DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022023

REVISED WRITTEN REQUEST
AMENDMENT 1

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

Dear Mr. Andrew:

Please refer to your correspondence dated July 29, 2009, requesting changes to FDA's February 2, 2009 Written Request for pediatric studies for fosaprepitant dimeglumine.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on February 2, 2009 remain the same. (Text added is underlined. Text deleted is strikethrough.)

NDA ~~21-549~~022023
~~NDA 22-023~~

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

Dear Mr. Andrew:

Reference is made to your ~~September 15, 2004 Proposed Pediatric Study Request for aprepitant and to your amended Proposed Pediatric Study Request dated February 14, 2006. Further reference is made to your~~January 18, 2008 Proposed Pediatric Study Request for fosaprepitant dimeglumine ~~dated January 18, 2008~~.

To obtain needed pediatric information on ~~aprepitant and~~ fosaprepitant dimeglumine, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section

505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the following studies.

~~Fosaprepitant has been found to have an EDTA disodium content of (b) (4) mg per vial of marketed product. The safety ramifications of this amount of EDTA in pediatric patients has not been established. Therefore, you must develop an age appropriate formulation of fosaprepitant for the following pediatric studies.~~

Study 1

~~Postoperative Nausea and Vomiting (PONV)~~Nonclinical Study

Fosaprepitant has been found to have an EDTA disodium content of (b) (4) mg per (b) (4) vial of marketed product. The safety of this amount of EDTA in pediatric patients has not been established. For this reason, you must conduct a nonclinical study as outlined below.

- ***Type of study*:**

A 4-week intravenous toxicity study of fosaprepitant in juvenile dogs (2 weeks of age) must be conducted. Fosaprepitant must be studied in at least 3 dose levels. The high dose used should be the MTD (maximum tolerated dose)/MFD (maximum feasible dose), or should show dose limiting toxicity. The study must include at least 4 animals per sex in each group. The study should assess coagulation parameters, cardiovascular parameters, blood pressure, heart rate, electrolytes, and clinical pharmacology parameters. In addition, complete hematology, clinical chemistry, and urinalysis parameters need to be assessed. Gross and histopathology examinations of all tissues from all animals need to be performed. The study protocol must be submitted and receive FDA concurrence prior to the start of the study.

~~These studies must take into account adequate (e.g., proportionate to study population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.~~

~~A single dose pharmacokinetic (PK) assessment of more than one dose level of aprepitant in pediatric patients at risk for PONV aged 0 to 17 years who are undergoing surgery, and a single dose PK assessment of more than one dose level of fosaprepitant (age appropriate I.V. formulation) in pediatric patients at risk for PONV aged 0 to 17 years who are under going surgery. Utilize either a traditional PK or population PK approach. Study 1 is to be completed prior to enrolling patients into Study 2, Study 3, and Study 4.~~

- ~~***Indication to be studied (PONV)/Objective of the study:***~~

~~The objective of Study 1 is to determine the aprepitant PK parameters after administration of both aprepitant and fosaprepitant in pediatric surgical patients aged 0 to 17 years.~~

- ***Age group in which study will be performed:***

Patients must be representative from each of the following 6 age groups: 0 to 1 month; 1 month to < 6 months; 6 months to < 2 years; 2 years to < 7 years; 7 to < 12 years; and 12 to 17 years.

- ***Number of Patients to be studied:***

The study must include a sufficient number of patients to characterize the single-dose PK of both formulations. The sample size for each age group in the proposed PK study should be able to estimate the PK parameter of clearance with a standard error of 20% or less. For a traditional PK approach, there must be at least a total of 86 evaluable patients per dose group divided among six age groups according to the table below:

Age group	**Minimum number of patients (oral administration)**	**Minimum number of patients (I.V. administration** – age appropriate formulation**)**
0 to 1 month	10	6
1 month to < 6 months	10	6
6 months to < 2 years	10	6
2 years to < 7 years	8	6
7 years to < 12 years	6	6
12 to 17 years	6	6

If a population PK approach is used, the number of subjects must be increased as appropriate. Approximately 4 blood samples per patient should be collected in 4 time brackets (instead of collection of blood samples at 4 fixed time points). Timing of blood samples must be such that the entire time course of plasma concentrations can be accurately captured.

- ***Study endpoints:***

PK endpoints will include the following PK parameters: C_t (concentration at end of infusion for intravenous formulation), Cmax, Tmax, AUC, $T_{1/2}$, clearance, and Vd_{ss}. Additionally, adverse events must be recorded and summarized. Vital signs, including blood pressure, must be monitored and collected.

- ***Drug information***
  - ***Dosage form:***
    - Age-appropriate formulations. Age-appropriate formulations for both routes of administration must be studied. Fosaprepitant has been found to have an EDTA disodium content of (b) (4) mg per vial of marketed product. The safety ramifications of this amount of EDTA in pediatric patients have not been established. Therefore, you must develop an age-appropriate formulation of fosaprepitant for the pediatric studies.
  - ***Route of administration:***
    - Aprepitant oral

- Fosaprepitant intravenous infusion (using an age appropriate I.V. formulation)

- ***Regimen:***
  - The initial single dose in Study 1 should be based on available data from the use of aprepitant in adult surgical patients. You should assess patients from age group 2 to 17 years first, followed by patients from the age groups < 2 years. Upward or downward dose adjustments for the younger age cohort must be based on the PK findings in the preceding older age cohort.

- ***Statistical information, including power of study and statistical assessments:***

The protocol must provide appropriate analyses and descriptive statistics of all PK data.

Study 2
Postoperative Nausea and Vomiting (PONV)

- ***Type of study:***

These studies must take into account adequate (e.g., proportionate to study population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

An adequate, well-controlled, and randomized parallel-group study to evaluate the safety and efficacy of aprepitant and fosaprepitant (age appropriate I.V. formulation) each, versus active control arm based upon superiority analysis in pediatric patients aged 0 to 17 years, who are undergoing surgery.

- ***Indication to be studied (PONV)/Objective of the study:***

The objective of Study 2 is to evaluate the efficacy and safety of aprepitant and fosaprepitant (age appropriate I.V. formulation) administered as a single dose, in the prevention of PONV in pediatric surgical patients aged 0 to 17 years.

- ***Age group in which study will be performed:***

Patients must be 0 to 17 years of age.

- ***Number of Patients to be studied:***

The number of patients is to be distributed approximately evenly over the five age groups, to the extent possible given the pre-operative setting. The oral and I.V. formulations must both be studied in all age groups.

