

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-023**

**APPROVABLE LETTER**



NDA 22-023

Merck & Co., INC  
Attn: Vijay K Tammara, Ph.D.  
Director, Regulatory Affairs  
Sumneytown Pike, P.O. Box 4, BLA-20  
West Point, PA 19486

Dear Dr. Tammara:

Please refer to your new drug application (NDA) dated March 31, 2006, received March 31, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Emend (fosaprepitant dimeglumine) For Injection, 115 mg.

We acknowledge receipt of your submissions dated June 02, July 06, 28, August 30, September 26, 29, December 07, 08, 19, 2006, February 12, 21, and March 16, 21, 2007.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you address the following deficiencies:

1. You informed us that the drug product production process is not considered robust and will require further process improvement changes (Letter to Agency, dated February 21, 2007). Consequently, the manufacturing process for the drug product has not been finalized. A full description of the final production process to be used for the manufacturing of fosaprepitant dimeglumine drug product is required for approval.
2. To date, only 1 month of stability data on three batches of drug product manufactured with the modified lyophilization process, has been submitted. An additional time point (at 3 months) is needed on these batches as further support for the process changes to date. Furthermore, please submit, in support of the final manufacturing process, three months of stability data on three additional batches of drug product manufactured with the final manufacturing process.

In addition, we have the following comments and requests for additional information:

1. Regarding the drug interaction with diltiazem (Study Protocol 011): For a closer evaluation of the effect of I.V. fosaprepitant on the systolic and diastolic pressures of hypertensive patients receiving oral diltiazem, please provide the following information:
  - A table for individual data listing of systolic and diastolic pressures at various time points for baseline, when diltiazem was given alone, and when diltiazem was coadministered with

fosaprepitant, respectively. Also include changes from baseline and fosaprepitant concentrations in different columns of the same table. Evaluate the relationship between fosaprepitant concentration and difference in systolic and diastolic pressures between the two treatments (with and without fosaprepitant).

- A table for maximum change from baseline and the time associated with this maximum change for systolic and diastolic pressures for each individual when diltiazem was given alone, and when diltiazem was coadministered with fosaprepitant. Also include summary statistics (mean, SD, max, min) in the table.

Please note that revised draft labeling is not being provided at this time. Further revisions to the submitted label may be required before this application can be approved.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

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

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with the Division of Gastroenterology Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Giuseppe Randazzo, Regulatory Project Manager, at (301) 796-0980.

Sincerely,

*{See appended electronic signature page}*

Joyce Korvick, M.D., MPH  
Acting Director  
Division of Gastroenterology Products  
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/

-----  
Joyce Korvick  
5/3/2007 05:25:33 PM