

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-549**

**Administrative Documents**

EXCLUSIVITY SUMMARY for NDA # 21-549 SUPPL # N/A  
Trade Name EMEND Generic Name aprepitant

Applicant Name Merck & Company HFD- 180  
Approval Date March 21, 2003

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/ X/ NO / \_\_\_/

b) Is it an effectiveness supplement? YES / \_\_\_/ NO / X/

If yes, what type(SE1, SE2, etc.)?

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / X/ NO / \_\_\_/

d) Did the applicant request exclusivity?

YES / \_\_\_/ NO / X/

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / \_\_\_/ NO / X/

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES / \_\_\_/ NO / X/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /\_\_\_/ NO /x/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /\_\_\_/ NO /x/

IF THE ANSWER TO QUESTION 1 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

{See appended electronic signature page}  
Signature of Preparer \_\_\_\_\_ Date \_\_\_\_\_  
Title: Brian Strongin, R.Ph., M.B.A.  
Regulatory Health Project Manager  
Division of GI and Coagulation Drug Products

{See appended electronic signature page}  
Signature of Office or Division Director \_\_\_\_\_ Date \_\_\_\_\_  
Title: Florence Houn, M.D.  
Director, ODE III

CC:  
Archival NDA  
HFD-180/RPM  
HFD-093/Mary Ann Holovac  
HFD-104/PEDS/T.Crescenzi

Form OGD-011347  
Revised 8/7/95; edited 3/8/95; revised 8/25/98, edited 3/6/00

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/s/

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Brian Strongin  
3/17/03 05:38:20 PM

Florence Houn  
3/18/03 07:24:37 AM

## PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA #: 21-549 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: 9/27/02 Action Date: 3/21/03

HFD-180      Trade and generic names/dosage form: EMEND (aprepitant) Capsules

Applicant: Merck & Company Therapeutic Class: Neurokinin 1 (NK<sub>1</sub>) Receptor Antagonist

Indication(s) previously approved: N/A

**Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.**

Number of indications for this application(s): 1

Indication #1: 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. Aprepitant is not indicated for treatment of established nausea and vomiting.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

### Section B: Partially Waived Studies

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. Birth Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 18 years Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- X Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): March 1, 2008

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA  
HFD-950/ Terrie Crescenzi  
HFD-960/ Grace Carmouze  
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960  
301-594-7337

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/s/

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Brian Strongin  
3/17/03 10:17:14 AM  
CSO

**MEMORANDUM****DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: March 25, 2003  
FROM: Florence Houn MD MPH  
SUBJECT: Office Director Memo  
TO: NDA 21-549 EMEND (aprepitant) Capsules

This memo documents my concurrence with the Division of Gastrointestinal and Coagulation Drug Product's recommendation for approval of EMEND, indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of highly emetogenic cancer chemotherapy. Aprepitant is the first competitive NK1-receptor antagonist being proposed for marketing. Issues related to the safety and effectiveness of this marketing application are well-documented in the Division's memos and in memos from the Office of Clinical Pharmacology and Biopharmaceutics. In addition, the Gastrointestinal Drugs Advisory Committee (GDAC) met over this application on March 6, 2003 and provided the Food and Drug Administration (FDA) with recommendations to approve this application with phase 4 studies and labeling of safety concerns over drug-drug interactions. Furthermore, for the record, the manufacturer's desired tradename for the product (EMEND) was subject of a dispute resolution by the company submitted to the Office of Drug Evaluation III on October 17, 2002 and responded to on October 30, 2002. The use of the product name EMEND will be accompanied by a risk management program to lower drug mix-ups and there will be periodic assessments of success of this program. This program is in the form of a phase 4 study agreement and has become part of the approval letter and is agreed to by the company. This memo discusses selected topic areas related to effectiveness and safety and FDA's rationale for decision-making.

Effectiveness

The primary response variable was complete response (no emesis and no rescue therapy) in the overall phase (time 0 to 120 hours post-cisplatin administration) and statistically and clinically significant in the treatment group versus standard therapy (72.7% versus 52.3%). Lack on independent statistical significance for secondary endpoints such as "no nausea" or "no significant nausea" was discussed on March 6, 2003 and the GDAC felt overall the drug is beneficial for the syndrome and that teasing out "nausea" versus "emesis" would be artificial in this population. In addition, while only one highly emetogenic chemotherapy agent (cisplatin) was uniformly used in the trials, concomitant chemotherapies of a wide variety were included. The FDA has previously used this as a benchmark for emetogenic therapy and labeling is not restricted to an indication for use only with cisplatin administration. The GDAC agreed with this. The mechanism for eliciting nausea and vomiting due to various chemotherapies is complex and not fully understood. It is believed cytotoxic agents cause release of serotonin (5-HT) from the enterochromaffin cells in the gut; stimulation of vagal afferent fibers, and activation of various nuclei in the brainstem, which initiate emetic response. Several 5-HT3 receptor antagonists have been approved for treatment of emesis related to chemotherapy. Substance P may also have a role in emesis, and it binds to NK1-receptors in the brain stem nuclei and this stimulates vomiting reflexes. This is a central action and aprepitant blocks substance P binding competitively, while 5-HT3 blockade is a peripheral action. These considerations lead FDA to conclude that emesis is multifactorial and effectiveness with aprepitant on emetic effects of cisplatin can be extrapolated to other cytotoxic agents. This conclusion was supported by the GDAC's deliberations.

The recommended dose of aprepitant is 125 mg po one hour prior to chemotherapy treatment on Day 1 and 80 mg po daily on Days 2 and 3.

### Safety

The major concern with safety is aprepitant's drug interaction profile. Aprepitant is extensively metabolized by CYP 3A4. At the above doses, aprepitant is an inhibitor of CYP 3A4 activity and resulted in more than a 3-fold increase in the exposure of midazolam, a sensitive CYP 3A4 substrate. Use of aprepitant for 28 days has shown it also to be an inducer of CYP 3A4. Many chemotherapy drugs are metabolized by CYP 3A4 and there is concern that because chemotherapeutics have a narrow safety margin for bone marrow, neurologic, and other toxicities, there may be an increased safety risk associated with administration of aprepitant with these chemotherapies. The NDA contains no data to formally assess this concern, although there were a variety of chemotherapeutic agents concomitantly given in the phase 3 data base.

These concerns were extensively discussed on March 6, 2003. Concerning drug-drug interactions with other chemotherapeutic agents that are 3A4 substrates, the GDAC recommended phase 4 studies to help with labeling. In addition, they recommended that labeling warn of possible interactions. Most of the CYP 3A4 substrates with QTc prolongation concerns, such as terfenadine and astemizole, have been removed from the market. Cisapride is still available under a limited access program under IND. The use of aprepitant for only 3 days may alleviate some concerns about use of this drug and statins and the resulting potential for increased risk of rhabdomyolysis. Aprepitant also induces CYP 2C9 after a couple of weeks of use. While available as bottles of 30 capsules for each dose, there is a unit of use package for the three days that should lessen concerns about induction and drug-drug interaction. Induction may interfere with oral contraceptive (OC) effectiveness. OCs are advised to be used by women of childbearing potential on chemotherapy due to teratogenic risks from the chemotherapy. Because there is concern for off-label use of EMEND in a more chronic setting, labeling will be explicit that use beyond the approved regimen of 3 days for chemotherapy prevention, should not be pursued because of drug-drug interactions that can be unpredictable.

Inducers of CYP 3A4 may affect the effectiveness of aprepitant. Inducers such as rifampin and other drugs will be labeled as possibly affecting drug effectiveness.

Thus, as a summary of labeling changes from the proposed package insert, FDA sought the following given the guidance from the GDAC:

- Clear warnings about drug-drug interactions
- Identification the 3A4 metabolized chemotherapies in the label and prioritizing this drug interaction
- Statement that use is for prevention of nausea and vomiting, and this is not a treatment of existing nausea and vomiting
- Statement that use should not be for longer than labeled due to possible complex and unpredictable drug interactions

In addition, there was debate between FDA and Merck on issues related to carcinogenicity findings, use of historical control data for preclinical findings, and labeling for Carcinogenicity, Nursing Mothers, and related sections of the label. Dr. Robert Osterberg and Dr. John Leighton assisted the Division at the request of both the company and the Division and supported the Division's labeling requests.

### Phase 4 Studies

Merck Research Laboratories is agreeing to phase 4 studies to better label drug-drug interactions and to conduct studies to evaluate the effectiveness of their risk management program to minimize drug mix ups with sound-alike drug names and EMEND.

We also discussed the benefits of testing efficacy without use of corticosteroids in the pediatric population. This was raised in the Advisory Committee meeting discussions by the patient representative.

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/s/

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Florence Houn  
3/25/03 07:15:35 AM  
MEDICAL OFFICER

## Division Director Summary Review of a New Drug Application

NDA: 21-549

Drug: EMEND™ (aprepitant) Capsules

Applicant: Merck & Co., Inc.

