

Gastrointestinal Drugs Advisory Committee

3/6/03

Questions

Drug Name: EMEND (aprepitant)

Applicant: Merck & Co., Inc.

NDA: 21-549

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?
2. Is the designation of “highly emetogenic chemotherapy” appropriate given the regimens used in the clinical studies?
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?
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?
 - 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?
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.