



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

FACSIMILE TRANSMITTAL SHEET

DATE: March 17, 2003

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

Document to be mailed: YES NO

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

*** TX REPORT ***

TRANSMISSION OK

TX/RX NO 2123
CONNECTION TEL 914843442516
CONNECTION ID
ST. TIME 03/17 18:49
USAGE T 01'42
PGS. SENT 6
RESULT OK



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

FACSIMILE TRANSMITTAL SHEET

DATE: March 12, 2003

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

Subject: Our mark-up of your proposed labeling for NDA 21-549 is attached.

Total no. of pages including cover: 2

Comments:

Please provide your response to our changes ASAP. Also, let me know if meeting on Friday, March 14 at 10-AM is acceptable. Thanks

Document to be mailed: YES NO

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Memo

To: Victor Raczkowski, MD
Acting Director, Division of Gastrointestinal and Coagulation Drug Products
HFD-180

From: Marci Lee, PharmD
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Through: Carol Holquist, RPh
Deputy Director, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Jerry Phillips, RPh
Associate Director, Office of Drug Safety
HFD-400

CC: Brian Strongin
Project Manager
HFD-180

Date: July 23, 2002

Re: ODS Consult 00-0298-2; Emend (Aprepitant Capsules); IND

This memorandum is in response to a June 25, 2002 request from Merck & Co., Inc. to reconsider the acceptability of the proprietary name, Emend. This is the second Trademark Appeal for Emend from the sponsor. The response to the first Trademark Appeal for Emend can be found in ODS Consult 00-0298-1 dated March 15, 2002. In addition, the initial risk assessment for this proposed name is included in the ODS Consult 00-0298 from December 14, 2001.

DMETS will respond to the points discussed in the sponsor's package dated June 25, 2002 below.

DMETS acknowledges that the medication errors of concern between AMEN and EMEND are those that occur when the pharmacists are doing their best to accurately dispense the correct medication. These medication errors are not a result of practitioners departing from standard safe pharmacy practice in the most egregious ways. The error scenarios described by the sponsor involve the pharmacist committing professional indiscretions and that is by no means what DMETS has in mind for a reason to oppose the use of EMEND.

Our concern is that the sound-alike name similarity between EMEND and AMEN sets the practitioners up for an error. If a medication error did occur between these products, it is likely that the sound-alike similarity in the names would be a major contributing factor. In any situation where a practitioner is interpreting an order for EMEND without specific information about the indication or dosing, there is potential for AMEN to be dispensed.

If a practitioner hears "AMEN" when receiving a verbal request for "EMEND", they are not breaking any laws when they dispense a medroxyprogesterone generic product in response to the request. In the case where the practitioner is already familiar with AMEN, there would be no reason for them to consult a drug reference. The generic substitution process could occur automatically. The pharmacist is behaving in a legal fashion but there is an undetected miscommunication that is contributing to the medication error. Substituting generic medroxyprogesterone for a verbal prescription interpreted as "AMEN" is not a violation of safe standard practice, nor is it a situation that requires the pharmacist to contact the prescriber. Finally, this is not a scenario, which can be described as a "complete variance" with the original prescription.

DMETS acknowledges that communication between the prescriber and pharmacist may include information that would prevent confusion between AMEN and EMEND. However, it would be irresponsible to ignore the potential for confusion that exists when this type of information is NOT communicated and there are no specific hints for the intended use of the medication or the patient diagnosis.

The materials from the Sponsor included some new information to consider with regard to the nomenclature and packaging for EMEND. DMETS notes that the sample prescriptions are written for "Emend TriPack". This may be helpful for preventing medication errors in some scenarios, especially in the outpatient practice settings. However, the prescribing habits of the physicians cannot be controlled so that this designation is always included.

The oncology practice setting can prevent some opportunities for errors because the practitioners would likely detect if the patient received AMEN instead of EMEND before they ingested the wrong medication. Although the system would prevent the patient from ingesting AMEN instead of EMEND, it does not prevent the patient arriving for their chemotherapy appointment with the wrong pre-medication.

1. The sponsor states, "As noted previously, the specific AMEN® product is no longer manufactured, nor is it available to dispensing professionals."
 - DMETS is not convinced at this time that AMEN is no longer available to dispensing professionals. AMEN appears to be available from several online pharmacies. Although we have not actually filled a prescription for AMEN online, the product is listed with prices on more than one website and there is the option to click on a "Fill a prescription" button.

- We do acknowledge that AMEN is no longer manufactured however there may be some residual product in the marketplace.
 - DMETS would like to acknowledge that it is not implausible to think that a prescriber would prescribe AMEN despite it being discontinued, especially since it appears in various drug references.
2. The sponsor states, "The tradename does still appear in some medication reference directories and drug compendiums as these sources are often belated in updating postings following the discontinuation of a product. As conveyed in correspondence from the Agency in January and April, 2002, the continued appearance of the tradename AMEN in electronic and printed reference material is the source of FDA concern. All such listings which MRL reviewed clearly show the generic name of the product as medroxyprogesterone."
- DMETS identified multiple drug references that included a listing for AMEN. Many of these were electronic and most of them are updated versions © 2002.
 - ePOCRATES is one example of a frequently updated drug information resource, which is commonly used by prescribers. When I select medroxyprogesterone, the program prompts me to

PLEASE SELECT:

AMEN
CYCRIN
PROVERA
medroxyprogesterone

- Although the AMEN listing in ePOCRATES states "Brand discontinued in the US", the risk for error between AMEN and EMEND still exists.
- The fact that the drug references clearly show the generic name of the product as medroxyprogesterone, does not prevent a practitioner from hearing AMEN when EMEND is prescribed verbally.
- Since AMEN was only available as 10 mg, a practitioner could hear AMEN and determine that a generic 10 mg medroxyprogesterone product could be dispensed. As long as the name AMEN can be found in drug information texts, there is potential for confusion with EMEND.
- A recent example of this medication error scenario occurred with E-Vista (hydroxyzine hydrochloride) and EVISTA (raloxifene hydrochloride). Although E-Vista is no longer marketed, there were errors reported where patients received hydroxyzine products instead of the prescribed EVISTA (raloxifene hydrochloride). One of the contributing factors in the error scenarios was the drug information references that continued to list E-Vista (hydroxyzine hydrochloride).
- DMETS would reconsider the acceptability of the proprietary name, EMEND, provided the sponsor commits to having AMEN removed from all available reference texts.

