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November 26, 2013

Donna Griebel, M.D., Director
Division of Gastroenterology Products
c/o Food and Drug Administration
Center for Drug Evaluation and Research

NDA 21-549: EMEND™ (aprepitant)

RESPONSE TO FDA PREA NON-COMPLIANCE LETTER
PREA DEFERRAL EXTENSION REQUEST

Dear Dr. Griebel:

Reference is made to the Investigational New Drug Application (50,283) for EMEND (aprepitant) submitted by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co. Inc.,(Merck), on April 9, 1996. Additional reference is made to the New Drug Application (NDA 21-549) for EMEND (aprepitant) approved on March 26, 2003 for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (CINV-HEC), including high-dose cisplatin. Additional reference is made to a letter from FDA dated January 21, 2005 in which FDA agreed to defer PREA pediatric studies for this application for patients 2 to 17 years of age until December 31, 2007.

The following deferred pediatric study, required under the Pediatric Research Equity Act (PREA), is considered to be a postmarketing study commitment:

1395-7: Deferred pediatric studies in patients 2 years to 17 years of age for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin.

Final Report Submission: December 31, 2007

Additional Reference is made to the Deferral Extension Request, submitted on January 2, 2013, in which Merck requested an extension to the PREA commitment due dates and to the Agency's correspondence on April 12, 2013 granting the deferral extension of Commitment 1395-7 until October 31, 2013.

Further reference is made to the following PREA pediatric study protocols and amendments which were submitted to IND 50,283 on the dates noted below.

- PN097: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Examine the Safety, Tolerability, and Efficacy of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting Associated With Emetogenic Chemotherapy in Adolescent Patients

    - Initial protocol submitted on 27 February 2004
    - Amendment PN097-01 submitted on 27 April 2005
    - Amendment PN097-02 submitted on 19 April 2006

- PN134: A Multi-center, Open-label, 5-Part Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Aprepitant and Fosaprepitant Dimeglumine in Pediatric Patients Receiving Emetogenic Chemotherapy

    - Initial protocol submitted on 18 November 2008.
    - Amendment PN134-01 submitted on 30 October 2009.
    - Amendment PN134-02 submitted on 31 August 2011
    - Amendment PN134-03 submitted on 18 June 2012

- PN208: A Phase III, Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial, to Examine the Efficacy and Safety of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Pediatric Patients

    - Initial protocol submitted on 31 August 2011
    - Amendment PN208-02 submitted on 26 July 2012
    - Amendment PN208-03 submitted on 28 September 2012

Additional reference is made to a meeting between representatives of Merck and FDA on June 6, 2012 to discuss the aprepitant pediatric development program, in which Merck proposed that submission of the following study data would be sufficient to fulfill the arepitant CINV-MEC and CINV–HEC PREA requirements:

- Protocol 097: pharmacokinetic data in patients 12 to 17 years of age
- Protocol 134: pharmacokinetic data for patients 6 months to 12 years of age
- Protocol 208: efficacy/safety data in CINV in patients 6 months to 17 years of age

Further reference is made to FDA pre-meeting minutes provided on June 4, 2012 in which FDA indicated "Your proposed strategy to address the aprepitant CINV PREA requirement seems reasonable. However, the final determination on whether your studies successfully fulfill your CINV PREA requirements will be made upon review of the final study reports."

Further reference is made to the submission, on October 30, 2013 of the Clinical Study Reports for the pediatric Protocols 097 and Protocol 208. Protocol 134 is a 5-part study that is ongoing, and the aprepitant pharmacokinetics data in pediatric patients 6 months to 12 years of age from this study are provided within the clinical study report for Protocol 208.

Final reference is made to the PREA non-compliance letter sent to Merck on November 6, 2013, in which FDA communicated that it had determined that Merck failed to submit the pediatric assessments by the required PREA target date which was deferred until October 31, 2013.

With this submission, Merck is providing a response to the non-compliance letter in Module 1.9.2 (Request for Deferral of Pediatric Studies).

Additionally, despite diligent efforts, Merck has not been able to provide complete data to satisfy the PREA commitment by the date specified in the approval letter. Therefore, Merck is requesting an extension of the PREA deferral for the studies intended to satisfy the commitment. The PREA deferral extension request is included in Module 1.9.2 (Request for Deferral of Pediatric Studies).

Please note that the same studies to satisfy the PREA commitment for NDA 21,549 in patients being treated with highly emetogenic chemotherapy are also being conducted to address the deferred pediatric study commitment to evaluate the use of aprepitant in the prevention of nausea and vomiting associated with moderately emetogenic chemotherapy (CINV-MEC, NDA 21,549 S-008). As such, the information in this submission is being referenced in a simultaneous submission to the aprepitant CINV-MEC sNDA to support that sNDA's pediatric PREA commitment.

This submission is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document. This submission is being transmitted through the FDA's electronic submission gateway. Merck has taken precautions to ensure that the contents are free of computer viruses (McAfee Agent, McAfee, Inc.), and we authorize the use of anti-virus software, as appropriate.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, public without first obtaining the written permission of Merck.

In my absence, questions concerning the content of this submission should be directed to Nikhil Mehta, Ph.D. at (267) 305-3123.

Sincerely yours,

Nicholas Andrew
Director
Worldwide Regulatory Affairs

cc w/attachments: CDER Pediatric and Maternal Health Staff at Pedsdrugs@fda.hhs.gov
(Attachments: Response to FDA PREA Non-Compliance Letter/PREA Deferral Extension Request)