Date: March 25, 2003

### Summary of Safety and Effectiveness

Aprepitant is a selective substance P neurokinin 1 (NK<sub>1</sub>) receptor antagonist that has been developed by Merck for the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV). Substance P and NK<sub>1</sub> receptors are present in the brainstem centers that mediate emesis. In animal models of CINV, aprepitant prevented both acute and delayed emesis due to cisplatin and other emetogens. The clinical development plan for aprepitant was to demonstrate that adding the drug to a standard antiemetic regimen consisting of a corticosteroid and a 5-HT<sub>3</sub> receptor antagonist results in improved prevention of acute and delayed CINV.

The proposed indication for aprepitant is as follows: "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 results of two Phase 3 studies (052 and 054) of identical design were submitted in support of the application. Both studies utilized the nanoparticle capsule formulation and were double-blind, multicenter, multinational, randomized trials in cisplatin-naïve male and female patients. Patients were randomized to either the aprepitant or the standard antiemetic regimen (Table 1). The dose of dexamethasone was reduced in the aprepitant arm to account for a drug interaction with aprepitant which results in increased blood levels of dexamethasone.

Table 1  
Treatment Regimens in Phase 3 Studies

Treatment Regimen	Day 1	Day 2 to 4
Aprepitant	Aprepitant 125 mg PO Dexamethasone 12 mg PO Ondansetron 32 mg IV	Aprepitant 80 mg PO daily (Days 2 and 3 only) Dexamethasone 8 mg PO Daily (morning) Dexamethasone placebo PO Daily (evening)
Standard	Aprepitant placebo PO Dexamethasone 20 mg PO Ondansetron 32 mg IV	Aprepitant placebo PO daily (Days 2 and 3 only) Dexamethasone 8 mg PO daily (morning) Dexamethasone 8 mg PO daily (evening)

All patients received cisplatin at a dose of  $\geq 50$  mg/m<sup>2</sup>. Ninety-five percent of patients received concomitant chemotherapy with another agent. The most common drugs co-administered with cisplatin were etoposide, fluorouracil, gemcitabine, vinorelbine, paclitaxel, cyclophosphamide, doxorubicin, and docetaxel.

Antiemetic activity was evaluated during the acute phase (0-24 hours after cisplatin treatment), the delayed phase (25-120 hours after cisplatin treatment), and the overall phase (0-120 hours after cisplatin treatment). The primary endpoint was complete response in the overall phase in Cycle 1. Complete response was defined as no emetic episodes and no use of rescue therapy. Key secondary endpoints included complete response in the acute and delayed phases. The results of the analyses of these endpoints are shown in the tables below:

**Table 2**  
**Number (%) of Patients with Complete Response – Protocol 052**

	Aprepitant Regimen n/m	Standard Therapy n/m
Overall	189/260 (73%)*	136/260 (52%)
Acute Phase	231/259 (89%)*	203/260 (78%)
Delayed Phase	196/260 (75%)*	145/260 (56%)

\*p<0.001 when compared to standard therapy

n/m = number of patients with response/number of patients included in the analysis

**Table 3**  
**Number (%) of Patients with Complete Response – Protocol 054**

	Aprepitant Regimen n/m	Standard Therapy n/m
Overall	163/260 (63%)*	114/263 (43%)
Acute Phase	216/261 (83%)*	180/263 (68%)
Delayed Phase	176/260 (68%)*	123/263 (47%)

\*p<0.001 when compared to standard therapy

n/m = number of patients with response/number of patients included in the analysis

Additional efficacy endpoints included no emesis, time to first emesis or rescue, no significant nausea, no nausea, complete protection, total control, and impact of CINV on daily life (FLIE total score). For definitions and results see the medical and statistical reviews.

Both protocols included extension phases that evaluated efficacy with subsequent cycles of chemotherapy. The efficacy advantage of the aprepitant regimen over standard therapy was maintained during subsequent cycles of chemotherapy.

Safety is reviewed in detail in the Medical Officer Review. In summary, “the most common adverse experiences that occurred more frequently (>2% difference) in the aprepitant group compared with the standard therapy group include: asthenia/fatigue

(17.8% and 11.8%), dizziness (6.6% and 4.4%), diarrhea (10.3% and 7.3%), cough (2.4% and 0.5%), and hiccups (10.8% and 5.6%).”

As is noted in the Clinical Pharmacology and Biopharmaceutics review, aprepitant is a moderate inhibitor of CYP3A4. Chemotherapy drugs that are known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine. The applicant analyzed the safety data by chemotherapy regimen and a significant number of patients received etoposide, vinorelbine, or paclitaxel in combination with cisplatin and the aprepitant regimen. Chemotherapy doses were not adjusted to account for possible drug interactions. Although some differences in toxicity between the two treatment groups were noted, the numbers are too small to make any conclusions. Few or no patients received docetaxel, vinblastine, vincristine, ifosfamide, irinotecan, or imatinib in combination with cisplatin and the aprepitant regimen. However, a docetaxel drug-drug interaction study that has accrued five patients showed no differences in PK with or without concomitant administration of aprepitant. Based on the advisory committee’s recommendations, these potential drug-drug interactions will be addressed in the package insert and by Phase IV studies (see below). Since it is not feasible to conduct a drug-drug interaction study with each of these chemotherapy drugs, the safety data with etoposide, vinorelbine, and paclitaxel will be supplemented by Phase IV drug interaction studies of aprepitant with docetaxel and either vinorelbine or irinotecan.

#### **Summary of Gastrointestinal Drugs Advisory Committee Meeting**

The application was presented to the Gastrointestinal Drugs Advisory Committee on March 6, 2003. The committee was asked the following questions:

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: 13 yes and 0 no on both questions.

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

Committee’s vote: 12 yes, 0 no, and 1 abstention.

3. Can the recommended regimen be expanded beyond that used in the clinical studies to include the use of any 5-HT<sub>3</sub> antagonist as part of the aprepitant regimen? If not, what additional studies would you recommend?

Committee’s vote: 9 yes, 3 no, and 1 abstention. Two committee members recommended post-marketing studies with dolasetron.

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 CYP3A4) 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, and 1 abstention

Several members of the committee added that postmarketing pharmacokinetic studies are needed to evaluate drug-drug interactions, particularly for drugs that are metabolized by CYP3A4, and to evaluate drug interactions with warfarin. One study design suggested included evaluating pulmonary function when the aprepitant regimen is used in combination with vinorelbine (e.g., in breast cancer).

- 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 and 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 insufficient. 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. It was stated that answers to this question had been provided during earlier discussions of previous questions.

### **Discipline Review Summary**

**Chemistry:** The chemistry review recommended approval but identified deficiencies which needed to be discussed and resolved with the Applicant before approval. The deficiencies were discussed in a telecon with the company on March 19, 2003. The outcome of the telecon was that the applicant agreed to Phase IV commitments regarding dissolution testing (see biopharm commitment 2). The EER is reported to be acceptable except for one site which was withdrawn by the applicant.

**Clinical Pharmacology and Biopharmaceutics:** The review concludes that the Human Pharmacokinetics and Biopharmaceutics section of the NDA is acceptable provided that a satisfactory agreement can be reached between the Agency and the sponsor regarding the language in the Package Insert and the Phase IV commitments.

**Package Insert:**

The most important change is the addition of a WARNINGS section which notes that aprepitant is an inhibitor of CYP3A4, identifies the chemotherapy drugs that are metabolized by CYP3A4, and separates them by drugs for which there is clinical safety information vs. those for which there is minimal or no safety information. During the labeling negotiations it was agreed that this information would be included in the PRECAUTIONS section instead of the WARNINGS section.

**Phase IV Commitments:**

1. Conduct *in vitro* metabolism interaction studies of aprepitant with various chemotherapy agents metabolized by CYP450 enzyme system.
2. Provide data regarding the effect of \_\_\_\_\_ at each \_\_\_\_\_ concentration with the capsule formulation. Meanwhile,  $Q=$  40% at 20 minutes with the proposed dissolution method is acceptable as an interim specification.
3. Conduct *in vivo* drug interaction studies to investigate the effect of aprepitant and the regimen (including corticosteroid and 5-HT<sub>3</sub> antagonist) on the safety, tolerability, and pharmacokinetics of chemotherapy agents metabolized by CYP3A4.
4. Conduct *in vivo* drug interaction study to investigate the effect of aprepitant on the safety, tolerability and pharmacokinetics of dolasetron (include patients who are poor metabolizers for CYP2D6 isozyme).

These commitments were modified during the negotiations with the applicant with the concurrence of the Clinical Pharmacology and Biopharmaceutics reviewer (see Phase IV Commitments below).

**DSI Inspection:** The inspection report is dated March 20, 2003. The report concluded that the data submitted in support of this NDA appear acceptable.