Need IMS Clearance prior to release of this information to the sponsor

3. Mechanisms by which the DMETS expects the medication errors to occur:

- The risk for confusion exists any time there is incomplete or ambiguous information communicated either verbally or in writing for a medication order.

Examples of ambiguous orders:

“Emend, take as directed, dispense three” (three capsules)

“Emend, take as directed, dispense one” (one pack)

“Emend, take as directed, dispense one month supply”

“I am calling to request a missing dose of Emend for Mrs. X in room 207-1”.

“Emend, take as directed, dispense five” (five packs because the patient has five appointments for chemotherapy). Similarly, one can dispense five tablets of AMEN (one course of therapy).

- Although, the example described by the Institute for Safe Medication Practices (ISMP) in APPENDIX A is actually between look-alike names, the same scenario can happen with AMEN and EMEND. A practitioner may call the pharmacy for a “missing dose” of EMEND. The pharmacist can hear AMEN and dispense generic medroxyprogesterone. In this situation, no additional information is communicated between the practitioners. One reason for this may be that the pharmacist usually has access to limited patient information and the patient’s medication record in the pharmacy computer system. Routinely, many pharmacists will verify the missing dose before dispensing. However, there are times when this step is bypassed.
 - APPENDIX B (EMEND) and APPENDIX C (AMEN) contain examples of ambiguous prescriptions that may be taken verbally from prescribers. These prescriptions specify no dosage strength and include “as directed” for instructions. DMETS anticipates that these are the types of prescriptions that will be seen when EMEND is introduced to the market. Prescribers tend to use “as directed” instead of saying or writing out complicated instructions. Furthermore, the proposed packaging configuration promotes this practice because the instructions are listed in detail on the “TRI-PACK” packaging. See APPENDIX D
4. The sponsor states, “The Agency should be aware that the preferred phonetic pronunciation for EMEND is with a long sounding e (pronounced ee). Proper enunciation would direct both ordering and dispensing professionals toward a name that starts with an E, not an A.”
- DMETS considers this a very low leverage strategy for medication error prevention. There is no way to control how practitioners pronounce a medication name. This is especially challenging when you consider the various different accents in our language.
 - In the verbal prescription study conducted by DMETS, all but one participant interpreted the medication order as “AMEND”. In addition, three study participants commented specifically that EMEND was too similar to AMEN.
 - Depending upon whether the speaker emphasizes the “D” at the end of the name, the sound may not be enough to differentiate the sound from AMEN.

5. The sponsor states, "Any verbal, written, or electronically submitted order for EMEND must include dosing instructions."
 - The sample prescription orders submitted by the sponsor ignore the possibility of prescribers using "as directed" in place of the complicated dosing schedule. The instructions are cumbersome and many will not take the time to prescribe them as the sponsor proposed in the sample prescriptions. See APPENDIX E.
 - The use of "as directed" can introduce enough ambiguity to the situation that can result in an error between AMEN and EMEND.
 - The sponsor cannot control how instructions are written/spoken by prescribers.
 - See APPENDIX C for ambiguous sample prescriptions for EMEND.

6. The sponsor states, "EMEND will be dispensed exclusively as a three-day regimen...As a result, no prescription could bear any form of "pm" instructions."
 - DMETS acknowledges that although it is unlikely to see "pm" dosing instructions for EMEND, it is possible that we will see "UD" for "use as directed" or "TAD" for "take as directed", which is equally ambiguous.

7. The sponsor states, "EMEND represents a new classification of medication (NK-1 antagonist); therefore, all prescriptions would bear the designation barring pharmacists from making substitutions."
 - DMETS considers this a non-issue if the practitioner interprets the EMEND verbal order as "AMEN". This scenario of error is NOT going to involve a practitioner hearing "EMEND" and think that they can substitute "AMEN" or its generic equivalents for "EMEND". The error will occur when in the mind of the practitioner they heard the order perfectly and it is for AMEN (medroxyprogesterone). The practitioner is not substituting for EMEND, they are dispensing a correct generic formulation for AMEN. This will likely occur when EMEND is new to the market and it is not yet familiar to practitioners.

8. The sponsor states, "In the retail setting, EMEND will be dispensed primarily in a three capsule tri-fold package or compliance pack. The EMEND product will be available only in capsule formulation."
 - DMETS acknowledges that the compliance pack will help to promote the safe use of EMEND. However, the package may also promote the use of "as directed" instructions from prescribers.
 - Although AMEN is a tablet and EMEND is a capsule, DMETS considers EMEND and AMEN to have increased risk for confusion because they are both oral solid dosage formulations. See APPENDIX F.
 - The "tablet" or "capsule" descriptor for medications is commonly omitted from the prescription. See APPENDIX B and APPENDIX C.
 - "Capsules" versus "tablets" is not likely to prevent medication errors in most scenarios.
 - Typically, the institutional setting will not have the medication-error-prevention benefit of the compliance pack.

- DMETS acknowledges it is unlikely that a pharmacist will dispense 12.5 of the 10 mg tablets and eight of the 10 mg tablets to make the 125 mg and 80 mg dose. However, the dosage strengths may not always be indicated on the prescriptions or verbal orders. The dosage strength for AMEN can be omitted because it was only available as a 10 mg oral tablet. The dosage strength for EMEND may be omitted if the prescriber intends for the TriPack to be dispensed or if this information is unintentionally omitted. There is also an increased risk if the verbal order is left on a voicemail machine because there is no opportunity to ask questions as the order is received.
9. The sponsor states, "In institutional settings individual EMEND capsules would be dispensed in accordance with the dosing regimen instructions illustrated above."
- DMETS would like to acknowledge that the statement above does not prevent medication errors due to sound-alike name similarity in the institutional setting.
10. The sponsor states, "The specifics of medroxyprogesterone acetate dosages and instructions depend on the indications...When AMEN was on the market, it was available only in a 10 mg pill. Presently, generic and proprietary versions of medroxyprogesterone acetate tablets include dosage strengths of 2.5 mg, 5 mg and 10 mg."
- DMETS predicts that a practitioner faced with selecting a generic equivalent for AMEN will without hesitation dispense any 10 mg medroxyprogesterone tablet since AMEN was only available as a 10 mg tablet.

In summary, for the reasons outlined above, the Division of Medication Errors and Technical Support (DMETS) does not recommend use of the proposed proprietary name, EMEND. The Division of Medication Errors and Technical Support will continue to consider the proprietary name EMEND objectionable for as long as AMEN continues to appear in commonly used drug information references. We would reconsider the acceptability of the proprietary name provided the sponsor commits to having AMEN removed from all available reference texts.

