DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022023

WRITTEN REQUEST – AMENDMENT 3

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

Dear Mr. Andrew:

Please refer to your correspondence dated July 22, 2016, 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, and as amended on April 8, 2011 and March 15, 2012, remain the same. (Text added is underlined. Text deleted is strikethrough.)

Background:
The 3-Day oral aprepitant regimen was approved in 2015 for prevention of chemotherapy-induced nausea and vomiting in pediatric patients 6 months and older. Pediatric exposures at the approved doses were, in general, within the range of aprepitant exposures observed in adults at the approved 3-Day oral dosing regimen suggesting that aprepitant exposures that are effective in adults are expected to be effective in children with similar risk factors. This finding supports the following approaches taken in this Written Request to establish dosing for 1-Day and 3-Day IV fosaprepitant in children:

- **1-Day IV fosaprepitant dosing.** The IV fosaprepitant adult clinical trials for prevention of chemotherapy induced nausea and vomiting were conducted primarily in patients receiving single day chemotherapy regimens. Efficacy of IV fosaprepitant in pediatric patients receiving single day chemotherapy regimens will be extrapolated from data in adults. Modeling and simulation will be used to derive 1-Day IV fosaprepitant dosing in children that will match adult exposures at the approved dose.

- **3-Day IV fosaprepitant dosing.** Given that pediatric patients most commonly receive multiple day chemotherapy regimens, pediatric PK, efficacy, and safety data from the 3-Day oral aprepitant program combined with data from the pediatric PK/PD study outlined

in this Written Request will be leveraged to derive 3-Day IV fosaprepitant dosing in pediatric patients receiving multiple day chemotherapy regimens. Modeling and simulation will be used to derive 3-Day IV fosaprepitant dosing in children that will match exposures with the approved 3-Day oral aprepitant dosing in children.

The original Written Request dated February 2, 2009, was amended on April 8, 2011 to remove pediatric studies in post-operative nausea and vomiting (PONV). Studies evaluating the efficacy and safety of IV fosaprepitant in surgical patients with PONV are not requested as the product is not compatible with Lactated Ringers solutions which are frequently used in the postoperative setting. Fosaprepitant is not approved for PONV in adults and the product label also indicates that fosaprepitant should not be used with Lactated Ringers solution.

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, 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. ~~This should include at least 8 evaluable patients. If you are unable to enroll 8 evaluable patients, diligent and reasonable efforts must be made to encourage enrollment in this age group. These efforts must be documented and submitted for the Agency's review prior to the conclusion of the study.~~

The PK protocol may use a ~~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 characterize the PK of aprepitant and evaluate the appropriateness of the fosaprepitant dose 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 dexamethasone dose in pediatric cancer patients aged 0 to 1 year receiving the combination regimen. Alternatively, this information may be derived from adequate pediatric data with oral aprepitant.
- 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:

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

***Number of patients to be studied*:**
A minimum of 10 patients must be enrolled in each age group for PK evaluation. The number of patients is to be distributed approximately evenly over the ~~four~~ five age groups to the extent possible, given the clinical setting. The sample size ~~should~~ must be sufficient to characterize the exposure-response relationship for the entire age range ~~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.

For the cohort of patients aged 0 to less than 6 months, a minimum of 10 patients must be evaluated. PK sampling from at least 8 evaluable patients who have received both dexamethasone and fosaprepitant should be obtained. If you are unable to enroll 8 evaluable patients, diligent and reasonable efforts must be made to encourage enrollment in this age group. These efforts must be documented and submitted for the Agency's review prior to the conclusion of the study.

A minimum of 100 patients must be enrolled in this study for safety assessment.

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.
- PK endpoints should include PK parameters for 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.