**Medical:** The medical review concludes that "The submitted trials support the approval of the aprepitant regimen for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of chemotherapy that include highly emetogenic doses of cisplatin with or without concomitant chemotherapy." The reviewer also recommends the following Phase IV studies:

1. Complete the pending docetaxel drug interaction study.
2. Conduct *in vitro* metabolism interaction studies of aprepitant with various chemotherapy agents metabolized by CYP450 enzyme system.

3. Conduct *in vivo* studies to investigate the effect of the aprepitant regimen on the safety, tolerability and pharmacokinetics of chemotherapy agents metabolized by CYP3A4
  - (a) irinotecan
  - (b) vinblastine
  - (c) imatinib
  - (d) vinorelbine
  - (e) etoposide
4. Conduct *in vivo* drug interaction study to investigate the effect of aprepitant on the safety, tolerability and pharmacokinetics of dolasetron (include patients who are poor metabolizers for CYP2D6 isozyme).
5. Conduct post marketing risk assessment for drug errors due to name similarity with the trade name EMEND® (i.e., AMEND®, VFEND®).

The commitments were modified during negotiations with the applicant with the concurrence of the medical review team (see Phase IV Commitments below).

**Pharmacology/Toxicology:** The review states that the NDA is approvable with recommendations for changes in the Carcinogenicity, Mutagenicity, Impairment of Fertility, Pregnancy, and Nursing Mothers sections of the labeling.

**Statistical:** The overall conclusions of the statistical reviewer are as follows:

1. The efficacy of MK-0869 is superior to that of standard therapy in prevention of acute and delayed vomiting associated with emetogenic cancer therapy.
2. The efficacy of MK-0869 is superior to that of standard therapy in prevention of acute and delayed nausea and vomiting associated with emetogenic cancer therapy.
3. However, the efficacy of MK-0869 regimen is also not superior to that of standard therapy in prevention of acute and delayed nausea associated with emetogenic cancer therapy.

#### **Phase IV Commitments**

The applicant has agreed to the following Phase IV commitments:

1. Merck will obtain pharmacokinetic interaction data on a total of 10 patients receiving concomitant aprepitant and docetaxel (an IV chemotherapy CYP3A4 substrate), instead of the originally planned 20 patients (Protocol 051, serial No. 242, IND  ).
2. Merck will conduct a drug interaction study to evaluate the effect of aprepitant on either vinorelbine or irinotecan.
3. Merck will conduct a drug interaction study in healthy subjects, including some who are CYP2D6 poor metabolizers, to evaluate the effect of aprepitant on dolasetron.

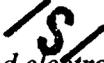
4. Merck will initiate a risk management program as outlined in our submission dated March 18, 2003 to ensure that health care providers understand the approved indication for EMEND and precautions with its use and to address and minimize potential for confusion with AMEN or VFEND and EMEND. Merck will submit all medication error reports relating to tradename confusion, both potential and actual, that occur with EMEND for a period of one year following the date of approval. All actual and potential errors will be submitted as 15-day reports regardless of patient outcome. Merck agrees to evaluate these data with FDA and, if needed, to implement interventions to further minimize risk of medication errors.

For the duration of the program, Merck also commits to providing the following: 1) reports on the proactive surveillance audit with retail pharmacists on a quarterly basis beginning no later than the fourth quarter of 2003; 2) an annual summary report beginning in the fourth quarter of 2003.

5. Merck will submit to FDA a report on the assessment of the inhibitory properties of aprepitant on CYP2C8 and CYP2B6 *in vitro* in human liver microsomes.
6. Merck commits to justify the use of \_\_\_\_\_ method, including \_\_\_\_\_ for the nanoparticle capsule formulation. Accordingly, based on the data presented in the response, the dissolution specification will be reviewed and, if warranted, revised.

#### **Recommended Regulatory Action**

The application should be approved.

  
(See appended electronic signature page)

Robert L. Justice, M.D., M.S.  
Director  
Division of Gastrointestinal and Coagulation  
Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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Robert Justice  
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MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research

DATE: 3/24/03

TO: Robert Justice MD, MS  
Director  
Division of Gastrointestinal and Coagulation Drug Products

FROM: Joyce A Korvick, MD, MPH  
Deputy Director (Acting Team Leader – GI Team 2)  
Division of Gastrointestinal and Coagulation Drug Products

SUBJECT: Medical Team Leader Review Summary  
NDA 21-549

APPLICANT: Merck & Company, INC.

SUBSTANCE: EMEND® (aprepitant) Capsules  
Chemical & Therapeutic Class: NK1-receptor antagonist

User Fee Goal Date: March 27, 2003

**Recommendation:** This review is in concurrence with the Medical Officer's primary recommendation approval of Emend in combination with other antiemetic agents, 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.

Phase 4 commitments:

1. Obtain pharmacokinetic interaction data on a total of 10 patients receiving concomitant Emend and docetaxel (an IV chemotherapy CYP3A4 substrate), instead of the originally planned 20 patients (Protocol 051, Serial No. 242, IND [redacted])
2. Conduct a drug interaction study to evaluate the effect of Emend on either vinorelbine or irinotecan.
3. Conduct a drug interaction study in healthy subjects, including some who are CYP2D6 poor metabolizers, to evaluate the effect of Emend on dolasetron.
4. Initiate a risk management program as outlined in your submission dated March 18, 2003 to ensure that health care providers understand the approved indication for EMEND and precautions with its use and to address and minimize potential for confusion with AMEN or VFEND and EMEND. Submit all medication error reports relating to tradename confusion, both potential and actual, that occur with EMEND for a period of one year following the date of approval. All actual and potential errors will be submitted as 15-day reports regardless of patient outcome. Evaluate these

data with FDA and, if needed, to implement interventions to further minimize risk of medication errors.

5. Submit to FDA a report on the assessment of the inhibitory properties of Emend on CYP2C8 and CYP2B6 *in vitro* in human liver microsomes.
  6. Justify the use of \_\_\_\_\_ in \_\_\_\_\_ : capsule formulation dissolution method, including studies on the \_\_\_\_\_ for the nanoparticle formulation.
- Accordingly, based on the data presented in the response, the dissolution specification will be reviewed and, if warranted, revised.

I. **Background:** Emend is the first in a class of competitive neurokinin-1 (NK-1) receptor antagonists and provides additional, substantial benefit to chemotherapy patients suffering serious complications of their therapies; i.e. chemotherapy induced nausea and vomiting (CINV). As such it was given priority review status. Several issues were identified in the review process and were the subject of a Gastrointestinal Advisory Committee Meeting held March 6, 2003. First, the indication of prevention of delayed nausea and vomiting due to chemotherapeutic agents is a new indication, which has not been granted previously to the currently labeled products. Second, the dose of cis-platin used was lower than that used to define highly emetogenic chemotherapy in previous approvals of CINV preventive therapies. Third, the applicant requested the label for use with any 5-HT3 antagonist, but only studied one in the phase 3 clinical trials. Finally, Emend is metabolized through the CYP450 enzyme system, and is a moderate CYP 3A4 inhibitor. There are chemotherapeutic agents that are metabolized by this pathway as well; therefore an important issue which was address are the drug-drug interactions which comprised a large portion of the committee's deliberations.

## II. Discipline review summary and commentary:

- A. **OPDRA :** Prior to the submission of this application Merck submitted a trade name proposal for Emend. At that time there was concern over the possibility of medication errors with an approved product named Amen. This drug was no longer being marketed in the US; however, the names are very similar. Both the Division of Gastrointestinal and Coagulation Drug Products and Office of Drug Safety found this trade name to be unacceptable. Merck pursued the dispute resolution mechanism through the Office of Drug Evaluation III for the proposed trade name, Emend. The Office Director, Dr. Houn, concluded that the name is acceptable due to the fact that there is a very low likelihood of actual errors occurring. Only small quantities of Amen are available in the US. In addition, the applicant proposed an educational campaign at the time of the marketing launch to ensure recognition of Emend as a newly marketed product not to be confused with Amen. The applicant accepted this proposal (see phase 4 commitments in the approval letter).
- B. **Chemistry:** Emend is a highly selective inhibitory of the neurokinin-1 (NK-1) receptor. The drug product is available as oral capsules in 80-mg and 125-mg strengths. Emend is a crystalline solid that is highly insoluble in water. The drug substance particles in the capsule formulation are in the nanometer range, enhancing

the uptake and minimizing the food effect. The chemists recommended approval of Emend with one phase 4 commitment regarding dissolution testing. "Merck will justify the use of \_\_\_\_\_ capsule formulation dissolution method, including studies on the \_\_\_\_\_ for the nanoparticle formation. Accordingly, based on the data presented in the response, the dissolution specification will be reviewed and, if warranted, revised." The medical review team is in agreement with this recommendation.