If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Marci Ann Lee
7/23/02 08:53:22 AM
PHARMACIST

Carol Holquist
7/23/02 09:12:48 AM
PHARMACIST

Jerry Phillips
7/23/02 01:34:16 PM
DIRECTOR

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 10-24-2000

DUE DATE: 11-30-2001

OPDRA CONSULT #: 00-0298

TO: Lilia Talarico, MD
Director, Division of Gastrointestinal and Coagulation Drug Products
HFD-180

THROUGH: Brian Strongin
Project Manager
HFD-180

PRODUCT NAME:
Emend (aprepitant capsules)
80 mg and 125 mg (proposed)

MANUFACTURER:
Merck Research Laboratories, a Division of Merck & Co., Inc.

IND #

SAFETY EVALUATOR: Marci Lee, Pharm.D.

SUMMARY: In response to a consult from the Division of Gastrointestinal and Coagulation Drug Products, OPDRA conducted a review of the proposed proprietary name, Emend, to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: OPDRA does not recommend the use of the proprietary name, Emend. Labels and labeling were not available for review at this time.

/S/

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 28, 2001
IND NUMBER:
NAME OF DRUG: Emend (aprepitant capsules) 80 mg and 125 mg
IND HOLDER: Merck & Co. Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Gastrointestinal and Coagulation Drug Products for assessment of the proposed proprietary drug name, Emend, regarding potential name confusion with other proprietary and/or generic drug names.

PRODUCT INFORMATION

Emend (aprepitant) is indicated for the prevention of chemotherapy-induced nausea and vomiting. Emend (aprepitant) is used in conjunction with other anti-emetic agents. The recommended dose is 125 mg by mouth with a 12 mg dose of dexamethasone approximately one hour prior to chemotherapy. For two days after the completion of chemotherapy, the recommended dose is 80 mg by mouth in the morning. The regimen following highly emetogenic chemotherapy also includes 8 mg of dexamethasone for two days. A 5HT3 antagonist should also be administered for both moderately and highly emetogenic chemotherapy. Emend will be available as 80 mg and 125 mg oral capsules.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts^{i,ii} as well as several FDA databasesⁱⁱⁱ for existing drug names which sound alike or look alike to *Emend* to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic search system (TESS) was conducted^{iv}. The Saegis^v Pharma-In-Use database was searched for drug names with potential for confusion. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies to simulate the prescription ordering process.

ⁱ MICROMEDEX Healthcare Intranet Series, 2001, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.). Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

ⁱⁱ Facts and Comparisons, 2001, Facts and Comparisons, St. Louis, MO.

ⁱⁱⁱ The Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.

^{iv} WWW location <http://tess.uspto.gov/bin/gate.exe?f=tess&state=ki4gp0.1.1>

^v Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name, *Emend*. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. Two proprietary names were identified in the Expert Panel Discussion that were thought to have potential for confusion with Emend. These products are listed in the table, along with the dosage forms available and usual FDA-approved dosage.

Product Name	Dosage form(s) Generic name	Usual adult dose	
Emend	aprepitant 80 mg and 125 mg capsules	125 mg po 1 hour before chemotherapy 80 mg po daily in the morning for two days after chemotherapy	Typically administered with dexamethasone and 5HT3 antagonist
Amen	medroxyprogesterone 10 mg oral tablet	5 to 10 mg by mouth daily for 5 to 10 days	Sound-alike
Anumed (Anu-med HC)	hydrocortisone acetate 25 mg suppository	25 mg rectally in the morning and at night for 2 weeks	Sound-alike

* Frequently used, not all inclusive

2. DDMAC did not object to the use of the name, Emend.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology

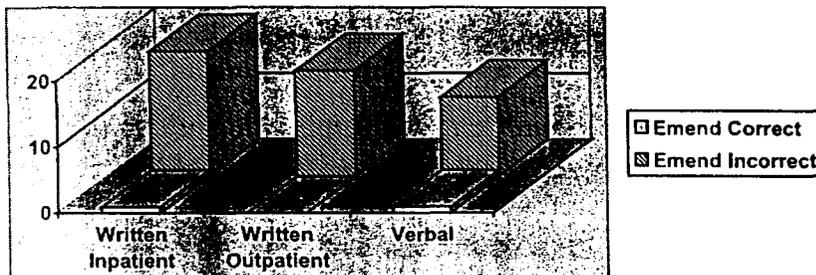
Three separate studies were conducted within FDA to determine the degree of confusion potential of Emend with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug names. These studies employed a total of 88 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescription for Emend. These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal inpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each participant was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Emend	
<i>Outpatient:</i> Emend 80 mg Sig: 1 cap qd x 3d # 6	<i>Outpatient:</i> Emend 80 mg one capsule daily for three days. Dispense 6 capsules
<i>Inpatient:</i> Emend 80 mg qd x 3 days	

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	"Emend" response	Other response
Written: Inpatient	30	20 (67 %)	1 (5 %)	19 (95 %)
Written Outpatient	30	16 (53 %)	0 (0 %)	16 (100 %)
Verbal: Outpatient	28	13 (46 %)	1 (8 %)	12 (92 %)
Total:	88	49 (56 %)	2 (4 %)	47 (96 %)



Among the two written prescription studies, 35 of 36 (97 %) participants interpreted the name incorrectly. Ten respondents misinterpreted the proposed name, Emend, as *Emanel*. Other incorrect responses were *Emand*, *Emarel*, *Emenel*, *Emonel*, *Emard*, *Emond*, *Enind*, *Enovid*, *Enrund*, *Ensyrd*, *Enund*, *Enurd*, *Enurid*, *Envoid*, *Epiard* and *Eviand*.

Among the verbal prescription study participants for Emend, 12 of 13 (92 %) participants interpreted the name incorrectly. However, all 12 incorrect responses were *Amend*, which is phonetically the same as Emend.

Although none of the incorrect responses were of marketed products, three respondents noted similarity between *Emend* and Amen in their response comments.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, Emend, the primary concerns raised by the expert panel were related to sound-alike and look-alike names that already exist in the US marketplace. We conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Emend could be confused with Amen or Anu-med. However, negative findings are not predicative as to what may occur once the drug is

widely prescribed, as these studies have limitations primarily due to a small sample size. Other misinterpretations did not overlap with any other currently approved drug names.