Age group
0 to 1 month
1 month to 2 years
> 2 years to 6 years

> 6 years to 11 years
> 11 years to 17 years

- ***Study endpoints:***
  - Clinical endpoints must include:
    - Complete response (defined as no vomiting and no rescue therapy) will be the primary endpoint for the acute phase (0-24 hours)
    - Number of emetic episodes during the treatment period
    - Use of rescue antiemetic medication
    - Time to rescue
    - Incidence of adverse events
    - Physical examinations
    - Vital signs, including blood pressure monitoring
    - Electrocardiograms
    - Clinical laboratory assessments, including serum electrolytes
    - Time to recovery from anesthesia

- ***Drug information***
  - ***Dosage form:***
    - Age-appropriate formulations. Age appropriate formulations for both routes of administration must be studied. Fosaprepitant has been found to have an EDTA disodium content of (b) (4) mg per vial of marketed product. The safety ramifications of this amount of EDTA in pediatric patients have not been established. Therefore, you must develop an age-appropriate formulation of fosaprepitant for the pediatric studies.
  - ***Route of administration:***
    - Aprepitant-oral
    - Fosaprepitant-intravenous infusion (using an age-appropriate I.V. formulation)
  - ***Regimen:***
    - The dose levels must be selected based on the results of Study 1 of aprepitant in prevention of PONV in pediatric surgical patients.

- ***Statistical information, including power of study and statistical assessments:***

The protocol must provide a statistical analysis plan for assessing the efficacy and safety of aprepitant and fosaprepitant each versus active control. The study must have at least 80% power to detect an effect (assessed by the primary endpoint) that aprepitant and fosaprepitant each are superior to active control. The protocol must be submitted and receive division concurrence prior to the start of the study.

Study ~~3~~2

Chemotherapy Induced Nausea and Vomiting (CINV) – 1 Day Emend Regimen

- ***Type of study*:**

~~These studies~~This study must take into account adequate (e.g., proportionate to ~~study~~ disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

A single dose, randomized, double-blind, PK ~~study~~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 ~~oral aprepitant and~~ intravenous fosaprepitant (age-appropriate I.V. formulation) in combination with a 5HT3 antagonist and dexamethasone in the pediatric patient age groups specified below. ~~Both oral and I.V. formulations must be used in each age group. The~~Available PK data from ~~Study 1~~pediatric studies of aprepitant must be used to design Study ~~3~~2. Study 1 must be completed and results reported to the Agency before children <12 years of age can be enrolled in Study 2.

This study must also characterize the PK parameters of dexamethasone. The PK protocol may use either a traditional PK approach or population PK approach.

- ***Indication to be studied:***

The prevention of acute and delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy (HEC/MEC).

- ***Objective of the study:***

The objectives of Study ~~3~~2 are:

- To evaluate the PK of aprepitant following ~~oral aprepitant or~~ intravenous fosaprepitant (age-appropriate I.V. formulation) in pediatric cancer patients aged ~~1 month~~0 to 17 years being treated with ~~moderately to~~ highly or moderately emetogenic chemotherapy; and
- To characterize the PK of dexamethasone and evaluate the appropriateness of the ~~aprepitant and~~ fosaprepitant (age-appropriate I.V. formulation) dose and the dexamethasone dose in pediatric cancer patients aged ~~1 month~~0 to 17 years receiving the combination regimen.
- To assess the exposure-response relationship of fosaprepitant as add-on therapy with the endpoint of Complete Response.

- ***Age groups in which the study will be performed*:**

Pediatric cancer patients must be representative from each of the following ~~five~~four age groups:
~~1 month to < 6 months; 6 months to < 2 years; 2 years to < 7 years; 7 years to < 12 years; and 12 to 17 years.~~

- < 2 years
- 2 to < 6 years
- 6 to < 12 years
- 12 to 17 years

- ***Number of ~~P~~patients to be studied*:**

~~The sample size for each age group in the proposed PK study should be able to estimate the PK parameter of clearance with a standard error of 20% or less.~~

~~If a traditional PK approach is used, there must be at least 74 evaluable patients distributed according to the table below:~~

~~**Age group**~~	~~**Minimum number of patients (oral administration)**~~	~~**Minimum number of patients (I.V. administration** – age appropriate formulation**)**~~
~~1 month to < 6 months~~	~~10~~	~~6~~
~~6 months to < 2 years~~	~~10~~	~~6~~
~~2 years to < 7 years~~	~~10~~	~~6~~
~~7 years to < 12 years~~	~~8~~	~~6~~
~~12 to 17 years~~	~~6~~	~~6~~

~~The number of subjects needed for Study 3 may be reduced if the PK characteristics in CINV patients could be reasonably predicted with acceptable accuracy using simulation and modeling. This approach might be considered acceptable under two constraints:~~

1. ~~Study 1 (PONV study) is well designed with an adequate number of blood samplings per patient for the full characterization of the PK characteristics in individual groups of pediatric patients. According to the Agency's new pediatric guidance, acceptable characterization of PK parameters should have 20% precision.~~
2. ~~Adult data (high/low doses) and pediatric data (low dose) can be bridged to assess any nonlinear kinetics in pediatric patients.~~

~~If a population PK approach is used, the number of subjects must be increased appropriately and proportionately. Approximately 4 blood samples per patient must be collected in four time brackets (instead of collecting blood samples at fixed time points).~~ The number of patients is to be distributed approximately evenly over the four age groups to the extent possible, given the clinical setting. The sample size should be sufficient to characterize the exposure-response relationship with modeling.

Timing of PK blood samples must be such that the ~~entire time course of aprepitant plasma concentrations is~~ PK parameters can be accurately ~~captured~~determined. The protocol must be submitted to the Agency for review prior to initiating the study.

- ***Study endpoints:***
  - PK endpoints must include PK parameters for both aprepitant and dexamethasone such as ~~C_1,~~ C_{max}, T_{max}, AUC, $T_{1/2}$, clearance, and Vd_{ss}, as applicable.
  - Dose-ranging study endpoints must include Complete Response (defined as no vomiting, no retching, and no use of rescue therapy) in the overall phase (0-120 hours), acute phase (0-24 hours), and delayed phase (>24 hours-120 hours). Time 0 is when chemotherapy administration is initiated.
  - Safety outcomes must include adverse events (recorded and summarized), physical examinations, v~~V~~ital signs~~,~~ (including blood pressure~~,~~), 12-lead electrocardiograms, and clinical laboratory assessments (including electrolytes and serum liver enzymes). All adverse events must be monitored ~~and collected~~until symptom resolution or until the condition stabilizes.