**C. Animal Pharmacology/ Toxicology:** The applicant included carcinogenicity testing in the application. There was extended discussion during the labeling review regarding the wording of this section (refer to pharm/tox review for specific details). Additional discussions were held between the Division and Dr. Osterberg and Dr. Lathan, both senior Toxicologists in Office of New Drugs. They concurred with the Division's approach to labeling. It was recommended that this discussion continue between the applicant and FDA after approval since Merck would like to harmonize this section of the label with its European label. Additional internal discussions will be held in the CAC to consider further changes to the approved label. The final recommendation by the pharm/tox group was approval of Emend with specific labeling recommendations. The medical group is in agreement with these recommendations.

**D. Biopharmaceutics:** Emend is a moderate CYP3A4 inhibitor. The following summarizes the review of Emend by the biopharmaceutics reviewer and is a direct quote from the review:

"Clinical Pharmacology studies have shown that Emend is extensively metabolized, primarily via oxidation by CYP3A4 isozyme. Emend at the recommended dose regimen is an inhibitor of CYP3A4 activity and resulted in more than three fold increase in the exposure of concomitantly administered midazolam, a sensitive CYP3A4 substrate. There are many cancer chemotherapeutic agents that are metabolized by CYP3A4 isozyme and concomitant administration of Emend may inhibit the metabolism of these chemotherapy agents resulting in increased toxicity. Sponsor has not adequately characterized the drug interaction potential of Emend with chemotherapy agents. Currently there is an ongoing drug interaction study with intravenously administered docetaxel. Proposed label recommends caution when Emend is to be administered with drugs that are primarily metabolized by CYP3A4 and contraindicates pimozone, terfenadine, astemizole, and cisapride. However, there is no data in the NDA to assess the degree of interaction of Emend with chemotherapy agents and no dosage adjustments could be recommended at this time."

"Another issue at the AC meeting was the generalizability of 5-HT<sub>3</sub> antagonists for coadministration with Emend for prevention of chemotherapy induced nausea and vomiting (CINV). The Phase III clinical studies were conducted with intravenous ondansetron. Pharmacokinetic drug interaction studies have shown that Emend does not affect the pharmacokinetics of intravenous ondansetron and orally administered granisetron (both CYP 3A4 substrates). There is no data on PK interaction with oral

ondansetron. However, the label for ondansetron states that since this drug is metabolized by multiple CYP450 isozymes, significant drug interactions are unlikely. Pharmacokinetic drug interaction with dolasetron is unlikely because this drug is metabolized by multiple pathways with carbonyl reductase and CYP2D6 being the main pathways and CYP3A4 plays a minor role. However, there is no clinical safety data on coadministration of Emend with dolasetron.”

The biopharmaceutics reviewer recommended approval of Emend with wording in the label, including contraindications to co-administration of Emend with pimozide, terfenadine, astemizole, or cisapride. In addition, the Precautions section of the label cautions the use of concomitant medicinal products, including chemotherapy agents that are primarily metabolized through CYP 3A4. It also explains the extent of clinical exposure information.

“Chemotherapy agents that are known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine and vincristine. In clinical studies, EMEND was administered commonly with etoposide, vinorelbine, or paclitaxel. The doses of these agents were not adjusted to account for potential drug interactions.

Due to the small number of patients in clinical studies who received the CYP3A4 substrates docetaxel, vinblastine, vincristine, or ifosfamide, particular caution and careful monitoring are advised in patients receiving these agents or other chemotherapy agents metabolized primarily by CYP3A4 that were not studied (see PRECAUTIONS, Drug Interactions).”

These recommendations were found to be acceptable to the medical review team, given the input of the advisory committee who agreed with approval and caution in the administration of these drugs. The docetaxel data gives some information regarding the potential level of interaction, however, the complete metabolic pathway is not certain for many of these drugs. The specific concern being potential toxicity with the potential for increased drug levels of chemotherapy agents. The Advisory Committee went on to recommend that additional information should be collected after marketing (see phase 4 commitments).

The therapeutic regimen, which was demonstrated by the phase 3 clinical studies to be effective and is being recommended for approval is as follows:

Emend is given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT3 antagonist. The recommended dose of Emend is 125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg once daily in the morning on Days 2 and 3. Emend has not been studied for the treatment of established nausea and vomiting.

In clinical studies, the following regimen was used:

	Day 1	Day 2	Day 3	Day 4
EMEND*	125 mg	80 mg	80 mg	None
Dexamethasone**	12 mg orally	8 mg orally	8 mg orally	8 mg orally
Ondansetron <sup>f</sup>	32 mg IV	none	none	None

\*EMEND was administered orally 1 hour prior to chemotherapy treatment on Day 1 and in the morning on Days 2 and 3.

\*\*Dexamethasone was administered 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. The dose of dexamethasone was chosen to account for drug interactions.

<sup>†</sup>Ondansetron was administered 30 minutes prior to chemotherapy treatment on Day 1.

Adjustments for the dexamethasone dose were recommended in the Dosage and Administration due to Emend's pharmacokinetic effect on concomitant use of dexamethasone. Finally, caution is given regarding the continuous, long-term use of Emend as it can induce the CYP 450 system after prolonged administration. This exposure was not studied clinically. Repeated use for the 4-day cycle is acceptable for prevention of CINV in multiple cycle chemotherapy regimens (see safety comments below).

Coadministration with any currently marketed HT-3 inhibitor was recommended by the Advisory committee based upon the pharmacokinetic data on hand. However, additional post-marketing pK studies with dolasetron were recommended. The medical team is in agreement with these recommendations.

#### **E. Clinical: Efficacy/Safety:**

1. **Efficacy:** The efficacy of Emend was demonstrated by two multi-center, double-blind, randomized controlled clinical trials. One study was performed in the US, and the second study was performed outside of the US. Both studies utilized the same design and endpoints. The primary endpoint was complete response (no emesis and no rescue therapy) in the overall phase (0 to 12 hours post cisplatin administration). Additional pre-specified endpoints of acute phase (0 to 24 hours) and delayed phase (25 to 120 hours) were also analyzed. Efficacy was based on evaluation of the following endpoints:

Primary endpoint:

- complete response (defined as no emetic episodes and no use of rescue therapy)

Other prespecified (secondary and exploratory) endpoints:

- complete protection (defined as no emetic episodes, no use of rescue therapy, and a maximum nausea visual analogue scale [VAS] score <25 mm on a 0 to 100 mm scale)
- no emesis (defined as no emetic episodes regardless of use of rescue therapy)
- no-nausea (maximum VAS <5 mm on a 0 to 100 mm scale)
- no significant nausea (maximum VAS <25 mm on a 0 to 100 mm scale)

A summary of the key study results from each individual study analysis is shown in Table 1 and in Table 2.

**Table 1**

**Percent of Patients Responding by Treatment Group and Phase for Study 1 — Cycle 1**

ENDPOINTS	Aprepitant Regimen (N= 260) <sup>†</sup> %	Standard Therapy (N= 261) <sup>†</sup> %	p-Value
<b>PRIMARY ENDPOINT</b>			
Complete Response			
Overall <sup>‡</sup>	73	52	<0.001
<b>OTHER PRESPECIFIED (SECONDARY AND EXPLORATORY) ENDPOINTS</b>			
Complete Response			
Acute phase <sup>§</sup>	89	78	<0.001
Delayed phase <sup>¶</sup>	75	56	<0.001
Complete Protection			
Overall	63	49	0.001
Acute phase	85	75	0.005
Delayed phase	66	52	<0.001
No Emesis			
Overall	78	55	<0.001
Acute phase	90	79	0.001
Delayed phase	81	59	<0.001
No Nausea			
Overall	48	44	>0.050
Delayed phase	51	48	>0.050
No Significant Nausea			
Overall	73	66	>0.050
Delayed phase	75	69	>0.050

<sup>†</sup>N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.

<sup>‡</sup>Overall: 0 to 120 hours post-cisplatin treatment.

<sup>§</sup>Acute phase: 0 to 24 hours post-cisplatin treatment.

<sup>¶</sup>Delayed phase: 25 to 120 hours post-cisplatin treatment.

Visual analogue scale (VAS) score range: 0 mm = no nausea; 100 mm = nausea as bad as it could be.

Table 1 includes nominal p-values not adjusted for multiplicity.