Amen and Emend can sound the same when spoken. Although the prescription studies did not directly confirm the potential for confusion with these names, twelve of the thirteen responses for the verbal prescription study were Amend. Additionally, three study participants included a message with their response stating that Emend is too similar to Amen. Although Amen and Emend are used to treat different conditions in a different practice setting and patient population, both medications are oral solid dosage forms and administered once daily on an intermittent basis. Amen is available as 10 mg oral tablet, unlike Emend. Although the dosing instructions for Emend provide a clue that the patient receiving this medication is also receiving cancer chemotherapy, there are times when prescriptions are incomplete and the risk for confusion is increased.

Anu-med (also Anu-med HC) can sound similar to Emend. Anu-med is available as a 25 mg rectal suppository. This dosage form is commonly used for patients with nausea and vomiting because it bypasses the oral route. However, Anu-med is used for the adjunctive treatment of ulcerative colitis of the rectum and other inflammatory conditions of the anorectum. The risk for confusion is further decreased because suppositories are likely to be stored separately from oral solids and Anu-med is typically administered twice daily, unlike Emend.

Labeling and labels are not available for review at this time.

IV. COMMENTS TO THE SPONSOR

In reviewing the proprietary name, Emend, the primary concerns raised by the expert panel were related to sound-alike and look-alike names that already exist in the US marketplace. We conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Emend could be confused with Amen or Anu-med. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. Other misinterpretations did not overlap with any other currently approved drug names.

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Anu-med (also Anu-med HC) can sound similar to Emend. Anu-med is available as a 25 mg rectal suppository. This dosage form is commonly used for patients with nausea and vomiting because it bypasses the oral route. However, Anu-med is used for the adjunctive treatment of ulcerative colitis of the rectum and other inflammatory conditions of the anorectum. The risk for confusion is further decreased because suppositories are likely to be stored separately from oral solids and Anu-med is typically administered twice daily, unlike Emend.

Labeling and labels are not available for review at this time.

V. RECOMMENDATIONS

OPDRA does not recommend the use of the proprietary name Emend.

Labeling and labels should be submitted for safety evaluation when they become available.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Marci Lee at 301-827-3242.

/S/

Marci Lee, Pharm.D.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

/S/

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

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/s/

Marci Ann Lee
12/12/01 02:57:46 PM
PHARMACIST

Jerry Phillips
12/12/01 03:11:48 PM
DIRECTOR

Martin Himmel
12/14/01 11:02:19 AM
MEDICAL OFFICER

Memo

To: Victor Raczowski, MD
Acting Director, Division of Gastrointestinal and Coagulation Drug Products
HFD-180

From: Marci Lee, PharmD
Safety Evaluator, Office of Drug Safety
HFD-400

Through: Carol Holquist, RPh
Deputy Director, Division of Medication Errors and Technical Support
HFD-400

Jerry Phillips, RPh
Associate Director, Office of Drug Safety
HFD-400

CC: Brian Strongin
Project Manager
HFD-180

Date: March 15, 2002

Re: ODS Consult 00-0298-1; Emend (aprepitant capsules); IND

This memorandum is in response to a February 15, 2002 request from Merck & Co., Inc. to reconsider the acceptability of the proprietary name, Emend.

The Division of Medication Errors and Technical Support in the Office of Drug Safety (formerly the Office of Post-Marketing Drug Risk Assessment) would like to acknowledge that although the AMEN product is no longer being manufactured, the trade name is still commonly found in numerous reference texts and resources. Despite a different indication and different dosing, there is still opportunity for errors to occur based on the strong similarity in the proprietary names. AMEN and EMEND can have almost the same sound depending on how the names are pronounced. Therefore, this potential for name confusion is our primary concern.

Although AMEN and EMEND are used to treat different conditions, there are some similarities, which may increase the likelihood for confusion. Both products are available as an oral solid dosage form and both products can be administered daily for a short course of therapy. AMEN and EMEND will likely be stored in both inpatient and outpatient pharmacies in the oral solid dosage form storage areas.

AMEN still appears in the most recent version of the Micromedex Integrated Index Query web-based drug information resource and the most recent version of the web-based Facts and Comparisons drug information resource. AMEN also appears to be available from at least one online pharmacy. 

As long as the name AMEN can be found in drug information texts, there is potential for confusion with EMEND. A recent example of this medication error scenario occurred with E-Vista (hydroxyzine hydrochloride) and EVISTA (raloxifene hydrochloride). Although E-Vista is no longer marketed, there were errors reported where patients received hydroxyzine products instead of the prescribed EVISTA (raloxifene hydrochloride). One of the contributing factors in the error scenarios was the drug information references that continued to list E-Vista (hydroxyzine hydrochloride).

In some cases, confusion between AMEN and EMEND could result in the dispensing of residual AMEN product that may be in the marketplace despite the fact that it is no longer manufactured. If AMEN was not available in a particular pharmacy, it is possible that a practitioner would use a drug information reference to determine alternative medroxyprogesterone products. In the case of AMEN, there are various brand and generic formulations of medroxyprogesterone. Therefore, it is possible for confusion to occur between AMEN and EMEND, which can result in a patient receiving medroxyprogesterone in error.

Also due to the strong similarity in the pronunciation of AMEN and EMEND, practitioners may confuse the spelling of the name when prescribing or receiving a verbal order.

The Division of Medication Errors and Technical Support will continue to consider the proprietary name EMEND objectionable for as long as AMEN continues to appear in commonly used drug information references. We would reconsider the acceptability of the proprietary name provided the sponsor commits to having AMEN removed from all available reference texts.

If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

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/s/

Marci Ann Lee
3/18/02 07:59:53 AM
PHARMACIST

Carol Holquist
3/18/02 08:19:31 AM
PHARMACIST

Jerry Phillips
3/22/02 01:15:43 PM
DIRECTOR

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

**LABELING (IMMEDIATE CONTAINER AND CARTON) –
DIVISION PROPOSED**

**Not Applicable. The Division accepted the sponsor's proposed labeling
without revision. See CMC Review #1 dated March 13, 2003**

**APPEARS THIS WAY
ON ORIGINAL**

**LABELING (IMMEDIATE CONTAINER AND CARTON) –
REVIEWS**

See CMC Review #1 dated March 13, 2003

**APPEARS THIS WAY
ON ORIGINAL**

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

MEMORANDUM OF MEETING MINUTES

MEETING DATE: January 24, 2003
TIME: 11:00AM
LOCATION: Parklawn Building, Potomac Conference Room
APPLICATION: NDA 21-549; Emend (aprepitant) Capsules
TYPE OF MEETING: Type C – Discussion of Merck's Draft Advisory Committee Background Information for the March 6, 2003 Gastrointestinal Drugs Advisory Committee Meeting

MEETING CHAIR: Hugo Gallo-Torres, M.D., Ph.D.