Known Drug Safety concerns and monitoring: The most common adverse reactions associated with fosaprepitant are fatigue, diarrhea, neutropenia, asthenia, anemia, peripheral neuropathy, leukopenia, dyspepsia, urinary tract infection, and pain in extremity. Other adverse events include infusion site reactions including pain at infusion site and thrombophlebitis. The common adverse reactions will be monitored during protocol-defined visits and laboratory examinations and will be managed as defined in the protocol and will 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 an 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 delayed phase (>24-120 hours) will be the primary endpoint.
- Complete response (defined as no vomiting, no retching, and no use of rescue therapy) in the acute phase (0-24 hours) followed by the overall phase (0-120 hours) will be key secondary endpoints. Time 0 is when chemotherapy administration is initiated.
- 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 3.

Indication to be studied:

The prevention of acute and delayed nausea and vomiting associated with moderately 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 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 delayed phase (>24-120 hours) will be the primary endpoint.
- Complete response (defined as no vomiting, no retching, and no use of rescue therapy) in the acute phase (0-24 hours) followed by the overall phase (0-120 hours) will be key secondary endpoints. Time 0 is when chemotherapy administration is initiated.
- 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 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 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 and 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 Day1 of the 3 day I.V./Oral/Oral regimen following intravenous fosaprepitant (age appropriate formulation) in combination with a 5HT3 antagonist in the pediatric patient age groups as specified below. Available PK data from adults 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 must use either a traditional PK approach of population PK approach.

Alternatively, a modeling and simulation approach may be used in lieu of a PK study to demonstrate similar PK of aprepitant in pediatric patients for the selected I.V. fosaprepitant dose as compared to the oral aprepitant dose on day 1 in the 3 day oral regimen that has demonstrated acceptable safety and efficacy profiles. The modeling and simulation must be based on PK data obtained from multiple dose levels of I.V. fosaprepitant and oral aprepitant in pediatric patients. that has demonstrated acceptable safety and efficacy profiles. The modeling and simulation must be based on PK data obtained from multiple dose levels of I.V. fosaprepitant and oral aprepitant in pediatric patients.

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 modeling:

The objective of Study 5 is:

- To demonstrate comparable PK 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*:**

- < 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 60-140% 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 ona 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 regimen.

~~o 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.~~

Additional required analysis
Chemotherapy Induced Nausea and Vomiting (CINV) 1-Day and 3-Day (I.V./I.V./I.V.) Emend Regimen

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

Objective of the modeling:

- 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

***Age groups in which the modeling will be performed*:**

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

Data Sources for Model Building:
The modeling and simulation must be based on PK data obtained from multiple dose levels of I.V. fosaprepitant and oral aprepitant in pediatric patients. Data from Study 2 and available PK data of aprepitant and fosaprepitant in pediatric patients across the development program will be used to develop the pediatric PK Model.

Modeling endpoints:
PK parameters $AUC_{0\text{-}24}$, C_{max}, C_{24}, C_{48}, and C_{72}, for aprepitant.

Model Building Methodology:
FDA concurrence must be obtained on the adequacy of the model and simulation results to support dosing recommendations for fosaprepitant in pediatric patients.

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 and by previous amendments dated April 8, 2011 and March 15, 2012, 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.

In accordance with section 505A(k)(1) of the Act, 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:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- 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/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

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 Mary Chung, Regulatory Project Manager, at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):
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., a subsidiary of Merck & Co., Inc.
Attention: Nicholas W. Andrew
Director, Regulatory Affairs
126 E. Lincoln Avenue
P.O. Box 2000, RY34-B293
Rahway, NJ 07065

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.

Background:
The 3-Day oral aprepitant regimen was approved in 2015 for prevention of chemotherapy-induced nausea and vomiting in pediatric patients 6 months and older. Pediatric exposures at the approved doses were, in general, within the range of aprepitant exposures observed in adults at the approved 3-Day oral dosing regimen suggesting that aprepitant exposures that are effective in adults are expected to be effective in children with similar risk factors. This finding supports the following approaches taken in this Written Request to establish dosing for 1-Day and 3-Day IV fosaprepitant in children:

- **1-Day IV fosaprepitant dosing.** The IV fosaprepitant adult clinical trials for prevention of chemotherapy induced nausea and vomiting were conducted primarily in patients receiving single day chemotherapy regimens. Efficacy of IV fosaprepitant in pediatric patients receiving single day chemotherapy regimens will be extrapolated from data in adults. Modeling and simulation will be used to derive 1-Day IV fosaprepitant dosing in children that will match adult exposures at the approved dose.