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**Table 2**  
**Percent of Patients Responding by Treatment Group and Phase for Study 2 — Cycle 1**

ENDPOINTS	Aprepitant Regimen (N= 261) <sup>1</sup> %	Standard Therapy (N= 263) <sup>1</sup> %	p-Value
<b>PRIMARY ENDPOINT</b>			
<b>Complete Response</b>			
Overall <sup>2</sup>	63	43	<0.001
<b>OTHER PRESPECIFIED (SECONDARY AND EXPLORATORY) ENDPOINTS</b>			
<b>Complete Response</b>			
Acute phase <sup>3</sup>	83	68	<0.001
Delayed phase <sup>4</sup>	68	47	<0.001
<b>Complete Protection</b>			
Overall	56	41	<0.001
Acute phase	80	65	<0.001
Delayed phase	61	44	<0.001
<b>No Emesis</b>			
Overall	66	44	<0.001
Acute phase	84	69	<0.001
Delayed phase	72	48	<0.001
<b>No Nausea</b>			
Overall	49	39	0.021
Delayed phase	53	40	0.004
<b>No Significant Nausea</b>			
Overall	71	64	>0.050
Delayed phase	73	65	>0.050

<sup>1</sup>N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.

<sup>2</sup>Overall: 0 to 120 hours post-cisplatin treatment.

<sup>3</sup>Acute phase: 0 to 24 hours post-cisplatin treatment.

<sup>4</sup>Delayed phase: 25 to 120 hours post-cisplatin treatment.

Visual analogue scale (VAS) score range: 0 mm = no nausea; 100 mm = nausea as bad as it could be.

Table 2 includes nominal p-values not adjusted for multiplicity.

These results are reviewed by the biostatistician and clinical medical reviewer and were found to support efficacy of Emend for the overall, acute and delayed phases of prevention of CINV.

It should be noted that both a literature review by the reviewing medical officer and the Advisory Committee Members recognized the dose of cis-platin used in this study to be highly emetogenic (50-75 mg/m<sup>2</sup>).

- Safety:** The most commonly reported adverse events reported in the phase 3 studies are listed in the table below.

Table 3

Percent of Patients With Clinical Adverse Experiences (Incidence  $\geq 3\%$ )  
in CINV Phase III Studies (Cycle 1)

	Aprepitant Regimen (N = 544)	Standard Therapy (N = 550)
<b>Body as a Whole/ Site Unspecified</b>		
Abdominal Pain	4.6	3.3
Asthenia/Fatigue	17.8	11.8
Dehydration	5.9	5.1
Dizziness	6.6	4.4
Fever	2.9	3.5
Mucous Membrane Disorder	2.6	3.1
<b>Digestive System</b>		
Constipation	10.3	12.2
Diarrhea	10.3	7.5
Epigastric Discomfort	4.0	3.1
Gastritis	4.2	3.1
Heartburn	5.3	4.9
Nausea	12.7	11.8
Vomiting	7.5	7.6
<b>Eyes, Ears, Nose, and Throat</b>		
Tinnitus	3.7	3.8
<b>Hemic and Lymphatic System</b>		
Neutropenia	3.1	2.9
<b>Metabolism and Nutrition</b>		
Anorexia	10.1	9.5
<b>Nervous System</b>		
Headache	8.5	8.7
Insomnia	2.9	3.1
<b>Respiratory System</b>		
Hiccups	10.8	5.6

The following table displays the actual exposure to each specific chemotherapeutic agent in the phase 3 clinical trials. The Applicant identified the following chemotherapies as CYP3A4 substrates: etoposide, vinca alkaloids (vinblastine, vincristine, and vinorelbine tartrate), Taxanes (docetaxel and paclitaxel), irinotecan, and ifosfamide. Because of the interest in coadministration with chemotherapeutic agents metabolized by CYP 3A4, the medical review specifically requested that adverse events be broken out according to these agents. The types of adverse events reported in this sub analysis were similar to those reported above. There were slightly more hematologic adverse events in the CYP 3A4 chemotherapy agent group, but there was not enough data to draw conclusions about the clinical significance of this difference because of the numbers of patients studied. In addition, examination of adverse events by individual CYP 3A4 chemotherapy substrates revealed a question regarding vinorelbine.

**Number (%) of Patients With Specific Antineoplastic Agents  
(Incidence >0% in One or More Treatment Groups) by Drug Category—  
CINV Phase III Studies (Cycle 1)**

	Aprepitant Regimen (N=547)		Standard Therapy (N=552)	
	n	(%)	n	(%)
Patients with one or more concomitant antineoplastic agents	520	(95.1)	530	(96.0)
Patients with no concomitant antineoplastic agent	27	(4.9)	22	(4.0)
<b>Antineoplastic and Immunomodulating Agents</b>				
<b>Antineoplastic Agent</b>	<b>520</b>	<b>(95.1)</b>	<b>530</b>	<b>(96.0)</b>
Bleomycin	21	(3.8)	23	(4.2)
Capecitabine	1	(0.2)	1	(0.2)
Carboplatin	0	(0.0)	1	(0.2)
Cyclophosphamide	50	(9.1)	43	(7.8)
Cytarabine	1	(0.2)	0	(0.0)
Dacarbazine	4	(0.7)	4	(0.7)
Docetaxel	11	(2.0)	14	(2.5)
Doxorubicin	38	(6.9)	44	(8.0)
Epirubicin	4	(0.7)	7	(1.3)
Etoposide	106	(19.4)	92	(16.7)
Fluorouracil	100	(18.3)	93	(16.8)
Gemcitabine	89	(16.3)	101	(18.3)
Ifosfamide	2	(0.4)	1	(0.2)
Irinotecan hydrochloride	0	(0.0)	1	(0.2)
Melphalan	0	(0.0)	1	(0.2)
Methotrexate	5	(0.9)	4	(0.7)
Mitomycin	14	(2.6)	5	(0.9)
Paclitaxel	52	(9.5)	58	(10.5)
Raltitrexed	2	(0.4)	3	(0.5)
Trastuzumab	1	(0.2)	3	(0.5)
Vinblastine	11	(2.0)	12	(2.2)
Vincristine	2	(0.4)	0	(0.0)
Vinorelbine tartrate	84	(15.4)	80	(14.5)
<p>Although a patient may have had 2 or more antineoplastic agents, the patient is counted only once within a category. The same patient may appear in different categories.</p> <p>Aprepitant Regimen = Aprepitant 125 mg P.O. on Day 1 and 80 mg P.O. once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.</p> <p>Standard Therapy = Ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg P.O. on Day 1 and 8 mg P.O. twice daily on Days 2 to 4.</p> <p>CINV = Chemotherapy-induced nausea and vomiting. P.O. = By mouth. IV = Intravenous. N = Number of adult patients.</p>				

Review of the vinorelbine data demonstrated a notable difference in the incidence of serious adverse events involving the respiratory system. Six of 82 patients (7.3%) in the Emend group compared to 1 out of 76 patients (1.3%) in the standard therapy group experienced a serious adverse event involving the respiratory system.

None of the patient receiving standard therapy reported respiratory insufficiency, whereas 4 patients in the Emend group developed a fatal respiratory insufficiency. These 4 patients (ANs 5097, 5109, 5114, and 6088) were randomized at the same study site (Site 018 in Protocol 054). The Applicant conducted an audit. The investigator reported that the cases of respiratory insufficiency represented progression of underlying malignant disease (lung cancer) and did not consider the events to be drug related. Analyzing the

data suggests that these deaths were not related to the patient developing either pneumonia or pleural effusions.

In addition to these four fatalities, 3 additional deaths (7) occurred in the Emend group. There were 2 fatalities in the corresponding standard therapy group.

Analysis of the data does not suggest that the Emend regimen increased the hematologic toxicity of vinorelbine tartrate. However, twice as many patients in the Emend regime developed a serious infection. There were 3 reported cases of sepsis or septic shock as serious adverse events in the Emend group compared to no cases in the standard therapy.

The Agency noted that the Emend regimen may have increased the pulmonary toxicity of vinorelbine tartrate, since all the fatal cases of respiratory insufficiency occurred in the Emend group. Given that no formal drug-drug interaction PK study was completed for vinorelbine tartrate (CYP3A4 substrate), the Agency discussed this issue at the Advisory Committee.

The Advisory Committee felt that these drugs could be used, however, recommended caution in the labeling and additional pharmacokinetic drug interaction studies be undertaken post-marketing (see phase 4 commitments). The medical review team is in agreement with this recommendation.

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## NDA 21-549

### EMEND (Aprepitant) Capsules 80 and 125 mg

#### CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Merck Research Laboratories  
PO Box 4, BLA  
West Point PA

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. Aprepitant is not indicated for the treatment of established nausea and vomiting.

Presentations: — bottles 75, 100, 250 (80 mg only) mL with desiccant, both strengths 75, 120, 250 count resp., and blisters 5 count, and blisters cards with one 125 mg and 2 80 mg capsules

EER Status: Acceptable

Consults: ODS – Potential for name confusion, so a Phase IV risk management program will be undertaken.

EMEND was submitted 2-SEP-2002. A IR letter was issued 17-MAR-2003, and was responded to in the amendment dated 20-MAR-2003. Clarifying TCons were conducted 17-MAR-03 and 19-MAR-03.