MEETING RECORDER: Brian Strongin, R.Ph., M.B.A.

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division Name & HFD#</u>
1. Robert Justice, M.D., M.S.	Director	Division of GI and Coagulation Drug Products, HFD-180
2. Joyce Korvick, M.D.	Deputy Director	Division of GI and Coagulation Drug Products, HFD-180
3. Hugo Gallo-Torres, M.D., Ph.D.	Medical Team Leader GI Drugs	Division of GI and Coagulation Drug Products, HFD-180
4. Gary Della'Zanna, D.O.	Medical Officer	Division of GI and Coagulation Drug Products, HFD-180
5. Ryan Barraco	Regulatory Health Project Manager	Division of GI and Coagulation Drug Products, HFD-180
6. Brian Strongin, R.Ph., M.B.A.	Regulatory Health Project Manager	Division of GI and Coagulation Drug Products, HFD-180
7. Tom Permutt, Ph.D.	Team Leader, Biometrics	Division of Biometrics II
8. Wen-Jen Chen, Ph.D.	Mathematical Statistician	Division of Biometrics II
9. Suresh Doddapaneni, Ph.D.	Team Leader, Clinical Pharmacology and Biopharmaceutics	Division of Pharmaceutical Evaluation II
10. Jarugula Venkateswa, Ph.D.	Clinical Pharmacology and Biopharmaceutics Reviewer	Division of Pharmaceutical Evaluation II
11. Myong-Jin Kim, Ph.D.	Clinical Pharmacology and Biopharmaceutics Reviewer	Division of Pharmaceutical Evaluation II

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
1. Dr. Keith Gottesdiener	Clinical Pharmacology	Merck Research Laboratories, Inc.
2. Dr. Kevin Petty	Clinical Pharmacology	Merck Research Laboratories, Inc.
3. Dr. Kevin Horgan	Clinical Research	Merck Research Laboratories, Inc.
4. Dr. Francesca Lawson	Clinical Research	Merck Research Laboratories, Inc.
5. Dr. Scott Reines	Clinical Research	Merck Research Laboratories, Inc.
6. Dr. David C. Evans	Drug Metabolism	Merck Research Laboratories, Inc.
7. Dr. Anup Mauumdar	Drug Metabolism	Merck Research Laboratories, Inc.
8. Dr. Richard Hargreaves	Preclinical Pharmacology	Merck Research Laboratories, Inc.
9. Dr. Dennis Erb	Regulatory Affairs	Merck Research Laboratories, Inc.
10. Dr. Charlene G. Sanders	Regulatory Affairs	Merck Research Laboratories, Inc.
11. Dr. Brian White-Guay	Regulatory Affairs	Merck Research Laboratories, Inc.
12. Mr. Tom Hassall	Regulatory Agency Relations	Merck Research Laboratories, Inc.
13. Ms. Denise Booker	Regulatory Coordination	Merck Research Laboratories, Inc.
14. Dr. Alexandra Carides	Statistics	Merck Research Laboratories, Inc.
15. Dr. Al Getson	Statistics	Merck Research Laboratories, Inc.
16. Dr. Balasamy Thiyagarajan	Statistics	Merck Research Laboratories, Inc.

BACKGROUND:

NDA 21-549 for Emend Capsules was submitted September 27, 2002 for use 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. This application will be the subject of discussion at the March 6, 2003 meeting of the Gastrointestinal Drugs Advisory Committee (GIDAC). In a submission dated January 6, 2003 Merck Research Laboratories, Inc. (MRL) requested a meeting to obtain Agency feedback concerning their GIDAC briefing document. In a submission dated January 15, 2003, MRL submitted their draft Advisory Committee Background Information.

MEETING OBJECTIVES:

To obtain the Agency's comments and recommendations regarding MRL's draft Advisory Committee Background Information dated January 15, 2003

DISCUSSION POINTS:

A. After introductions, discussion turned to MRL's questions. The questions are italicized below followed by the Division's responses in bold. (NOTE: the Division did not receive MRL's questions until January 23 and did not have time to prepare responses in advance.)

1. *As of the date of this correspondence, the Advisory Committee (AC) meeting to discuss NDA 21-549: EMEND has been scheduled for Thursday, March 6, 2003. It is our understanding that EMEND will be reviewed by the Gastrointestinal Advisory Committee.*

a. *As this drug will be used in the setting of chemotherapy agents, does the Division plan to invite consultants to the Advisory Committee (voting or non-voting) with a background in oncology?*

Yes.

b. *Are there plans to include an industry representative on the Advisory Committee?*

Yes.

c. *When will the final list of Advisory Committee members and consultants be sent to us?*

The final list of GIDAC members and consultants will be sent when the conflict of interest screening is finished and the ACS know who may participate in the meeting.

2. *The complete response endpoint was the primary endpoint for the Phase IIb and III studies. Complete response was also used as the primary endpoint for two out of four Phase IIa studies. The two remaining studies used a no emesis endpoint. For consistency and to facilitate the comparison between studies, complete response has been highlighted in the background package and in our presentation.*

a. *Does the Division concur with this plan for presenting efficacy data with an emphasis on the complete response endpoint throughout both the AC briefing document and our main presentation?*

We have no objection to this plan.

3. *Aprepitant has a unique efficacy profile, which includes distinctive efficacy in the prevention of both acute and delayed symptoms, compared to the 5-HT₃ receptor antagonists. Thus, the primary endpoint for the Phase III program evaluates complete response over a 5-day interval (overall). We have also included analyses in the AC briefing document for the acute and delayed phases separately in support of our indication. We are also planning to include these analyses in our main presentation.*

a. *Does the Division concur with this approach to presentation of the efficacy data?*

While we generally agree with this approach, we will request the opinion of the GIDAC on this issue.

- b. *What additional information, if any, do you believe would be helpful to the advisory committee regarding the efficacy profile of aprepitant?*

We suggest including a discussion of the nausea component with an analysis of nausea in patients that did not receive rescue therapy.

4. *The development program incorporated cisplatin as the benchmark for highly emetogenic chemotherapy. This benchmark has been used in the development program for other antiemetic agents. We believe that data obtained for the program can be generalized to all highly emetogenic chemotherapy.*

a. *Does the Agency concur with this generalization?*

b. *What additional data would be helpful in supporting the generalization of cisplatin to all highly emetogenic chemotherapy?*

These questions will be posed to the GIDAC.