- **3-Day IV fosaprepitant dosing.** Given that pediatric patients most commonly receive multiple day chemotherapy regimens, pediatric PK, efficacy, and safety data from the 3-Day

oral aprepitant program combined with data from the pediatric PK/PD study outlined in this Written Request will be leveraged to derive 3-Day IV fosaprepitant dosing in pediatric patients receiving multiple day chemotherapy regimens. Modeling and simulation will be used to derive 3-Day IV fosaprepitant dosing in children that will match exposures with the approved 3-Day oral aprepitant dosing in children.

The original Written Request dated February 2, 2009, was amended on April 8, 2011 to remove pediatric studies in post-operative nausea and vomiting (PONV). Studies evaluating the efficacy and safety of IV fosaprepitant in surgical patients with PONV are not requested as the product is not compatible with Lactated Ringers solutions which are frequently used in the postoperative setting. Fosaprepitant is not approved for PONV in adults and the product label also indicates that fosaprepitant should not be used with Lactated Ringers solution.

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, 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.

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 characterize the PK of aprepitant and evaluate the appropriateness of the fosaprepitant dose 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 dexamethasone dose in pediatric cancer patients aged 0 to 1 year receiving the combination regimen. Alternatively, this information may be derived from adequate pediatric data with oral aprepitant.
- 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:

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

***Number of patients to be studied*:**
A minimum of 10 patients must be enrolled in each age group for PK evaluation. The number of patients is to be distributed approximately evenly over the five age groups to the extent possible, given the clinical setting. The sample size must be sufficient to characterize the exposure-response relationship for the entire age range.

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.

For the cohort of patients aged 0 to less than 6 months, a minimum of 10 patients must be evaluated. PK sampling from at least 8 evaluable patients who have received both dexamethasone and fosaprepitant should be obtained. If you are unable to enroll 8 evaluable patients, diligent and reasonable efforts must be made to encourage enrollment in this age group. These efforts must be documented and submitted for the Agency's review prior to the conclusion of the study.

A minimum of 100 patients must be enrolled in this study for safety assessment.

Study endpoints:

- PK endpoints must include PK parameters for aprepitant such as C_{max}, T_{max}, AUC, $T_{1/2}$, clearance, and Vd_{ss}, as applicable.
- PK endpoints should include PK parameters for 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.

Known Drug Safety concerns and monitoring: The most common adverse reactions associated with fosaprepitant are fatigue, diarrhea, neutropenia, asthenia, anemia, peripheral neuropathy, leukopenia, dyspepsia, urinary tract infection, and pain in extremity. Other adverse events include infusion site reactions including pain at infusion site and thrombophlebitis. The common adverse reactions will be monitored during protocol-defined visits and laboratory examinations and will be managed as defined in the protocol and will 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 an 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.

Additional required analysis
Chemotherapy Induced Nausea and Vomiting (CINV) 1-Day and 3-Day (I.V./I.V./I.V.) Emend Regimen

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

Objective of the modeling:
- 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

***Age groups in which the modeling will be performed*:**

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

Data Sources for Model Building:
The modeling and simulation must be based on PK data obtained from multiple dose levels of I.V. fosaprepitant and oral aprepitant in pediatric patients. Data from Study 2 and available PK data of aprepitant and fosaprepitant in pediatric patients across the development program will be used to develop the pediatric PK Model.

Modeling endpoints:
PK parameters AUC_{0-24}, C_{max}, C_{24}, C_{48}, and C_{72}, for aprepitant.

Model Building Methodology:
FDA concurrence must be obtained on the adequacy of the model and simulation results to support dosing recommendations for fosaprepitant in pediatric patients.

Study 2 and Additional Required Analysis

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. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

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 http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.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 must 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 240-276-9327.

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/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872 .

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 Mary Chung, Regulatory Project Manager, at (301) 796-0260.

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
10/13/2016