The **drug substance** is manufactured by Merck Sharp and Dohme Quimica, Barceloneta PR. Drug substance characterization and manufacturing are adequate. The structure has 3 chiral centers. Adequate process controls are in place. The DS exists in 2 morpnic forms, with the form selected, Type 1 being more stable. The impurity profile is well defined and impurities are found at consistently low levels. — is a critical process to produce nano-particles. Early formulations did not use a — and had significantly lower bioavailability. Specifications are considered adequate. The 1 acceptance criterion will be re-evaluated after additional manufacturing experience is gained. A re-test period of 24 months is supported by submitted stability data.

#### **Conclusion**

Drug substance is acceptable.

The **drug product** is an 80 and 125 mg immediate release capsule. The product is manufactured at the Merck, West Point, PA site. Nano-particles of drug substance are beads. The formulation and commercial

manufacturing process are the same as that for the clinical and bio batches. The manufacturing process and controls are considered acceptable. Specifications are considered adequate with the exception of the dissolution method. The firm provided justification based upon a study done with the earlier tablet formulation. The sponsor has agreed to provide a study justifying use by phase IV agreement, to be submitted Q2-03. Expiry of 24 months is supported by submitted stability data. The stability protocol has been updated to provide for particle size determination. PI, immediate container and carton labeling is acceptable. On the physicians sample the firm has agreed to move the word "complementary" to a more prominent location.

All associated DMFs are acceptable.

**Conclusion**

Drug product is acceptable.

**Overall Conclusion**

From a CMC perspective the application is recommended for an approval action.

Eric P Duffy, PhD  
Director, DNDC II ONDC

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# MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 24, 2003

FROM: David A. Place, Ph.D.  
Reviewing Chemist  
(301) 827-7502

SUBJECT: NDA 21-549: Clarifications and Comments on CMC Issues for Emend Capsules

THROUGH: Liang Zhou, PhD  
Chemistry Team Leader, Division of New Drug Chemistry II

TO: Electronic File  
NDA 21-549

On March 21, 2003, Merck responded to our CMC concerns. These issues are summarized below. All responses are satisfactory.

## I. Drug Substance

- A. The supplier protocol and Certificate of Analysis for \_\_\_\_\_ used in the drug substance manufacture are provided.
- B. Merck uses \_\_\_\_\_ They detail the purity of each \_\_\_\_\_ They do not actually employ \_\_\_\_\_ as stated in the original submission.
- C. The sponsor will reevaluate the \_\_\_\_\_ specification once commercial production has been fully established, and report any tightening of the specification in an annual report.
- D. Impurities have been listed as specified and unspecified per ICHQ3A and 6A.

## II. Drug Product

- A. The sponsor commits to a Phase 4 study of the dissolution medium and specification. They propose to report the results to the FDA by 2Q03.
- B. The encapsulated drug product is packaged in \_\_\_\_\_ with \_\_\_\_\_ desiccant included. This protects the bulk capsules during transit to their packaging destinations, where they are placed into bottles or blister packages.
- C. The sponsor has agreed to continue using the test for particle size as a release and stability test and specification. The sponsor may request, through a future supplement, to discontinue this test and specification.
- D. The dye leak test for the blister packs has been performed so far on \_\_\_\_\_ packages. No failures have been observed.

III. Labeling

- A. The sponsor has agreed to move the word "Complimentary" from the edge of the package to a prominent place on the face of the label.
- B. The sponsor did not provide a shipping label for the drug product. This is not a CMC review issue. This information will be requested and reviewed when the firm is subjected to cGMP inspection.

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**MEMORANDUM****DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE:** March 25, 2003

**FROM:** Supervisory Pharmacologist,  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

**SUBJECT:** NDA 21,549 (EMEND)-Pharmacology Review- Comments & Safety Issues Raised  
by Dr. John Leighton

**TO:** NDA 21,549

Dr. Leighton's comments are addressed in the same order listed in his memorandum dated March 21, 2003.

- 1) The sponsor included the studies of the prodrug (L-758,298) in the NDA for completeness and they were reviewed by Dr. Chakder. These studies with the exception of the Ames test have no impact on the preclinical assessment of aprepitant. L-758,298 is rapidly converted to aprepitant (MK-0869/L-754,380) in vivo in rat and in vitro in incubations with liver microsomal fractions. Thus in the Ames test, one can infer that L-758,298 has been converted to MK-0869 in the presence of rat liver S-9 fraction. Oral developmental toxicology (Segment II. Teratology) studies of MK-0869 (L-754,030) in rats and rabbits were also conducted (Review pages 263-274).
- 2) Maximum feasible doses of MK-0869 ( — particle size) 1000 mg/kg, b.i.d. have been employed by the sponsor in prenatal and postnatal toxicity study in rats (Study #01-736-0, Review page 267), oral fertility study in female rats (Study #01-735-0, Review page 238), oral fertility study in male rats (Study # 01-737-0, Review page 242), and oral toxicokinetic study in pregnant rats (Study # 01-732-0, Review page 70). The results of these studies do not demonstrate a greater degree of absorption. The saturation of absorption expected in the rat carcinogenicity study prevailed in these studies also. Thus in the rat carcinogenicity study, the observed exposure levels (AUC 0-24hr) at 125 mg/kg, b.i.d. were 7.19 mcg.hr/ml in male rats and 26.9 mcg.hr/ml in female rats, i.e. 0.4 to 1.4 times the human exposure (AUC 0-24hr=19.6 mcg.hr/ml) at the recommended dose of 125 mg/day. The exposure levels in pregnant rats, 28.1 +/- 2.3 mcg.hr/ml at 125 mg/kg, b.i.d. and 31.3 +/-1.6 mcg.hr/ml at 1000 mg/kg, b.i.d. were almost equal (Review page 71).
- 3) Adequate specific enzyme induction studies of MK-0867 in rodents are lacking. During the labeling negotiation sessions (teleconference), the sponsor has been informed that adequate studies to support their contention of mechanisms for the tumors in the carcinogenicity studies are lacking. No clinical data are available to indicate lack of relevance.

- 4) ---
- 5) Historical control data from the testing laboratories are included in the review portion in the context of the observed tumors in each study,
- 6) The findings of the carcinogenicity studies are scheduled to be discussed at the CAC Executive Committee meeting on April 1, 2003.

**/S/**

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Jasti B. Choudary, B.V. Sc., Ph.D.      Date  
Supervisory Pharmacologist, HFD-180

Cc:  
NDA  
HFD-180  
HFD-181/CSO  
HFD-180/Dr. Chakder  
HFD-180/Dr. Choudary

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/s/

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Jasti Choudary  
3/25/03 07:45:50 PM  
PHARMACOLOGIST

## **STATISTICAL REVIEW AND EVALUATION (CLINICAL STUDIES)**

**NDA:** 21-549

**APPLICANT:** Merck and Co., INC.

**NAME OF DRUG:** Emend (Aprepitant) Capsules 80 mg/125 mg

**INDICATION:** Prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of highly emetogenic cancer chemotherapy.

**USER FEE DUE DATE:** March 27, 2003

**DRUG CLASSIFICATION:** 1P

**DOCUMENT REVIEWED:** Labeling submission dated January 7, 2003.

**STATISTICAL REVIEWER:** Wen-Jen Chen, Ph.D.

**KEY WORDS/PHRASES:** Clinical studies; NDA review; Multiple endpoints.

### **BACKGROUND**

In this submission, the sponsor proposed a draft labeling package, according to the results from the two phase III Studies P052 and P054, for the use of Aprepitant in prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of highly emetogenic cancer chemotherapy.

Based on the draft labeling package proposed by the sponsor, this reviewer would like to comment on the issues of the statistical data presented in this submission and recommend what data should and should not be incorporated in the labeling package.

### **Reviewer's Comments and Recommendations**

1. Issues on the endpoints proposed for labeling package

In the labeling package, the sponsor proposed to present the efficacy results by Table 1 and Figure 1 on the following six endpoints of Cycle 1: complete response, complete protection, no impact on daily life, no emesis, no significant nausea, and time to first emesis in overall phase.

For the endpoint of no impact on daily life, the original p-values for the two-phase III Studies P052 and P054 were 0.021 and 0.007 respectively, less than 0,05 significant level. However, noted by this reviewer, the sponsor performed many analyses based on the secondary and exploratory endpoints pre-specified in the protocol. No impact on daily life was one of the pre-specified secondary endpoints. Therefore, some significant results may not be real effect ascribed to aprepitant but occurred by chance due to multiple comparisons. In order to avoid the false positive results induced by multiple comparisons, this reviewer performed Hochburg step-up procedure to adjust the original p-values. After multiplicity adjustment procedure performed on the 21 multiple comparisons formed by the pre-specified secondary and exploratory endpoints, the significant results for no impact on daily life shown by original p-values for the two-phase III studies are not significant (adjusted p-values 0.25 and 0.063, respectively for Studies P052 and P054). The adjusted p-value 0.063 for study P054 is close to 0.05 significant level and may indicate some effect of aprepitant better than the standard therapy on no impact of daily life. However, for Study P052, after multiplicity adjustments, the effect of aprepitant on no impact on daily life shows no better than that of the standard therapy (adjusted p-value = 0.25). Thus, from the statistical perspective, the efficacy data submitted by the sponsor did not provide substantial evidence to support that aprepitant is significantly better than standard therapy for no impact on daily life.