5. *As previously discussed with FDA, we have utilized the safety data from the Safety Update Report for the ACM briefing document and presentation. It will be important that we are discussing issues from the same database.*

a. *Does the Agency also plan on utilizing the data from the Safety Update Report in its AC briefing document and presentation?*

Yes, we also plan to use these data.

6. *The information contained in the AC briefing document is a synopsis of the relevant information pertaining to the proposed indication and usage.*

a. *Does the Division have any comments or concerns regarding our briefing document overall and with respect to the discussion of drug interactions and the approach to safety analysis with regards to chemotherapy regimens?*

b. *Is there information that the Division would consider pertinent to the AC discussions, which is either not included or should be expanded in the briefing document?*

See the comments and recommendations that follow regarding the draft Advisory Committee Background Information.

7. *What does the Agency consider to be the key questions for the Advisory Committee?*

a. *What will be the Division's position in their briefing document to the Advisory Committee meeting and what will be the timing of the release of the Agency's background material to the ACS?*

The Division's briefing document will be released to the public 14 business days prior to the GIDAC meeting.

b. *When will the list of questions be shared with us?*

The list of questions will be provided within a few days of the GIDAC meeting.

8. *Our planned presentation will focus on the clinical efficacy, safety and drug interaction profile of aprepitant. We will also briefly discuss the pathophysiology of emesis as well as the non-clinical pharmacology, pharmacokinetics, and safety evaluation of aprepitant.*

a. *What topics does the Division plan to address in your presentation?*

Our presentation will focus on the areas in which we need GIDAC input, such as drug-drug interactions with chemotherapeutic agents and various clinical issues including a general discussion of the safety profile and the adequacy of the repeat-cycle efficacy data.

B. Additional Comments Regarding MRL's Draft Advisory Committee Background Information

The following comments and recommendations were provided regarding the draft Advisory Committee Background Information for NDA 21-549 dated January 15, 2003:

1. Regarding Table 37, page 120, we recommend splitting this table into individual tables for each chemotherapeutic agent. Include a list of specific Prespecified Adverse Events with incidences for each event. Also, list Serious Clinical Adverse Experiences separately with incidences for each. A suggested mock-up follows:

Drug/Chemical	Investigational Regimen	Standard Therapy
	n/N (%)	n/N (%)
Anemia		
Febrile Neutropenia		
Neutropenia		
Thrombocytopenia		
Serious Clinical Adverse Experiences (list)		

(NOTE: MRL promised to expand Table 37 as recommended.)

**APPEARS THIS WAY
ON ORIGINAL**

- In addition, if the doses of concomitant chemotherapy are known, include tables of adverse events by dose of chemotherapeutic agent. Include Prespecified Adverse Events and Serious Adverse Experiences with incidences greater than 5%. A suggested mock-up follows.

	Aprepitant Regimen	Standard Therapy
≥ 100mg/m²	n/N (%)	n/N (%)
Anemia		
Febrile Neutropenia		
Neutropenia		
Thrombocytopenia		
Serious Clinical Adverse Experiences (list)		
≥75mg/m² (<100mg/m²)	n/N (%)	n/N (%)
Anemia		
Febrile Neutropenia		
Neutropenia		
Thrombocytopenia		
Serious Clinical Adverse Experiences (list)		
<75mg/m²	n/N (%)	n/N (%)
Anemia		
Febrile Neutropenia		
Neutropenia		
Thrombocytopenia		
Serious Clinical Adverse Experiences (list)		

(NOTE: Although they may not be able to incorporate this change into the Background Document, MRL promised to try to provide this type of table for the Division's review and comment.)

- Address why granisetron was the 5-HT₃ Inhibitor used in earlier Emend clinical trials and ondansetron was used in later clinical trials.
- Include a discussion of the preclinical and clinical data supporting the statement that Emend has no QT_c effects.
- Change the phrase, "maximal protection" in the last sentence on page 96 to a protocol defined endpoint.
- The following sentence appears on page 97: "The efficacy of the aprepitant regimen is unaffected by age, race, or gender." Clarify this statement to reflect that a gender effect was seen when Studies 052 and 054 were analyzed separately.

ACTION ITEMS:

The Agency and MRL will attempt to schedule a meeting in late February, 2003 to preview GIDAC presentations.

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/s/

Brian Strongin
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information



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Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: March 17, 2003

To: Steven Aurecchia, M.D.	From: Brian Strongin, R.Ph., M.B.A.
Company: Merck & Co., Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (484) 344-2516	Fax number: (301) 443-9285
Phone number: (484) 344-4662	Phone number: (301) 827-7310
Subject: .CMC Information Request Regarding NDA 21-549	

Total no. of pages including cover: 2

Comments:

Please respond to the attached information request regarding NDA 21-549 ASAP. If you would like to have a teleconference regarding these requests, we are available Wednesday, March 19. Thanks

Document to be mailed: YES NO

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Please respond to the following comments and information requests ASAP.

I. Drug Substance

- A. Please provide the supplier protocol and Certificate of Analysis for _____ used in the drug substance manufacture.
- B. The tests and specifications for _____ should be clarified. The use of _____ is discouraged since it can contain many potential impurities. See USP <1231>.
- C. The last five batches made had _____ detected. Please suggest a tighter specification that would be in keeping with your manufacturing capabilities.
- D. Impurities should be listed as specified and unspecified per ICHQ3A and 6A.

II. Drug Product

- A. Justify the use of _____ in the capsule dissolution test. This test should be performed under conditions close to physiological for it to be relevant to the drug pharmacokinetics. This is especially important because of the small particle size of the aprepitant drug substance.
- B. The drug product is formulated at one site and packaged at two other locations. How is this bulk material packaged, labeled, and controlled during transport? How long will this bulk material be kept before encapsulation?
- C. Your release and stability specifications no longer contain a test for particle size. You eliminated this specification due to historical data. However, considering that particle size is so critical to the performance of the drug product, it is advisable to perform the test at least for selected time points.
- D. You describe a dye leak test for the blister packs. Please present the actual results of this test.

III. Labeling

- A. On the "Trifold package of 3 – complimentary" package, the "Complimentary" text should be printed in a more prominent place (not just on the edge, where it is likely to be missed). This change should take place during the next printing of the labels.
- B. Outer Carton Labels

Clarify if a printed outer carton labeling has been submitted for all drug-packaging presentations. If not, one should be submitted prior to marketing of the product.