- ***Drug information***
  - ***Dosage form:***
    - ~~Age-appropriate formulations. Age-appropriate formulations for both routes of administration must be studied.~~You must develop an age-appropriate formulation of fosaprepitant with reduced EDTA content. Fosaprepitant has been found to have an EDTA disodium content of (b) (4) mg per (b) (4) vial of marketed product. The safety ~~ramifications~~ of this amount of EDTA in pediatric patients ~~have~~has not been established. ~~Therefore, you must develop an age-appropriate formulation of fosaprepitant for the pediatric studies.~~
  - ***Route of administration:***
    - ~~Aprepitant oral~~
    - ~~Fosaprepitant i~~Intravenous infusion (using an age-appropriate I.V. formulation)
  - ***Regimen:***
    - The initial single dose~~s~~ in Study ~~3~~2 should be based on available data from the use of aprepitant or fosaprepitant in adult cancer patients and aprepitant pediatric ~~Study 1 undergoing treatment with moderately to highly emetogenic chemotherapy~~studies. You ~~can~~should assess patients from ages ~~groups~~ 2 to 17 years first, followed by patients ~~from age groups~~ < 2 years. ~~Upward or downward dose~~Dose adjustments for the successive younger age cohort must be based on the PK findings ~~in~~from the preceding older age cohort.
    - The use and/or dose of 5HT3 antagonist and/or corticosteroid must be based on a recognized standard of care used in the prevention of CINV in pediatric cancer patients undergoing treatment with ~~moderately to~~ highly or moderately emetogenic chemotherapy.
    - In the study protocol, you must propose a dosing regimen for ~~aprepitant and~~ fosaprepitant (using age-appropriate I.V. formulation), dexamethasone, and a 5HT3 antagonist, and you must provide the rationale for the chosen dosing regimen.
    - If emesis or nausea occurs, rescue with an approved therapy is permitted.

- ***Statistical information, including power of study and statistical assessments:***

The protocol must provide appropriate analyses and descriptive statistics of all PK and clinical response data consistent with the age groups noted earlier. In addition, appropriate analysis must be performed to characterize the exposure-response relationship.

Study 43

Chemotherapy Induced Nausea and Vomiting: Highly Emetogenic Chemotherapy (CINV-HEC) – 1 Day Emend Regimen

- ***Type of study*:**

~~These studies~~This study must take into account adequate (e.g., proportionate to ~~study~~disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

An adequate, placebo-controlled, double-blind, randomized, ~~parallel group,~~ add-on ~~design~~ study to evaluate the safety and efficacy of ~~aprepitant and~~ a single dose of fosaprepitant (age-appropriate I.V. formulation), in combination with a 5HT3 antagonist ~~with or without dexamethasone (as appropriate),~~ as compared to standard therapy (a 5HT3 antagonist ~~with or without dexamethasone, as appropriate~~) in pediatric cancer patients ~~age 1 month~~0 to 17 years old undergoing treatment with highly ~~and moderately~~ emetogenic chemotherapy. This study must be designed to demonstrate superiority of ~~combination antiemetic therapy with~~the fosaprepitant ~~or aprepitant~~regimen versus standard therapy. Dexamethasone should be used, as appropriate, for the prevention of CINV as standard of care. The ~~pharmacokinetic~~PK and dose ranging data from Study ~~1~~2, and ~~Study 3~~available aprepitant pediatric PK data, must be used to determine dosing for Study ~~4~~3.

- ***Indication to be studied:***

The prevention of acute and delayed nausea and vomiting associated with highly ~~and moderately~~ emetogenic cancer chemotherapy (HEC).

- ***Objective of the study:***

The objective~~s~~ of Study ~~4~~3 ~~are~~is:

- To evaluate the safety and efficacy of ~~aprepitant and~~ fosaprepitant (using an age-appropriate I.V. formulation) as part of a combination antiemetic therapy ~~(5HT3 antagonist with or without dexamethasone, as appropriate)~~ in pediatric cancer patients ~~age 1 month~~0 to 17 years old being treated with highly ~~and moderately~~ emetogenic chemotherapy for ~~preventing~~the prevention of acute and delayed chemotherapy-induced nausea and vomiting.

- ***Age group in which the study will be performed*:**

The safety and efficacy study will enroll pediatric cancer patients ~~ages 1 month~~0 to 17 years ~~old~~of age.

- ***Number of ~~P~~patients to be studied*:**

The number of patients is to be distributed approximately evenly over the four age groups outlined in Study 2. Diligent and reasonable efforts must be made to encourage enrollment across all age groups, including younger children, and these efforts must be documented in the study report.

~~The study of efficacy and safety must include a sufficient number of patients to detect an effect on the primary endpoint. A stratified randomization technique is recommended to randomize pediatric patients age 1 month to 17 years old into aprepitant and fosaprepitant (using an age appropriate I.V. formulation) as part of a combination antiemetic therapy (5HT3 antagonist with or without dexamethasone, as appropriate) group and standard 5HT3 antagonist with or without dexamethasone (as appropriate) therapy group. Since co-administration of dexamethasone may have a confounding antiemetic effect on the antiemetic outcomes, the randomization should be stratified by dexamethasone at baseline (combination antiemetic regimen with or without dexamethasone) in addition to the type of emetogenic chemotherapy, i.e. highly or moderately emetogenic, to assure the two treatment arms are balanced for each of the four categories formed by the combinations of dexamethasone at baseline and the type of emetogenic therapy.~~

~~Because the use of corticosteroids in pediatric cancer patients varies depending on the type of tumor, it is acceptable to remove the requirement for concomitant dexamethasone from the study regimen and standard regimen.~~

- ***Study endpoints:***
  - Clinical endpoints must include:
    - Complete response (defined as no vomiting, no retching, and no use of rescue therapy) ~~will be the primary endpoint for~~in the overall phase (0-120 hours) will be the primary endpoint. Time 0 is when chemotherapy administration is initiated.
    - Complete response (defined as no vomiting, no retching, and no use of rescue therapy) in the acute phase (0-24 hours) and delayed phase (>24-120 hours) will be key secondary endpoints
    - Number of emetic episodes during the treatment period (0-120 hours)
    - Use of rescue antiemetic medication
    - Time to rescue
    - ~~Incidence of adverse events, including febrile neutropenia~~
    - ~~Physical examinations~~
    - ~~Vital signs, including blood pressure monitoring~~
    - ~~Electrocardiograms~~
    - ~~Clinical laboratory assessments, including serum electrolytes~~

  - Safety Endpoints
    - Safety outcomes must include adverse events (recorded and summarized), physical examinations, vital signs (including blood pressure), 12-lead electrocardiograms, and clinical laboratory assessments (including

electrolytes with ionized serum calcium and serum liver enzymes). All adverse events must be monitored until symptom resolution or until the condition stabilizes.

