

EMEND for injection	12 Years to 17 Years	150 mg intravenously over 30 minutes, completing the infusion approximately 30 minutes prior to chemotherapy
	2 Years to less than 12 Years	4 mg/kg (maximum dose 150 mg) intravenously over 60 minutes, completing the infusion approximately 30 minutes prior to chemotherapy
	6 Months to less than 2 Years	5 mg/kg (maximum dose 150 mg) intravenously over 60 minutes, completing the infusion approximately 30 minutes prior to chemotherapy

<table>
<tr><td></td><td>3 day regimen for pediatrics:
<table>
<tr><th>Age Group</th><th colspan="2">Drug</th><th>Day 1</th><th>Day 2</th><th>Day 3</th></tr>
<tr><td rowspan="2">6 Months to Less than 12 Years</td><td rowspan="2">EMEND</td><td>EMEND for injection</td><td>3 mg/kg
(maximum dose 115 mg)
intravenously over 60 minutes, completing the infusion approximately 30 minutes prior to chemotherapy</td><td>--</td><td>--</td></tr>
<tr><td>EMEND for oral suspension</td><td>--</td><td>2 mg/kg orally
(maximum 80 mg)</td><td>2 mg/kg orally
(maximum 80 mg)</td></tr>
<tr><td rowspan="2">12 Years to less than 17 Years</td><td rowspan="2">EMEND</td><td>EMEND for injection</td><td>115 mg
intravenously over 30 minutes, completing the infusion approximately 30 minutes prior to chemotherapy</td><td>--</td><td>--</td></tr>
<tr><td>EMEND capsules or EMEND for oral suspension</td><td>--</td><td>80 mg orally</td><td>80 mg orally</td></tr>
</table></td></tr>
<tr><td>How Supplied</td><td>Lyophilized powder in single-dose glass vial</td></tr>
<tr><td>Storage</td><td>Emend for injection vials must be refrigerated, store at 2°C to 8°C (36°F to 46°F). The reconstituted final drug solution is stable for 24 hours at ambient room temperature [at or below 25°C (77°F)].</td></tr>
<tr><td>Container Closure</td><td>N/A</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On February 27, 2018, we searched the L: drive and AIMS using the terms, fosaprepitant, to identify reviews previously performed by DMEPA.

B.2 Results

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

APPENDIX C. HUMAN FACTORS STUDY – N/A

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On February 28, 2018, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

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

D.2 Results

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

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

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

[c]Abraham, S. Label and Labeling Review for Emend for injection (NDA 22023/S-014). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 10 31. 32 p. OSE RCM No.: 2016-1954.

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

APPENDIX F. OTHER – N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following Emend for injection labels and labeling submitted by Merck and Co. on October 3, 2017.

- Prescribing Information (image not shown)

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/s/

SHERLY ABRAHAM
03/01/2018

SARAH K VEE
03/01/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 28, 2018

To: Mary Chung, Regulatory Project Manager, (DGIEP)

Joette Meyer, Associate Director for Labeling, (DGIEP)

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Team Leader, OPDP

Subject: OPDP Labeling Comments for Emend (fosaprepitant) for injection, for intravenous use

NDA: 22023/Supplement 17

In response to DGIEP's consult request dated November 14, 2017, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for the NDA submission for Emend. This supplement (S17) updated section 1, 2.2, and 5.2.

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DGIEP on February 15, 2018. We have no comments on the PI.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on February 27, 2018.

Thank you for your consult. If you have any questions, please contact Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
02/28/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	February 27, 2018
To:	Donna Griebel, MD Director **Division of Gastroenterology and Inborn Errors Products (DGIEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meeta Patel, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	EMEND (fosaprepitant)
Dosage Form and Route:	for injection, for intravenous use
Application Type/Number:	NDA 022023
Supplement Number:	S-017
Applicant:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

1 INTRODUCTION

On October 3, 2017, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. submitted for the Agency's review a Prior Approval Supplement (PAS) to their New Drug Application (NDA) 022023/S-017 for EMEND (fosaprepitant) for injection. This efficacy supplement includes non-clinical and pediatric clinical data along with a pediatric assessment to fulfill the Applicant's Written Request for pediatric exclusivity and Pediatric Research Equity Act (PREA) PMR 1663-3 for EMEND (fosaprepitant) for injection. This PAS provides for the proposed extended indication of EMEND (fosaprepitant) for injection for the prevention of chemotherapy induced nausea and vomiting in pediatric patients 6 months of age and older treated with highly and moderately emetogenic chemotherapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Gastroenterology and Inborn Errors Products (DGIEP) on November 14, 2017 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for EMEND (fosaprepitant) for injection.

2 MATERIAL REVIEWED

- Draft EMEND (fosaprepitant) for injection PPI received on October 3, 2017 and received by DMPP and OPDP on February 15, 2018.
- Draft EMEND (fosaprepitant) for injection Prescribing Information (PI) received on October 3, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 15, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
02/27/2018

MEETA N PATEL
02/27/2018

SHARON W WILLIAMS
02/27/2018