Food and Drug Administration
Center for Drug Evaluation and Research
Holiday Inn, The Ballroom, 2 Montgomery Village Avenue, Gaithersburg, MD.

Summary Minutes of the Gastrointestinal Drugs Advisory Committee

March 6, 2003

Members Present

Michael Camilleri, M.D., Chair	Joel Richter, M.D.
David Colin Metz, M.D.	Byron Cryer, M.D.
Robert Alan Levine, M.D.	John Thomas LaMont, M.D.
Ronald Fogel, M.D.	Susan Cohen, Consumer Rep.

Consultants

David Kelsen, M.D.	Otis Brawley, M.D.
Howard McLeod, Pharm.D.	Michael Prochan, Ph.D.
Zeruesenay Desta, Ph.D.	Ruth Hoffman, Patient Rep.

FDA Participants

Florence Houn, M.D., M.P.H.	Robert Justice, M.D.
Gary Della'Zanna, D.O., M.Sc.,	Venkat Jarugula, M.D.

These summary minutes for the March 6, 2003 meeting of the Gastrointestinal Drugs Advisory Committee were approved on March 14, 2003.

I certify that I attended the March 6, 2003 meeting of the Gastrointestinal Drugs Advisory, and that these minutes accurately reflect what transpired.

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Thomas H. Perez, M.P.H., R.Ph.	Michael Camilleri, M.D.
Executive Secretary	Chair

The Gastrointestinal Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met March 6, 2003 at the Holiday Inn, 2 Montgomery Village Avenue, Gaithersburg, MD.

The Committee discussed new drug application (NDA) 21-549, EMEND™ (aprepitant) Capsules, Merck & Co., Inc., for the following indication: "EMEND, in combination with other antiemetic agents, is indicated 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."

The Committee had received a briefing document from the FDA, and a background package from Merck in preparation for this meeting.

There were approximately 170 persons present in the meeting. The meeting was called to order at 8:35 a.m. by the Acting Chair, Michael Camilleri, M.D. The Committee members and discussants introduced themselves. Thomas H. Perez, Executive Secretary of the Gastrointestinal Drugs Advisory Committee read the Meeting Statement. Welcome and opening comments were provided by Robert Justice, M.D., Director, Division of Gastrointestinal and Coagulation Drug Products

Merck representatives began their presentations at 8:50 a.m. The presentations proceeded as follows.

Introduction	Dennis M. Erb, Ph.D.
Background and Rationale & Clinical Pharmacology	Kevin J. Petty, M.D., Ph.D.
Clinical Efficacy	Kevin J. Horgan, M.D.
Clinical Safety	Scott A. Reines, M.D., Ph.D.
Summary and Conclusions	Scott A. Reines, M.D., Ph.D.

The Merck presentations were followed by a 25-minute question and answer period.

FDA representatives began their presentations at 11:20 a.m. and proceeded as follows.

Clinical Summary	Gary Della'Zanna, D.O., M.Sc., Division of Gastrointestinal and Coagulation Drug Products
Biopharmacology Summary	Venkat Jarugula, Ph.D., Clinical Pharmacology and Biopharmaceuticcs Reveiwer

The FDA presentations were followed by a 25-minute question and answer period.

The meeting had a lunch break at 12:15 and was reconvened at 1:15 p.m.

There were no participants for the Open Public Hearing and the Committee began to discuss the meeting questions presented by the FDA. A thorough discussion of the questions followed, and the open public meeting was adjourned at 3:10 p.m.

The meeting transcript will be made available on the web in approximately three weeks. Transcripts may be accessed at the following web address www.fda.gov/ohrms/dockets/ac/acmenu.htm.

The Committee discussed the following questions.

Questions for the Committee

1. Has the aprepitant regimen been demonstrated to be effective in the prevention of nausea and vomiting in the acute phase? In the delayed phase?
   Committee's Vote
   In the Acute Phase: 13 Yes 0 No
   In the Delayed Phase: 13 Yes 0 No

2. Is the designation of "highly emetogenic chemotherapy" appropriate given the regimens used in the clinical studies?
   Committee's Vote: 12 Yes 0 No 1 Abstain

3. Can the recommended regimen be expanded beyond that used in the clinical studies to include the use of any 5-HT3 antagonist as part of the aprepitant regimen? If not, what additional studies would you recommend?
   Committee's Vote: 9 Yes 3 No 1 Abstain
   Several members of the committee added that postmarketing studies are needed.

4. Aprepitant is an inhibitor of the CYP3A4 metabolic pathway. For chemotherapeutic drugs that are metabolized by this pathway, moderate inhibition of their metabolism could result in serious or life-threatening toxicity.

   a) The applicant has analyzed the safety data by chemotherapy regimen and a significant number of patients received etoposide, vinorelbine, or paclitaxel (substrates for CYP 3A4) in combination with cisplatin and the aprepitant regimen. Is this data sufficient to support the safety of aprepitant in combination with these drugs? If not, what additional studies would you recommend and should these be done pre-approval or post-approval?
      Committee's Vote: 9 Yes 3 No 1 Abstain
      Several members of the committee added that postmarketing studies are needed; including evaluating the outcome of the cancer, further studies of pulmonary function when used in combination with vinorelbine, studies to evaluate pharmacokinetics particularly for drugs that are metablolized by CYP 3A4 and drug interactions with warfarin.

   b) Few or no patients received docetaxel, vinblastine, vincristine, ifosfamide, irinotecan, or imatinib (substrates of CYP 3A4) in combination with cisplatin and the aprepitant regimen. The docetaxel drug-drug interaction study has accrued only five patients. Is there sufficient data to support the safety of aprepitant in combination with these drugs? If not, what additional studies would you recommend and should these studies be done pre-approval or post-approval?
      Committee's Vote: 0 Yes 13 No
      The Committee recommended that labeling should list the drugs where there is sufficient safety information and the drugs where the safety data is insuficient. Stated limitations included the prophylactic use of aprepitant for 5 days to treat chemotherapy induced nausea and vomiting. Also it was recommended that postmarketing studies be performed to determine effects of drugs most likely to be used in combination with aprepitant.

5. Does the Committee have specific concerns regarding potential drug-drug interactions with other chemotherapeutic agents or other drug classes? If yes, please discuss them and whether any additional studies are recommended.
   The Committee consensus was Yes. One example provided was the need to study warfarin, particularly in elderly patients. It was stated that answers to this question had been provided during earlier discussions of previous questions.