- ***Drug information***
  - ***Dosage form:***
    - ~~Age-appropriate formulations. Formulations for both routes of administration must be studied.~~ You must develop an age-appropriate formulation of fosaprepitant with reduced EDTA content. Fosaprepitant has been found to have an EDTA disodium content of (b) (4) mg per (b) (4) vial of marketed product. The safety ~~ramifications~~ of this amount of EDTA in pediatric patients ~~have~~has not been established. ~~Therefore, you must develop an age-appropriate formulation of fosaprepitant for the pediatric studies.~~
  - ***Route of administration:***
    - ~~Aprepitant oral~~
    - ~~Fosaprepitant i~~Intravenous infusion (using an age-appropriate I.V. formulation)
  - ***Regimen:***
    - The safety and efficacy must be studied in pediatric cancer patients ~~age 1 month~~0 to 17 years old undergoing treatment with highly ~~and moderately~~ emetogenic chemotherapy. The study must be well-controlled and randomized ~~with~~using an ~~arm of aprepitant and~~ active control group on standard therapy. The study will include two arms as follows:
      - Single dose regimen of fosaprepitant (age-appropriate I.V. formulation) as part of combination antiemetic therapy (5HT3 antagonist with or without dexamethasone, as appropriate) ~~and an arm of~~
      - Active control: standard antiemetic therapy (5HT3 with or without dexamethasone therapy~~.~~)

- ***Statistical information, including power of study and statistical assessments:***

For the clinical outcome data, the protocol must provide a statistical analysis plan for assessing efficacy and safety for a single dose of ~~aprepitant and~~ fosaprepitant as part of ~~a~~ combination antiemetic therapy ~~(5HT3 antagonist with or without dexamethasone, as appropriate)~~ as compared to ana control arm of standard ~~5HT3 with or without dexamethasone antiemetic~~ therapy (5HT3 antagonist). The study must ~~have~~enroll a sufficient number of patients to provide at least 80% power to reject the null hypothesis that the combination of antiemetic therapy with fosaprepitant is not superior to standard antiemetic therapy at a one-sided significance level of 2.5%, assessed by the primary endpoint. With at least 80% power, the study should be able to detect a clinically meaningful effect (assessed by the primary endpoint) to show that ~~aprepitant and~~ fosaprepitant as part of ~~a~~ combination antiemetic therapy ~~(5HT3 antagonist with or without dexamethasone, as appropriate)~~ is superior to standard antiemetic therapy. You must also clearly state the null and the alternative hypotheses. The primary endpoint analysis should be stratified by age group and use of dexamethasone.

In addition, if you plan to include certain secondary endpoints in the labeling package, you need to provide a multiplicity adjustment method to control the overall Type I error rate for secondary efficacy comparisons between the fosaprepitant regimen and standard therapy.

The protocol must be submitted and receive division concurrence prior to the start of the study.

Study 4

Chemotherapy Induced Nausea and Vomiting: Moderately Emetogenic Chemotherapy (CINV-MEC) – 1 Day Emend Regimen

- ***Type of study*:**

This study must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

An adequate, placebo-controlled, double-blind, randomized, add-on study to evaluate the safety and efficacy of a single dose of fosaprepitant (age-appropriate I.V. formulation), in combination with a 5HT3 antagonist, as compared to standard therapy (a 5HT3 antagonist) in pediatric cancer patients 0 to 17 years old undergoing treatment with moderately emetogenic chemotherapy. This study must be designed to demonstrate superiority of the fosaprepitant regimen versus standard therapy. Dexamethasone should be used, as appropriate, for the prevention of CINV as standard of care. The PK and dose ranging data from Study 2, and available aprepitant pediatric PK data, must be used to determine dosing for Study 4.

- ***Indication to be studied:***

The prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy (MEC).

- ***Objective of the study:***

The objective of Study 4 is:

  - To evaluate the safety and efficacy of fosaprepitant (using an age-appropriate I.V. formulation) as part of a combination antiemetic therapy in pediatric cancer patients 0 to 17 years old being treated with moderately emetogenic chemotherapy for the prevention of acute and delayed chemotherapy-induced nausea and vomiting.

- ***Age group in which the study will be performed*:**

The safety and efficacy study will enroll pediatric cancer patients 0 to 17 years of age.

- ***Number of patients to be studied*:**

The number of patients is to be distributed approximately evenly over the four age groups outlined in Study 2. Diligent and reasonable efforts must be made to encourage enrollment across all age groups, including younger children, and these efforts must be documented in the study report.

- ***Study endpoints:***
  - Clinical endpoints must include:
    - Complete response (defined as no vomiting, no retching, and no use of rescue therapy) in the overall phase (0-120 hours) will be the primary endpoint. Time 0 is when chemotherapy administration is initiated.
    - Complete response (defined as no vomiting, no retching, and no use of rescue therapy) in the acute phase (0-24 hours) and delayed phase (>24-120 hours) will be key secondary endpoints
    - Number of emetic episodes during the treatment period (0-120 hours)
    - Use of rescue antiemetic medication
    - Time to rescue
  - Safety Endpoints
    - Safety outcomes must include adverse events (recorded and summarized), physical examinations, vital signs (including blood pressure), 12-lead electrocardiograms, and clinical laboratory assessments (including electrolytes with ionized serum calcium and serum liver enzymes). All adverse events must be monitored until symptom resolution or until the condition stabilizes.

- ***Drug information***
  - ***Dosage form:***
    - You must develop an age-appropriate formulation of fosaprepitant with reduced EDTA content. Fosaprepitant has been found to have an EDTA disodium content of (b) (4) mg per (b) (4) vial of marketed product. The safety of this amount of EDTA in pediatric patients has not been established.
  - ***Route of administration:***
    - Intravenous infusion (using an age-appropriate I.V. formulation)
  - ***Regimen:***
    - The safety and efficacy must be studied in pediatric cancer patients 0 to 17 years old undergoing treatment with moderately emetogenic chemotherapy. The study must be well-controlled and randomized using an active control group on standard therapy. The study will include two arms as follows:
      - Single dose regimen of fosaprepitant (age-appropriate I.V. formulation) as part of combination antiemetic therapy (5HT3 antagonist with or without dexamethasone, as appropriate)
      - Active control: standard antiemetic therapy (5HT3 with or without dexamethasone therapy)

- ***Statistical information, including power of study and statistical assessments:***

For the clinical outcome data, the protocol must provide a statistical analysis plan for assessing efficacy and safety for a single dose of fosaprepitant as part of combination antiemetic therapy, as compared to a control arm of standard therapy (5HT3 antagonist). The study must enroll a sufficient number of patients to provide at least 80% power to reject the null hypothesis that the combination of antiemetic therapy with fosaprepitant is not superior to the standard antiemetic therapy at a one-sided significance level of 2.5%, assessed by the primary endpoint. With at least 80% power, the study should be able to detect a clinically meaningful effect (assessed by the primary endpoint) to show that fosaprepitant as part of combination antiemetic therapy is superior to standard antiemetic therapy. You must also clearly state the null and the alternative hypotheses. The primary endpoint analysis should be stratified by age group and use of dexamethasone.