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/s/

Brian Strongin
3/17/03 11:27:49 AM
CSO

Liang Zhou
3/17/03 11:34:24 AM
CHEMIST

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 Center for Drug Evaluation and Research
 Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: March 17, 2003**To:** Steven Aurcchia, M.D.**From:** Brian Strongin, R.Ph., M.B.A.**Company:** Merck & Co., Inc.Division of Division of Gastrointestinal &
Coagulation Drug Products**Fax number:** (484) 344-2516**Fax number:** (301) 443-9285**Phone number:** (484) 344-4662**Phone number:** (301) 827-7310**Subject:** .CMC Information Request Regarding NDA 21-549**Total no. of pages including cover:** 2**Comments:**

Please respond to the attached information request regarding NDA 21-549 ASAP. If you would like to have a telconference regarding these requests, we are available Wednesday, March 19. Thanks

Document to be mailed: YES NO

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Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: March 4, 2003

To: Steven A. Aurecchia, M.D.	From: Brian Strongin, R.Ph., M.B.A.
Company: Merck & Co., Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (484) 344-2516	Fax number: (301) 443-9285
Phone number: (484) 344-4662	Phone number: (301) 827-7310
Subject: Clinical Information Request and Comment Regarding NDA 21-549	

Total no. of pages including cover: 2

Comments:

Please respond to the attached information request regarding NDA 21-549 ASAP. Thanks

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In order to complete our clinical review of NDA 21-549 please respond to the following information request ASAP. Thanks.

Please clarify whether the clinical studies were conducted in accordance with the Declaration of Helsinki or in accordance with Good Clinical Practice.

In addition, we have the following comment:

We have reviewed the comments regarding the FDA briefing document in your submission dated February 20, 2003 and will address your concerns during the Agency's oral presentation at the March 6 meeting.

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Brian Strongin
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FACSIMILE TRANSMITTAL SHEET

DATE: March 4, 2003

To: Steven A. Aurecchia, M.D.	From: Brian Strongin, R.Ph., M.B.A.
Company: Merck & Co., Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (484) 344-2516	Fax number: (301) 443-9285
Phone number: (484) 344-4662	Phone number: (301) 827-7310
Subject: Clinical Information Request and Comment Regarding NDA 21-549	

Total no. of pages including cover: 2

Comments:

Please respond to the attached information request regarding NDA 21-549 ASAP. Thanks

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Center for Drug Evaluation and Research
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FACSIMILE TRANSMITTAL SHEET

DATE: February 6, 2003

To: Charlene G. Sanders, M.D.	From: Brian Strongin, R.Ph., M.B.A.
Company: Merck & Co., Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (484) 344-2516	Fax number: (301) 443-9285
Phone number: (484) 344-2850	Phone number: (301) 827-7310
Subject: .Statistical Information Request Regarding NDA 21-549	

Total no. of pages including cover: 2

Comments:

Please respond to the attached information request regarding NDA 21-549 ASAP. Thanks

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In order to complete our statistical review of NDA 21-549; please provide the following information for both Studies P052 and P054.

- I. For both Studies P052 and P054 provide the following data (of Cycle 1) for both modified-intent-to-treat and per-protocol populations in electronic format consistent with the guidance, *Regulatory Submissions in Electronic Format; General Considerations*. We suggest that the following variables be included:

Study number;
 Investigator or Center code;
 Region;
 Patient number/name;
 Treatment name;
 Population type (modified-intent-to-treat or per-protocol populations);
 Use of concomitant chemotherapy (yes or no);
 Gender;
 Age;
 Race;
 Cisplatin Dose;
 Cisplatin Dose Stratum (High: if received dose ≥ 70 mg/m², Low: otherwise);
 Complete Response in overall phase (success or failure);
 Complete Response in acute phase (success or failure);
 Complete Response in delayed phase (success or failure);
 Complete Protection in overall phase (success or failure);
 Complete Protection in acute phase (success or failure);
 Complete Protection in delayed phase (success or failure);
 Total Control in overall phase (success or failure);
 Total Control in acute phase (success or failure);
 Total Control in delayed phase (success or failure);

- II. Perform the following two analyses for each efficacy variable listed in I.:
- i. For each Cisplatin Dose Stratum, generate a table to demonstrate the number of patients with success by treatment group and phase, separately using MITT and Per-protocol patient populations.
 - ii. For each Cisplatin Dose Stratum, perform the statistical efficacy analyses by phase. described in the protocol (at page 1138 of Volume 26).

To the data set described by I, add additional variables as needed (but not included in the above data set) for the above analyses. Also, modify the programs to be able to input data from the data set described by I.

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/s/

Brian Strongin
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FACSIMILE TRANSMITTAL SHEET

DATE: February 6, 2003

To: Charlene G. Sanders, M.D.	From: Brian Strongin, R.Ph., M.B.A.
Company: Merck & Co., Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (484) 344-2516	Fax number: (301) 443-9285
Phone number: (484) 344-2850	Phone number: (301) 827-7310
Subject: Statistical Information Request Regarding NDA 21-549	

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

Please respond to the attached information request regarding NDA 21-549 ASAP. Thanks

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Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: January 30, 2003

To: Charlene G. Sanders, M.D.	From: Brian Strongin, R.Ph., M.B.A.
Company: Merck & Co., Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (484) 344-2516	Fax number: (301) 443-9285
Phone number: (484) 344-2850	Phone number: (301) 827-7310
Subject: Clinical Information Request Regarding NDA 21-549	

Total no. of pages including cover: 2

Comments:

Please respond to the attached information request regarding NDA 21-549 ASAP. Thanks

Document to be mailed: YES NO

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Please explain why 9 patients were reported with a serious AE of neutropenia in the Aprepitant Regimen compared to 2 in Standard Therapy in table E-120 (Clinstat folder, Page E-390) when only 6 patients were reported with Laboratory Adverse Experiences of neutropenia in the Aprepitant Regimen compared to 7 in Standard Therapy. Table E-122 (Clinstat folder, page E-398).