## 2. Issues on data presented in Table 1

In Table 1, the sponsor presented efficacy results on complete response, complete protection, no impact on daily life, no emesis, and no significant nausea using data combined from the two-phase III Studies P052 and P054.

However, to present the efficacy results, instead of using combined data from the two-phase III studies, the sponsor should present efficacy results on complete response, complete protection, no emesis, and no significant nausea using data separately from each of the two-phase III Studies P052 and P054. In order to incorporate the concern about the multiple comparison issue described in item 1, except for the significant nausea in overall and delayed phases, the original p-values for complete response, complete protection, and no emesis in the three phases are recommended presented as “p-value < 0.01”, as the sponsor did in the efficacy summary table.

In addition, as indicated in item 1, the result for endpoint of no impact on daily life should be removed from this table due to lack of substantial evidence provided to support the superiority of aprepitant to the standard therapy.

## 3. Issues on data presented by Figure 1

For Figure 1, two following issues are noted by this reviewer:

- i. Kaplan-Meier survival curve is recommended put as a footnote for the title of Figure 1.
- ii. To present the efficacy result on time to the first emesis, instead of presenting the survival curve on emesis using data from combined two-phase III studies, the sponsor should

present the figure separately for each of the two-phase III studies. However, since the survival curves for time to the first emesis for the two-phase III studies are similar, the sponsor can choose one of the two curves from the two-phase III studies to present. In addition, the percent of patients in vertical axis should be presented in a full scale from 0% to 100%. Finally, In order to cope with the multiple comparison issue described in item 1, the original p-value for the treatment comparison on time to the first emesis is recommended presented as “p-value < 0.01”.

4. Issues on data presented by Figure 2

The following two issues noted in Figure 2 need to be corrected:

- i. The percent of patients with no emesis and no significant nausea by treatment group and cycles should be presented separately for each of the two-phase III studies. In addition, as suggested by item 3, the percent of patients in vertical axis should be presented in a full scale from 0% to 100%.
- ii. The dash line between two cycles should be removed.

5. Adding efficacy analysis results by gender to the labeling package

This reviewer notes that for Study P052, the percentage differences of MK-0869 therapy minus standard therapy on complete response in three phases for males are much smaller than that of females and are not significant. However, on the contrary, for Study P054, the percentage differences of MK-0869 therapy minus standard therapy on complete response in overall and delayed phases for males are around 10% larger than that of females and are highly significant. The non-superiority of MK-0869 regimen to the standard therapy in males is not replicated in Study P054. Accordingly, the non-significant results for males shown by Study P052 are not considered critical. However, to be aware of the concern on the non-significant results for MK0869 versus the standard therapy for males, the efficacy comparisons between the two treatment groups on complete response in three phases are recommended presented by gander separately for each of the two-phase III studies in labeling package.

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/s/  
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Wen-Jen Chen  
3/18/03 11:44:22 AM  
BIOMETRICS

Thomas Permutt  
3/18/03 11:46:01 AM  
BIOMETRICS  
concur

S. Edward Nevius  
3/19/03 03:30:05 PM  
BIOMETRICS  
Concur with review.

**Division of Gastrointestinal & Coagulation Drug Products**

**ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION**

**Application Number:** NDA 21-549

**Name of Drug:** Emend™ (aprepitant) Capsules

**Sponsor:** Merck Research Laboratories (MRL)

**Material Reviewed**

**Type of Submission (i.e., paper, electronic, or combination):** Combination

**Submission Date:** September 27, 2002

**Receipt Date:** September 30, 2002

**Filing Date:** November 29, 2002

**User-fee Goal Date:** March 30, 2003 (if Priority); July 30, 2003 (if Standard)

**Proposed Indication:** Aprepitant, 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 cis-platinum

**Other Background Information:** IND [redacted] for MK-0869 (MRL's previous designation for aprepitant) was submitted April 9, 1996 by MRL to investigate MK-0869, an NK<sub>1</sub> receptor antagonist, for the prevention of chemotherapy-induced emesis.

End-of-Phase 2 meetings to discuss MRL's proposed clinical development program were held April 14, 1999 and September 21, 2001. A pre-NDA meeting was held January 22, 2002. A teleconference regarding the proposed tradename, Emend™, was held August 23, 2002.

Efficacy and safety are supported by Studies 052 and 054, both of which are entitled, "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study, Conducted Under In-House Blinding Conditions, to Examine the Safety, Tolerability, and Efficacy of MK-0869 for the Prevention of Chemotherapy-Induced Nausea and Vomiting Associated with High-Dose Cisplatin".

**Review**

Although this application was a combination paper and electronic submission, the electronic submission was comprehensive and is the subject of this review. All items were located in the September 27, 2002 submission in the EDR.

**PART I: OVERALL FORMATTING<sup>a,d,e</sup>**

[Note: Items 1,2,3,4, & 5 must be submitted in paper.]	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Cover Letter	Y		cover.pdf
2. Form FDA 356h (original signature)	Y		356h.pdf
a. Establishment information	Y		Attachment 1 to 356h.pdf
b. Reference to DMF(s) & Other Applications	Y		Attachment 2 to 356h.pdf
3. User Fee FDA Form 3397	Y		Ndatoc.pdf, user fee cover sheet bookmark
4. Patent information & certification	Y		Ndatoc.pdf, patent information bookmark
5. Debarment certification (Note: Must have a definitive statement)	Y		Ndatoc.pdf, debarment certification bookmark
6. Field Copy Certification	Y		Ndatoc.pdf, field copy certification bookmark
7. Financial Disclosure	Y		Ndatoc.pdf, financial information bookmark
8. Comprehensive Index	Y		Ndatoc.pdf with bookmarks
9. Pagination	Y		Each volume paginated separately
10. Summary Volume	Y		Ndatoc.pdf, Summary bookmark
11. Review Volumes	Y		All review volumes have been distributed to the appropriate reviewers.

12. Labeling (PI, container, & carton labels)	Y		Ndatoc.pdf, Labeling bookmark (labeltoc.pdf)
a. unannotated PI	Y		Labeltoc.pdf, Proposed labeling text package insert bookmark
b. annotated PI	Y		Ndatoc.pdf, Summary Table of Contents bookmark, proposed text of labeling bookmark
c. immediate container	Y		Ndatoc.pdf, Labeling bookmark, Container label bookmark
d. carton	Y		Ndatoc.pdf, Labeling bookmark, Carton labels bookmark
e. patient package insert (PPI)	Y		Ndatoc.pdf, Labeling bookmark, patient product information bookmark
f. foreign labeling (English translation)		N	Will request if necessary
13. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	Y		Ndatoc.pdf, Case Report Tabulations bookmark
14. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	Y		Ndatoc.pdf, Case Report Forms bookmark

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY<sup>b,d,e</sup>

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	Y		Ndatoc.pdf, Summary bookmark, Overview bookmark page A-4

2. Foreign Marketing History	Y		Ndatoc.pdf, Summary bookmark, Commercial Marketing History bookmark
3. Summary of Each Technical Section	Y		Ndatoc.pdf, Summary bookmark
a. Chemistry, Manufacturing, & Controls (CMC)	Y		Ndatoc.pdf, Summary bookmark, Chemistry, Manufacturing and Controls bookmark
b. Nonclinical Pharmacology/Toxicology	Y		Ndatoc.pdf, Summary bookmark, Nonclinical toxicology summary bookmark
c. Human Pharmacokinetic & Bioavailability	Y		Ndatoc.pdf, Summary bookmark, Nonclinical Pharmacodynamics Summary bookmark and Nonclinical Pharmacokinetics Summary bookmark
d. Microbiology		N	N/A
e. Clinical Data & Results of Statistical Analysis	Y		Ndatoc.pdf, Summary bookmark, Worldwide Clinical Summary bookmark
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	Y		Ndatoc.pdf, Summary bookmark, Worldwide Clinical Summary bookmark, page C-118
5. Summary of Safety	Y		Ndatoc.pdf, Summary bookmark, Worldwide Clinical Summary bookmark, page C-68
6. Summary of Efficacy	Y		Ndatoc.pdf, Summary bookmark, Worldwide Clinical Summary bookmark, page C-35

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS<sup>c,d,e</sup>

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. List of Investigators	Y		Clinstat Folder, clintoc.pdf A list of investigators is included in each study report.