In addition, if you plan to include certain secondary endpoints in the labeling package, you need to provide a multiplicity adjustment method to control the overall Type I error rate for the secondary efficacy comparisons between the fosaprepitant regimen and standard therapy.

The protocol must be submitted and receive division concurrence prior to the start of the study.

Study 5

Chemotherapy Induced Nausea and Vomiting (CINV)
3 Day (I.V./Oral/Oral) Emend Regimen

- ***Type of study*:**

This study must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

A PK study of fosaprepitant to characterize aprepitant PK parameters on Day 1 of the 3-day I.V./Oral/Oral regimen 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 adult and pediatric studies of aprepitant must be used to design Study 5. Study 1 must be completed and results reported to the Agency before children <12 years of age can be enrolled in Study 5.

The PK protocol may use either a traditional PK approach or population PK approach.

- ***Indication to be studied:***

The prevention of acute and delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy (HEC/MEC).

- ***Objective of the study:***

The objective of Study 5 is:

  - To demonstrate comparable PK of aprepitant between oral and IV regimens following intravenous fosaprepitant (age-appropriate I.V. formulation) in the 3-day (IV/oral/oral) pediatric cancer patients aged 0 to 17 years being treated with highly or moderately emetogenic chemotherapy

- ***Age groups in which the study will be performed*:**

Pediatric cancer patients must be representative from each of the following four age groups unless adequate justification can be made to waive a specific age group:

  - < 2 years
  - 2 to < 6 years
  - 6 to < 12 years
  - 12 to 17 years

- ***Number of patients to be studied*:**

The study must be prospectively powered to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution for aprepitant in each age group. Timing of blood samples must be such that the full plasma concentration-time profile of aprepitant is accurately captured.

- ***Study endpoints:***
  - PK endpoints must include PK parameters for both aprepitant and dexamethasone such as C_{max}, T_{max}, AUC, $T_{1/2}$, clearance, and Vd, as applicable.
  - Safety outcomes must include adverse events (recorded and summarized), physical examinations, vital signs (including blood pressure), 12-lead electrocardiograms, and clinical laboratory assessments (including electrolytes and serum liver enzymes). All adverse events must be monitored until symptom resolution or until the condition stabilizes.

- ***Drug information***
  - ***Dosage form:***
    - You must develop an age-appropriate formulation of fosaprepitant with reduced EDTA content. Fosaprepitant has been found to have an EDTA disodium content of (b) (4) mg per (b) (4) vial of marketed product. The safety of this amount of EDTA in pediatric patients has not been established.
  - ***Route of administration:***
    - Intravenous infusion (using an age-appropriate I.V. formulation)
  - ***Regimen:***
    - The doses in Study 5 should be based on available data from the use of aprepitant or fosaprepitant in healthy adults, adult cancer patients, and from aprepitant pediatric studies. You should assess patients from ages 2 to 17 years first, followed by patients < 2 years. Dose adjustments for the

successive younger age cohort must be based on the PK findings from the preceding older age cohort.

- The use and/or dose of 5HT3 antagonist and/or corticosteroid must be based on a recognized standard of care used in the prevention of CINV in pediatric cancer patients undergoing treatment with highly or moderately emetogenic chemotherapy.
- In the study protocol, you must propose a dosing regimen for fosaprepitant (using age-appropriate I.V. formulation), dexamethasone, and a 5HT3 antagonist, and you must provide the rationale for the chosen dosing regimen.
- If emesis or nausea occurs, rescue with an approved therapy is permitted.

- ***Statistical information, including power of study and statistical assessments:***

The protocol must provide appropriate analyses and descriptive statistics of all PK data consistent with the age groups noted earlier.

Studies ~~1,~~ 2, 3, ~~and~~ 4, and 5

Use an age-appropriate formulation in the studies described above. The content of EDTA in the current I.V. formulation (fosaprepitant dimeglumine) is considered too high for the pediatric population. Therefore, you must develop ~~I.V. and oral~~an age-appropriate formulation~~s~~ for the pediatric population. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric populations, you must seek marketing approval for that age-appropriate formulation.

If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric populations studied (i.e., receives marketing approval), 2) the Agency publishes the exclusivity determination notice required under section 505A(e)(1) of the Act, and 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice reflecting the fact that the approved pediatric formulation has not been marketed, in accordance with section 505A(e)(2).

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age-appropriate formulation may be conducted in adults.

- *Drug specific safety concerns to be monitored*: Fosaprepitant is a pro-drug of aprepitant and will be readily converted to aprepitant in the human body. Therefore, fosaprepitant shares the following safety concerns regarding aprepitant. Aprepitant has a complex metabolism. Aprepitant is a substrate, a weak-to-moderate inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9.

  Aprepitant may increase the rate of warfarin metabolism and decreases its activity as measured by International Normalized Ratio (INR). Thus, you should exclude pediatric patients taking warfarin from these studies.

  Coadministration of aprepitant and hormonal contraceptives may affect the efficacy of the birth control. We recommend that your protocol incorporate barrier method contraception for the CINV studies.

  Coadministration of fosaprepitant and diltiazem may result in episodes of lower blood pressure. Blood pressure must be monitored in your studies.

  ~~Since fosaprepitant is a prodrug of aprepitant and will be converted to aprepitant in the human body, fosaprepitant shares all the safety concerns regarding aprepitant.~~

  ~~The fosaprepitant formulation contains a high EDTA disodium level. You should develop an age-appropriate formulation of fosaprepitant for the pediatric studies.~~

- *Labeling that may result from the studies*: You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the studies demonstrate that ~~aprepitant and~~ fosaprepitant ~~are~~is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the studies. Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the studies.