Table E-120

Number (%) of Patients With Specific Serious Clinical Adverse Experiences (Incidence >0% in One or More Treatment Groups) by Body System in Patients Receiving Concomitant Therapy Metabolized by CYP3A4—
CINV Phase III Studies (Cycle 1)

	Aprepitant Regimen (N=275)		Standard Therapy (N=265)	
	n	(%)	n	(%)
Patients with one or more serious adverse experiences	42	(15.3)	36	(13.6)
Patients with no serious adverse experience	233	(84.7)	229	(86.4)
Body as a Whole/Site Unspecified	19	(6.9)	9	(3.4)
Abdominal pain	2	(0.7)	0	(0.0)
Abnormal consciousness	0	(0.0)	1	(0.4)
Chills	0	(0.0)	1	(0.4)
Collapse	0	(0.0)	1	(0.4)
Dehydration	7	(2.5)	1	(0.4)
Dizziness	1	(0.4)	1	(0.4)
Fever	3	(1.1)	1	(0.4)
Fistula	1	(0.4)	0	(0.0)
Infection	0	(0.0)	1	(0.4)
Malignant neoplasm	2	(0.7)	0	(0.0)
Metastatic neoplasm of known primary	1	(0.4)	0	(0.0)
Sepsis	2	(0.7)	0	(0.0)
Septic shock	3	(1.1)	0	(0.0)
Syncope	1	(0.4)	2	(0.8)
Unknown cause of death	0	(0.0)	1	(0.4)
Upper respiratory infection	1	(0.4)	0	(0.0)

Hemic and Lymphatic System	16	(5.8)	8	(3.0)
Anemia	1	(0.4)	0	(0.0)
Febrile neutropenia	6	(2.2)	4	(1.5)
Leukopenia	1	(0.4)	2	(0.8)

	Aprepitant Regimen (N=275)		Standard Therapy (N=265)	
	n	(%)	n	(%)
Neutropenia	9	(3.3)	2	(0.8)
Pancytopenia	0	(0.0)	1	(0.4)
Thrombocytopenia	1	(0.4)	0	(0.0)

Table E-122

Number (%) of Patients With Specific Laboratory Adverse Experiences (Incidence $\geq 2\%$ in One or More Treatment Groups) by Laboratory Test Category in Patients Receiving Concomitant Therapy Metabolized by CYP3A4—CINV Phase III Studies (Cycle 1)

	Aprepitant Regimen (N=275)		Standard Therapy (N=265)	
	n/m	(%)	n/m	(%)
Patients with one or more laboratory adverse experiences	62/272	(22.8)	52/260	(20.0)
Patients with no laboratory adverse experience	210/272	(77.2)	208/260	(80.0)
Blood Chemistry	34/270	(12.6)	28/259	(10.8)
Alanine aminotransferase increased	13/269	(4.8)	9/256	(3.5)
Blood urea nitrogen increased	9/270	(3.3)	12/258	(4.7)
Hypophosphatemia	1/1	(100.0)	0/†	
Serum creatinine increased	10/270	(3.7)	14/258	(5.4)
Total serum protein decreased	0/2	(0.0)	1/2	(50.0)
Troponin I increased	0/†		1/1	(100.0)
Hematology	13/272	(4.8)	16/258	(6.2)
Granulocytes decreased	1/1	(100.0)	0/1	(0.0)
Neutrophils decreased	6/271	(2.2)	7/256	(2.7)
Prothrombin time decreased	0/2	(0.0)	1/2	(50.0)
Urinalysis	32/266	(12.0)	22/254	(8.7)
Proteinuria	30/266	(11.3)	20/253	(7.9)

† Indicates there was no associated laboratory test or there were no patients for whom the laboratory test was recorded postbaseline.

Although a patient may have had 2 or more laboratory adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.

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.

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.

CINV = Chemotherapy-induced nausea and vomiting.

P.O. = By mouth.

IV = Intravenous.

N = Number of randomized Cycle 1 patients who received concomitant therapy metabolized by CYP3A4.

n/m = Number of randomized Cycle 1 patients who received concomitant therapy metabolized by CYP3A4 with laboratory adverse experiences/number of randomized Cycle 1 patients who received concomitant therapy metabolized by CYP3A4 for whom the laboratory test was recorded postbaseline.

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Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: January 30, 2003

To: Charlene G. Sanders, M.D.	From: Brian Strongin, R.Ph., M.B.A.
Company: Merck & Co., Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (484) 344-2516	Fax number: (301) 443-9285
Phone number: (484) 344-2850	Phone number: (301) 827-7310

Subject: Clinical Information Request Regarding NDA 21-549

Total no. of pages including cover: 2

Comments:

Please respond to the attached information request regarding NDA 21-549 ASAP. Thanks

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FACSIMILE TRANSMITTAL SHEET

DATE: January 23, 2003

To: Charlene G. Sanders, M.D.	From: Brian Strongin, R.Ph., M.B.A.
Company: Merck & Co., Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (484) 344-2516	Fax number: (301) 443-9285
Phone number: (484) 344-2850	Phone number: (301) 827-7310
Subject: Comments and Recommendations Regarding the draft Advisory Committee Background Information for NDA 21-549 dated January 15, 2003	

Total no. of pages including cover: 2

Comments:

Please note the following comments and recommendations.

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We have the following comments and recommendations regarding the draft Advisory Committee Background Information for NDA 21-549 dated January 15, 2003:

1. Regarding Table 37, page 120, we recommend splitting this table into individual tables for each chemotherapeutic agent. Include a list of specific Prespecified Adverse Events with incidences for each event. Also, list Serious Clinical Adverse Experiences separately with incidences for each. A suggested mock-up follows:

Docetaxel	Docetaxel Regimen	Standard Therapy
	n/N (%)	n/N (%)
Anemia		
Febrile Neutropenia		
Neutropenia		
Thrombocytopenia		
Serious Clinical Adverse Experiences (list)		

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2. In addition, if the doses of concomitant chemotherapy are known, include tables of adverse events by dose of chemotherapeutic agent. Include Prespecified Adverse Events and Serious Adverse Experiences with incidences greater than 5%. A suggested mock-up follows.

Docetaxel		
≥ 100mg/m ²	n/N (%)	n/N (%)
Anemia		
Febrile Neutropenia		
Neutropenia		
Thrombocytopenia		
Serious Clinical Adverse Experiences (list)		
≥75mg/m ² (<100mg/m ²)	n/N (%)	n/N (%)
Anemia		
Febrile Neutropenia		
Neutropenia		
Thrombocytopenia		
Serious Clinical Adverse Experiences (list)		
<75mg/m ²	n/N (%)	n/N (%)
Anemia		
Febrile Neutropenia		
Neutropenia		
Thrombocytopenia		
Serious Clinical Adverse Experiences (list)		

3. Address why granisetron was the 5-HT₃ Inhibitor used in earlier Emend clinical trials and ondansetron was used in later clinical trials.
4. Include a discussion of the preclinical and clinical data supporting the statement that Emend has no QT_c effects.
5. Change the phrase, “maximal protection” in the last sentence on page 96 to a protocol defined endpoint.

6. The following sentence appears on page 97: "The efficacy of the aprepitant regimen is unaffected by age, race, or gender." Clarify this statement to reflect that a gender effect was seen when Studies 052 and 054 were analyzed separately.

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