2. Controlled Clinical Studies			
a. Table of all studies	Y		Clinstat Folder, clintoc.pdf
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	Y		See Attachment #1
c. Optional overall summary & evaluation of data from controlled clinical studies		N	Not provided
3. Integrated Summary of Efficacy (ISE)	Y		Clinstat Folder, clintoc.pdf, Integrated Summary of Efficacy bookmark
4. Integrated Summary of Safety (ISS)	Y		Clinstat Folder, clintoc.pdf, Integrated Summary of Safety bookmark
5. Drug Abuse & Overdosage Information		N	N/A
6. Integrated Summary of Benefits & Risks of the Drug	Y		Clinstat Folder, clintoc.pdf, Integrated Summary of Benefits and Risks bookmark
7. Gender/Race/Age Safety & Efficacy Analysis of Studies	Y		<u>Efficacy</u> : Clinstat Folder, clintoc.pdf, Integrated Summary of Efficacy bookmark page D-191  <u>Safety</u> : Unable to locate, will request the location if necessary

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS<sup>d,e</sup>

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population		N	Agency will allow a deferral of the submission of pediatric data per the January 29, 2002 Pre-NDA meeting.
2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.)		N	Electronic Submission, none requested
a. Proposed unannotated labeling in MS WORD		N	N/A
b. Stability data in SAS data set format (only if paper submission)		N	N/A
c. Efficacy data in SAS data set format (only if paper submission)		N	N/A
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)		N	N/A
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)		N	N/A
3. Exclusivity Statement (optional)		N	Not provided

Y=Yes (Present), N=No (Absent)

<sup>a</sup>"GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

<sup>b</sup>"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

<sup>c</sup>"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND

STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

<sup>d</sup>"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-GENERAL CONSIDERATIONS" (JANUARY 1999).

"GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-NDAS" (JANUARY 1999).

#### **Conclusions**

From an administrative standpoint, this application is fileable. A 45-Day planning/filing meeting has been scheduled for November 7, 2002. Foreign labeling (Item I, 12, e) and an analysis of safety data by gender, race, and age will be requested if necessary.

#### **ATTACHMENTS**

Attachment #1

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**NDA 21-549**  
**Administrative Review**  
**Attachment #1**

**Study 052:** A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study, Conducted Under In-House Blinding Conditions, to Examine the Safety, Tolerability, and Efficacy of MK-0869 for the Prevention of Chemotherapy-Induced Nausea and Vomiting Associated with High-Dose Cisplatin

Synopsis – Clinstat Folder, clintoc.pdf, Reference 052 bookmark, Synopsis bookmark

Protocol – Clinstat Folder, clintoc.pdf, Reference 052 bookmark, List of Appendices bookmark, Category 3: Study Documents bookmark, page 1059

Related Publications – Clinstat Folder, clintoc.pdf, Reference 052 bookmark, List of Appendices bookmark, Category 1: Publication/prepublication Manuscript bookmark

List of Investigators – Clinstat Folder, clintoc.pdf, Reference 052 bookmark, Investigators and Study Administrative Structure bookmark

Integrated Clinical and Statistical Report – Clinstat Folder, clintoc.pdf, Reference 052 bookmark

**Study 054:** A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study, Conducted Under In-House Blinding Conditions, to Examine the Safety, Tolerability, and Efficacy of MK-0869 for the Prevention of Chemotherapy-Induced Nausea and Vomiting Associated with High-Dose Cisplatin

Synopsis – Clinstat Folder, clintoc.pdf, Reference 054 bookmark, Synopsis bookmark

Protocol – Clinstat Folder, clintoc.pdf, Reference 054 bookmark, List of Appendices bookmark, Category 3: Study Documents bookmark, page 1030

Related Publications – Clinstat Folder, clintoc.pdf, Reference 054 bookmark, List of Appendices bookmark, Category 1: Publication/prepublication Manuscript bookmark

List of Investigators – Clinstat Folder, clintoc.pdf, Reference 054 bookmark, Investigators and Study Administrative Structure bookmark

Integrated Clinical and Statistical Report – Clinstat Folder, clintoc.pdf, Reference 054 bookmark

cc:

Draft: BKS/October 29, 2002

Final: BKS/October 29, 2002

Filename: reviews/Emend Admin Review.doc

**ADMINISTRATIVE REVIEW**

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/s/

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Brian Strongin  
10/29/02 01:26:56 PM  
CSO

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PGS. SENT	21	
RESULT	OK	



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation III

**FACSIMILE TRANSMITTAL SHEET**

**DATE: 3/26/03**

<b>To:</b> Steven Aurecchia	<b>From:</b> Brian Strongin
<b>Company:</b> Merck	
<b>Fax number:</b> (484) 344-2516	<b>Fax number:</b> 301-443-9285
<b>Phone number:</b> (484) 344-4662	<b>Phone number:</b> 301-827-7310
<b>Subject:</b> EMEND AP Letter	

**Total no. of pages including cover: 21**

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Office of Drug Evaluation III

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: 3/26/03**

**To: Steven Aurecchia**

**From: Brian Strongin**

**Company: Merck**

**Fax number: (484) 344-2516**

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**Phone number: 301-827-7310**

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# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-549	Efficacy Supplement Type SE- N/A	Supplement Number N/A
Drug: EMEND® (aprepitant) Capsules		Applicant: Merck Research Laboratories
RPM: Brian Strongin, R.Ph., M.B.A.		HFD-180 Phone # 7-7473
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): N/A
❖ Application Classifications:		
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
• Chem class (NDAs only)		1
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		March 27, 2003
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified

❖ Exclusivity (approvals only)		
• Exclusivity summary		X (March 18, 2003)
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!		( ) Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)		X - October 29, 2002
❖ Actions		
• Proposed action		(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)		N/A
• Status of advertising (approvals only)		(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications		
• Press Office notified of action (approval only)		(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated		( ) None ( ) Press Release (X) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))		
• Division's proposed labeling (only if generated after latest applicant submission of labeling)		X - (March 24, 2003)
• Most recent applicant-proposed labeling		X (Submitted January 7, 2003)
• Original applicant-proposed labeling		X (Submitted September 27, 2002)
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)		X (DDMAC Labeling Review – February 27, 2003; DMETS Tradename Review – December 14, 2001; March 22, 2002; and July 23, 2002)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)		X
❖ Labels (immediate container & carton labels)		
• Division proposed (only if generated after latest applicant submission)		X
• Applicant proposed		X (Submitted February 27, 2003)
• Reviews		X (See CMC Review #1)
❖ Post-marketing commitments		
• Agency request for post-marketing commitments		N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments		X (March 21, 2003)
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)		X
❖ Memoranda and Telecons		X
❖ Minutes of Meetings		
• EOP2 meeting (indicate date)		X – April 14, 1999 and September 21, 2000
• Pre-NDA meeting (indicate date)		X – January 22, 2002

• Pre-Approval Safety Conference (indicate date; approvals only)	X – (March 18, 2003)
• Other	X – January 24, 2003. Discussion of GIDAC Briefing Document
❖ Advisory Committee Meeting	
• Date of Meeting	March 6, 2003
• 48-hour alert	X
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	X – FR Notice of GIDAC meeting
<b>Summary Application Review</b>	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	X (March 26, 2003)
<b>Clinical Information</b>	
❖ Clinical review(s) (indicate date for each review)	X (March 14, 2003)
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	See Clinical Review #1
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	X (March 13, 2003 and March 19, 2003)
❖ Biopharmaceutical review(s) (indicate date for each review)	X (March 13, 2003)
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X (March 20, 2003)
• Bioequivalence studies	N/A
<b>CMC Information</b>	
❖ CMC review(s) (indicate date for each review)	X (March 14, 2003)
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	X (CMC Review #1, March 13, 2003)
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	Date completed: (March 26, 2003) (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (X) Not yet requested

<b>Nonclinical Pharm/Tox Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	X (March 13, 2003)
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	X (January 23, 2003)
❖ CAC/ECAC report	N/A

7/2/02

APPEARS THIS WAY  
ON ORIGINAL



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation III

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** March 17, 2003

<b>To:</b> Steven A. Aurecchia, M.D.	<b>From:</b> Brian Strongin, R.Ph., M.B.A.
<b>Company:</b> Merck Research Laboratories.	Division of Division of Gastrointestinal & Coagulation Drug Products
<b>Fax number:</b> (484) 344-2516	<b>Fax number:</b> (301) 443-9285
<b>Phone number:</b> (484) 344-4662	<b>Phone number:</b> (301) 827-7310

**Subject:** Our mark-up of your proposed labeling for the patient package insert for NDA 21-549 is attached.

**Total no. of pages including cover:** 2

**Comments:**

Please provide your response to our changes ASAP. Thanks

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**Document to be mailed:**             YES             NO

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5 pages redacted from this section of  
the approval package consisted of draft labeling