- *Timeframe for submitting reports of the studies:* Reports of the above studies must be submitted to the Agency on or before ~~June 30, 2012~~December 31, 2017. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15

months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated February 2, 2009, as amended by this letter, must be submitted to the Agency on or before December 31, 2017, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, call Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Complete Copy of Written Request as Amended

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022023

WRITTEN REQUEST

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

Dear Mr. Andrew:

Reference is made to your January 18, 2008 Proposed Pediatric Study Request for fosaprepitant dimeglumine.

To obtain needed pediatric information on fosaprepitant dimeglumine, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the following studies.

Study 1

Nonclinical Study

Fosaprepitant has been found to have an EDTA disodium content of (b) (4) mg per (b) (4) vial of marketed product. The safety of this amount of EDTA in pediatric patients has not been established. For this reason, you must conduct a nonclinical study as outlined below.

- ***Type of study*:**
A 4-week intravenous toxicity study of fosaprepitant in juvenile dogs (2 weeks of age) must be conducted. Fosaprepitant must be studied in at least 3 dose levels. The high dose used should be the MTD (maximum tolerated dose)/MFD (maximum feasible dose), or should show dose limiting toxicity. The study must include at least 4 animals per sex in each group. The study should assess coagulation parameters, cardiovascular parameters, blood pressure, heart rate, electrolytes, and clinical pharmacology parameters. In addition, complete hematology, clinical chemistry, and urinalysis parameters need to be assessed. Gross and histopathology examinations of all tissues from all animals need to be performed. The study protocol must be submitted and receive FDA concurrence prior to the start of the study.

Study 2

Chemotherapy Induced Nausea and Vomiting (CINV) – 1 Day Emend Regimen

- ***Type of study*:**

This study must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

A single dose, randomized, double-blind, 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.

This study must also characterize the PK parameters of dexamethasone. The PK protocol may use either a traditional PK approach or population PK approach.

- ***Indication to be studied:***

The prevention of acute and delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy (HEC/MEC).

- ***Objective of the study:***

The objectives of Study 2 are:

- To evaluate the PK of aprepitant following intravenous fosaprepitant (age-appropriate I.V. formulation) in pediatric cancer patients aged 0 to 17 years being treated with highly or moderately emetogenic chemotherapy; and
- To characterize the PK of dexamethasone and evaluate the appropriateness of the fosaprepitant (age-appropriate I.V. formulation) dose and the dexamethasone dose in pediatric cancer patients aged 0 to 17 years receiving the combination regimen.
- To assess the exposure-response relationship of fosaprepitant as add-on therapy with the endpoint of Complete Response.

- ***Age groups in which the study will be performed*:**

Pediatric cancer patients must be representative from each of the following four age groups:

- < 2 years
- 2 to < 6 years
- 6 to < 12 years
- 12 to 17 years

- ***Number of patients to be studied*:**

The number of patients is to be distributed approximately evenly over the four age groups to the extent possible, given the clinical setting. The sample size should be sufficient to characterize the exposure-response relationship with modeling.

Timing of PK blood samples must be such that the PK parameters can be accurately determined. The protocol must be submitted to the Agency for review prior to initiating the study.

- ***Study endpoints:***
  - PK endpoints must include PK parameters for both aprepitant and dexamethasone such as C_{max}, T_{max}, AUC, $T_{1/2}$, clearance, and Vd_{ss}, as applicable.
  - Dose-ranging study endpoints must include Complete Response (defined as no vomiting, no retching, and no use of rescue therapy) in the overall phase (0-120 hours), acute phase (0-24 hours), and delayed phase (>24 hours-120 hours). Time 0 is when chemotherapy administration is initiated.
  - Safety outcomes must include adverse events (recorded and summarized), physical examinations, vital signs (including blood pressure), 12-lead electrocardiograms, and clinical laboratory assessments (including electrolytes and serum liver enzymes). All adverse events must be monitored until symptom resolution or until the condition stabilizes.

- ***Drug information***
  - ***Dosage form:***
    - You must develop an age-appropriate formulation of fosaprepitant with reduced EDTA content. Fosaprepitant has been found to have an EDTA disodium content of (b) (4) mg per (b) (4) vial of marketed product. The safety of this amount of EDTA in pediatric patients has not been established.
  - ***Route of administration:***
    - Intravenous infusion (using an age-appropriate I.V. formulation)
  - ***Regimen:***
    - The initial single doses in Study 2 should be based on available data from the use of aprepitant or fosaprepitant in adult cancer patients and aprepitant pediatric studies. You should assess patients from ages 2 to 17 years first, followed by patients < 2 years. Dose adjustments for the successive younger age cohort must be based on the PK findings from the preceding older age cohort.
    - The use and/or dose of 5HT3 antagonist and/or corticosteroid must be based on a recognized standard of care used in the prevention of CINV in pediatric cancer patients undergoing treatment with highly or moderately emetogenic chemotherapy.
    - In the study protocol, you must propose a dosing regimen for fosaprepitant (using age-appropriate I.V. formulation), dexamethasone, and a 5HT3 antagonist, and you must provide the rationale for the chosen dosing regimen.

- If emesis or nausea occurs, rescue with an approved therapy is permitted.

- ***Statistical information, including power of study and statistical assessments:***

The protocol must provide appropriate analyses and descriptive statistics of all PK and clinical response data consistent with the age groups noted earlier. In addition, appropriate analysis must be performed to characterize the exposure-response relationship.

Study 3

Chemotherapy Induced Nausea and Vomiting: Highly Emetogenic Chemotherapy (CINV-HEC) – 1 Day Emend Regimen

- ***Type of study*:**

This study must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

An adequate, placebo-controlled, double-blind, randomized, add-on study to evaluate the safety and efficacy of a single dose of fosaprepitant (age-appropriate I.V. formulation), in combination with a 5HT3 antagonist, as compared to standard therapy (a 5HT3 antagonist) in pediatric cancer patients 0 to 17 years old undergoing treatment with highly emetogenic chemotherapy. This study must be designed to demonstrate superiority of the fosaprepitant regimen versus standard therapy. Dexamethasone should be used, as appropriate, for the prevention of CINV as standard of care. The PK and dose ranging data from Study 2, and available aprepitant pediatric PK data, must be used to determine dosing for Study 3.

- ***Indication to be studied:***

The prevention of acute and delayed nausea and vomiting associated with highly emetogenic cancer chemotherapy (HEC).

- ***Objective of the study:***

The objective of Study 3 is:

- To evaluate the safety and efficacy of fosaprepitant (using an age-appropriate I.V. formulation) as part of combination antiemetic therapy in pediatric cancer patients 0 to 17 years old being treated with highly emetogenic chemotherapy for the prevention of acute and delayed chemotherapy-induced nausea and vomiting.

- ***Age group in which the study will be performed*:**

The safety and efficacy study will enroll pediatric cancer patients 0 to 17 years of age.

- ***Number of patients to be studied*:**

The number of patients is to be distributed approximately evenly over the four age groups outlined in Study 2. Diligent and reasonable efforts must be made to encourage enrollment across all age groups, including younger children, and these efforts must be documented in the study report.

- ***Study endpoints:***
  - Clinical endpoints must include:
    - Complete response (defined as no vomiting, no retching, and no use of rescue therapy) in the overall phase (0-120 hours) will be the primary endpoint. Time 0 is when chemotherapy administration is initiated.
    - Complete response (defined as no vomiting, no retching, and no use of rescue therapy) in the acute phase (0-24 hours) and delayed phase (>24-120 hours) will be key secondary endpoints
    - Number of emetic episodes during the treatment period (0-120 hours)
    - Use of rescue antiemetic medication
    - Time to rescue

  - Safety Endpoints
    - Safety outcomes must include adverse events (recorded and summarized), physical examinations, vital signs (including blood pressure), 12-lead electrocardiograms, and clinical laboratory assessments (including electrolytes with ionized serum calcium and serum liver enzymes). All adverse events must be monitored until symptom resolution or until the condition stabilizes.

- ***Drug information***
  - ***Dosage form:***
    - You must develop an age-appropriate formulation of fosaprepitant with reduced EDTA content. Fosaprepitant has been found to have an EDTA disodium content of (b) (4) mg per (b) (4) vial of marketed product. The safety of this amount of EDTA in pediatric patients has not been established.
  - ***Route of administration:***
    - Intravenous infusion (using an age-appropriate I.V. formulation)
  - ***Regimen:***
    - The safety and efficacy must be studied in pediatric cancer patients 0 to 17 years old undergoing treatment with highly emetogenic chemotherapy. The study must be well-controlled and randomized using an active control group on standard therapy. The study will include two arms as follows:
      - Single dose regimen of fosaprepitant (age-appropriate I.V. formulation) as part of combination antiemetic therapy (5HT3 antagonist with or without dexamethasone, as appropriate)
      - Active control: standard antiemetic therapy (5HT3 with or without dexamethasone therapy)

- ***Statistical information, including power of study and statistical assessments:***

For the clinical outcome data, the protocol must provide a statistical analysis plan for assessing efficacy and safety for a single dose of fosaprepitant as part of combination antiemetic therapy, as compared to a control arm of standard therapy (5HT3 antagonist). The study must enroll a sufficient number of patients to provide at least 80% power to reject the null hypothesis that the combination of antiemetic therapy with fosaprepitant is not superior to standard antiemetic therapy at a one-sided significance level of 2.5%, assessed by the primary endpoint. With at least 80% power, the study should be able to detect a clinically meaningful effect (assessed by the primary endpoint) to show that fosaprepitant as part of combination antiemetic therapy is superior to standard antiemetic therapy. You must also clearly state the null and the alternative hypotheses. The primary endpoint analysis should be stratified by age group and use of dexamethasone.

In addition, if you plan to include certain secondary endpoints in the labeling package, you need to provide a multiplicity adjustment method to control the overall Type I error rate for secondary efficacy comparisons between the fosaprepitant regimen and standard therapy.

The protocol must be submitted and receive division concurrence prior to the start of the study.

Study 4

Chemotherapy Induced Nausea and Vomiting: Moderately Emetogenic Chemotherapy (CINV-MEC) – 1 Day Emend Regimen

- ***Type of study*:**

This study must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

An adequate, placebo-controlled, double-blind, randomized, add-on study to evaluate the safety and efficacy of a single dose of fosaprepitant (age-appropriate I.V. formulation), in combination with a 5HT3 antagonist, as compared to standard therapy (a 5HT3 antagonist) in pediatric cancer patients 0 to 17 years old undergoing treatment with moderately emetogenic chemotherapy. This study must be designed to demonstrate superiority of the fosaprepitant regimen versus standard therapy. Dexamethasone should be used, as appropriate, for the prevention of CINV as standard of care. The PK and dose ranging data from Study 2, and available aprepitant pediatric PK data, must be used to determine dosing for Study 4.

- ***Indication to be studied:***

The prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy (MEC).

- ***Objective of the study:***

The objective of Study 4 is:

  - To evaluate the safety and efficacy of fosaprepitant (using an age-appropriate I.V. formulation) as part of a combination antiemetic therapy in pediatric cancer patients 0 to 17 years old being treated with moderately emetogenic chemotherapy for the prevention of acute and delayed chemotherapy-induced nausea and vomiting.

- ***Age group in which the study will be performed*:**

The safety and efficacy study will enroll pediatric cancer patients 0 to 17 years of age.

- ***Number of patients to be studied*:**

The number of patients is to be distributed approximately evenly over the four age groups outlined in Study 2. Diligent and reasonable efforts must be made to encourage enrollment across all age groups, including younger children, and these efforts must be documented in the study report.

- ***Study endpoints:***
  - Clinical endpoints must include:
    - Complete response (defined as no vomiting, no retching, and no use of rescue therapy) in the overall phase (0-120 hours) will be the primary endpoint. Time 0 is when chemotherapy administration is initiated.
    - Complete response (defined as no vomiting, no retching, and no use of rescue therapy) in the acute phase (0-24 hours) and delayed phase (>24-120 hours) will be key secondary endpoints
    - Number of emetic episodes during the treatment period (0-120 hours)
    - Use of rescue antiemetic medication
    - Time to rescue

  - Safety Endpoints
    - Safety outcomes must include adverse events (recorded and summarized), physical examinations, vital signs (including blood pressure), 12-lead electrocardiograms, and clinical laboratory assessments (including electrolytes with ionized serum calcium and serum liver enzymes). All adverse events must be monitored until symptom resolution or until the condition stabilizes.

- ***Drug information***
  - ***Dosage form:***
    - You must develop an age-appropriate formulation of fosaprepitant with reduced EDTA content. Fosaprepitant has been found to have an EDTA disodium content of (b) (4) mg per (b) (4) vial of marketed product. The safety of this amount of EDTA in pediatric patients has not been established.

- ***Route of administration:***
  - Intravenous infusion (using an age-appropriate I.V. formulation)
- ***Regimen:***
  - The safety and efficacy must be studied in pediatric cancer patients 0 to 17 years old undergoing treatment with moderately emetogenic chemotherapy. The study must be well-controlled and randomized using an active control group on standard therapy. The study will include two arms as follows:
    - Single dose regimen of fosaprepitant (age-appropriate I.V. formulation) as part of combination antiemetic therapy (5HT3 antagonist with or without dexamethasone, as appropriate)
    - Active control: standard antiemetic therapy (5HT3 with or without dexamethasone therapy)

- ***Statistical information, including power of study and statistical assessments:***

For the clinical outcome data, the protocol must provide a statistical analysis plan for assessing efficacy and safety for a single dose of fosaprepitant as part of combination antiemetic therapy, as compared to a control arm of standard therapy (5HT3 antagonist). The study must enroll a sufficient number of patients to provide at least 80% power to reject the null hypothesis that the combination of antiemetic therapy with fosaprepitant is not superior to the standard antiemetic therapy at a one-sided significance level of 2.5%, assessed by the primary endpoint. With at least 80% power, the study should be able to detect a clinically meaningful effect (assessed by the primary endpoint) to show that fosaprepitant as part of combination antiemetic therapy is superior to standard antiemetic therapy. You must also clearly state the null and the alternative hypotheses. The primary endpoint analysis should be stratified by age group and use of dexamethasone.

In addition, if you plan to include certain secondary endpoints in the labeling package, you need to provide a multiplicity adjustment method to control the overall Type I error rate for the secondary efficacy comparisons between the fosaprepitant regimen and standard therapy.

The protocol must be submitted and receive division concurrence prior to the start of the study.

Study 5

Chemotherapy Induced Nausea and Vomiting (CINV)
3 Day (I.V./Oral/Oral) Emend Regimen

- ***Type of study*:**

This study must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

A PK study of fosaprepitant to characterize aprepitant PK parameters on Day 1 of the 3-day I.V./Oral/Oral regimen 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 adult and pediatric studies of aprepitant must be used to design Study 5. Study 1 must be completed and results reported to the Agency before children <12 years of age can be enrolled in Study 5.

The PK protocol may use either a traditional PK approach or population PK approach.

- ***Indication to be studied:***

The prevention of acute and delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy (HEC/MEC).

- ***Objective of the study:***

The objective of Study 5 is:

  - To demonstrate comparable PK of aprepitant between oral and IV regimens following intravenous fosaprepitant (age-appropriate I.V. formulation) in the 3-day (IV/oral/oral) pediatric cancer patients aged 0 to 17 years being treated with highly or moderately emetogenic chemotherapy

- ***Age groups in which the study will be performed*:**

Pediatric cancer patients must be representative from each of the following four age groups unless adequate justification can be made to waive a specific age group:

  - < 2 years
  - 2 to < 6 years
  - 6 to < 12 years
  - 12 to 17 years

- ***Number of patients to be studied*:**

The study must be prospectively powered to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution for aprepitant in each age group. Timing of blood samples must be such that the full plasma concentration-time profile of aprepitant is accurately captured.

- ***Study endpoints:***
  - PK endpoints must include PK parameters for both aprepitant and dexamethasone such as C_{max}, T_{max}, AUC, $T_{1/2}$, clearance, and Vd, as applicable.
  - Safety outcomes must include adverse events (recorded and summarized), physical examinations, vital signs (including blood pressure), 12-lead electrocardiograms, and clinical laboratory assessments (including electrolytes and serum liver enzymes). All adverse events must be monitored until symptom resolution or until the condition stabilizes.

- ***Drug information***
  - ***Dosage form:***
    - You must develop an age-appropriate formulation of fosaprepitant with reduced EDTA content. Fosaprepitant has been found to have an EDTA disodium content of (b) (4) mg per (b) (4) vial of marketed product. The safety of this amount of EDTA in pediatric patients has not been established.
  - ***Route of administration:***
    - Intravenous infusion (using an age-appropriate I.V. formulation)
  - ***Regimen:***
    - The doses in Study 5 should be based on available data from the use of aprepitant or fosaprepitant in healthy adults, adult cancer patients, and from aprepitant pediatric studies. You should assess patients from ages 2 to 17 years first, followed by patients < 2 years. Dose adjustments for the successive younger age cohort must be based on the PK findings from the preceding older age cohort.
    - The use and/or dose of 5HT3 antagonist and/or corticosteroid must be based on a recognized standard of care used in the prevention of CINV in pediatric cancer patients undergoing treatment with highly or moderately emetogenic chemotherapy.
    - In the study protocol, you must propose a dosing regimen for fosaprepitant (using age-appropriate I.V. formulation), dexamethasone, and a 5HT3 antagonist, and you must provide the rationale for the chosen dosing regimen.
    - If emesis or nausea occurs, rescue with an approved therapy is permitted.

- ***Statistical information, including power of study and statistical assessments:***

The protocol must provide appropriate analyses and descriptive statistics of all PK data consistent with the age groups noted earlier.

Studies 2, 3, 4, and 5

Use an age-appropriate formulation in the studies described above. The content of EDTA in the current I.V. formulation (fosaprepitant dimeglumine) is considered too high for the pediatric population. Therefore, you must develop an age-appropriate formulation for the pediatric population. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric populations, you must seek marketing approval for that age-appropriate formulation.

If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric populations studied (i.e., receives marketing approval), 2) the Agency publishes the exclusivity determination notice required under section 505A(e)(1) of the Act, and 3) you have not marketed the formulation within one year after the Agency publishes such notice, the

Agency will publish a second notice reflecting the fact that the approved pediatric formulation has not been marketed, in accordance with section 505A(e)(2).

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age-appropriate formulation may be conducted in adults.

- *Drug specific safety concerns to be monitored*: Fosaprepitant is a pro-drug of aprepitant and will be readily converted to aprepitant in the human body. Therefore, fosaprepitant shares the following safety concerns regarding aprepitant. Aprepitant has a complex metabolism. Aprepitant is a substrate, a weak-to-moderate inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9.

  Aprepitant may increase the rate of warfarin metabolism and decreases its activity as measured by International Normalized Ratio (INR). Thus, you should exclude pediatric patients taking warfarin from these studies.

  Coadministration of aprepitant and hormonal contraceptives may affect the efficacy of the birth control. We recommend that your protocol incorporate barrier method contraception for the CINV studies.

  Coadministration of fosaprepitant and diltiazem may result in episodes of lower blood pressure. Blood pressure must be monitored in your studies.

- *Labeling that may result from the studies*: You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the studies demonstrate that fosaprepitant is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the studies. Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the studies.

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. These postmarketing adverse event reports should be submitted as narrative and tabular reports.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the studies:* Reports of the above studies must be submitted to the Agency on or before December 31, 2017. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the studies. If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the studies, but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 301-827-5911.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/cder/pediatric/index.htm

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

JULIE G BEITZ
04/08/2011