CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-549

Chemistry Review(s)

Review of Chemistry, Manufacturing, and Controls

NDA 21–549

Emend® (Aprepitant) Capsules 80/125 mg

Merck Research Laboratories

by

Chemistry Reviewer: David A. Place, PhD

Division of New Drug Chemistry II – HFD-820

for

Clinical Review Division: HFD–180

Division of Gastrointestinal and Coagulation Drug Products

Table of Contents

Chemistry Review Data Sheet

1. **NDA** 21–549

2. **REVIEW #** 1

3. **REVIEW DATE:** 26–FEB–2003

4. **REVIEWER:** David A. Place, PhD, HFD-820

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Document Date
N A	

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Original	27–SEP–2002

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Merck & Co., Inc.
Address:	PO Box 4, BLA–20, West Point, PA 19486–0004
Representative:	Charlene Sanders, MD, Director, Regulatory Affairs
Telephone:	(484) 344–2850

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name: Emend®
b) Non-Proprietary Name: Aprepitant
c) Code Name # (ONDC only): MK-0869 and L-754030
d) Chem. Type Submission Priority (ONDC only):
- Chem. Type: 1
- Submission Priority: P

9. **LEGAL BASIS FOR SUBMISSION:** Not Applicable to NDAs

10. **PHARMACOLOLGICAL CATEGORY/INDICATION:** Antiemetic: For the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high–dose cisplatinum.

11. **DOSAGE FORM:** Gelatin capsules, 80 and 125 mg.

12. **STRENGTH/POTENCY:** 80 and 125 mg

13. **ROUTE OF ADMINISTRATION:** Oral

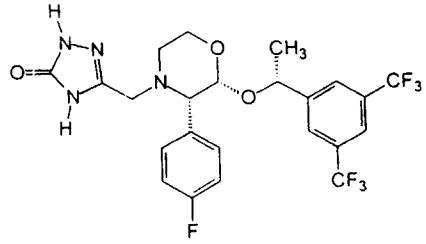
14. **Rx/OTC DISPENSED:** __X__ Rx ____ OTC

15. **SPOTS** (Special Products On–Line Tracking System)

_____SPOTS product – Form Completed X Not a SPOTS product

16. **CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

Chemical Name(s): 5-[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4 morpholinyl]methyl]-1,2-dihydro-3*H*-1,2,4-triazol-3-one



CAS Registry No. 170729–80–3
Molecular Formula: $C_{23}H_{21}F_7N_4O_3$
Molecular Weight: 534.43

17. RELATED/SUPPORTING DOCUMENTS:

A. **DMFs:**

DMF =	TYPE	HOLDER	ITEM REFERENCED	CODE [note1]a	STATUS [note2]b	DATE REVIEW COMPLETED	COMMENTS
	I			1	Adequate	20-Feb-2003	*2nd review needed*
	I			1	Adequate	25-Feb–2003	*2nd review needed*
	II			3	Adequate	30-Dec-2002	
	III			3	Adequate	27-Aug-2002	
	III			3	Adequate	Feb-2001	DMF strike force
	III			1	Adequate	14-Feb-2003	*2nd review needed*
	III			1	Adequate	14-Feb-2003	*2nd review needed*
	III			3	Adequate	13-Jun-2002	
	III			3	Adequate	Feb-2001	Reviewed in
	III			1	Adequate	14-Feb-2003	*2nd review needed*
	III			1	Adequate	14-Feb-2003	*2nd review needed*
	III			3	Adequate	6-Jan-2003	
	III			1	Adequate	22-Oct-2002	
	III			1	Adequate	14-Feb-2003	*2nd review needed*

a Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

b Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	[redacted]	Aprepitant IND

US Patent (Expires): 5,719,147 (6/29/2012)
5,538,982 (7/23/2013)
6,048,859 (6/29/2012)
6,096,742 (7/1/2018)
6,235,735 (6/29/2012)

Exclusivity: Five years requested.

18. STATUS:

ONDC:

CONSULTS/ CMC Related Reviews	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable (all sites)		
Pharm/Tox			
Biopharm	Full review–see section on dissolution		
LNC	USAN Approved	N/A	
Methods Validation	To be requested after resubmission		
OPDRA	Acceptable		
EA	Categorical Exclusion Satisfactory	3/11/03	David Place
Microbiology		N/A	

OGD:

CONSULTS/ CMC Related Reviews	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	N/A		
Methods Validation	N/A		
Labeling	N/A		
Bioequivalence	N/A		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW (OGD Only): ***Not Applicable***

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

Chemistry Review for NDA 21–549

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The chemistry recommendation is "Approval". Certain concerns and questions should be discussed and resolved with the sponsor before NDA approval is official. See Deficiency Letter to Applicant.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The sponsor should commit to those items identified in the Deficiency Letter to Applicant.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Aprepitant is a highly selective inhibitor of the neurokinin-1 (NK-1) receptor. Oral capsules, 80 and 125 mg. containing the new drug, aprepitant, have been developed for the prevention or reduction in severity of CINV, chemotherapyinduced nausea and vomiting. It inhibits both acute and delayed phases of cisplatin–induced emesis.

Aprepitant is a crystalline solid that is practically insoluble in water. The drug substance particles in the capsule formulation is in the nanometer range. This formulation resulted in enhanced bioavailability in clinical studies. By making the particles small, it greatly expands the surface area of the drug substance exposed in vivo, enhancing uptake and minimizing the food effect.

Both the 80 and 125 mg capsules will be packaged in bottles of 30 capsules, blister packs with one or five capsules, and a combination vlister pack with one 125 mg and two 80 mg capsules. The drug product will have an expiry period of two years, with a future extension possible based on stability data.

B. Description of How the Drug Product is Intended to be Used

The drug will be given to patients before and during chemotherapy treatment with cisplatin or other highly emetogenic cancer chemotherapy. It is to be coadministered with a corticosteroid (e.g., dexamethasone) and a 5-HT_3 antagonist (e.g., Ordansetron). The first dose of 125 mg is to be given one hour prior to chemotherapy and once daily doses of 80 mg on the mornings of the following two days. It should be taken with care if the patient is concurrently being treated by other with drugs that are metabolized by cytochrome P450 isozyme 3A4, such as cisapride, pimozide, and the no–longer–marketed antihistamines, terfenadine and astemizole. Other possible drug interactions are listed in the labeling and patient instructions.

C. Basis for Approvability or Not-Approval Recommendation

The submission contains minor deficiencies and errors in several key sections. Therefore, the application is approvable.

III. Administrative

A. Reviewer's Signature

Chemist David A. Place, PhD /S/ Date: 12-MAR-2003

B. Endorsement Block Same date as draft review

Chemistry Team Leader Liang Zhou, PhD _____ Date:
Project Manager Brian Strongin _____ Date:

cc: Orig. NDA 21-549
HFD-160/Division File
HFD-820/ChemDivDir/EDuffy
HFD-180/MO/
HFD-180/Pharm
HFD-180/DivDir

Redacted 67

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confidential

commercial

information

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Place
3/14/03 03:10:56 PM
CHEMIST

Liang Zhou
3/14/03 06:00:07 PM
CHEMIST

EA Review

See CMC Review #1 dated March 13, 2003

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: 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

The Office of Compliance has issued an Acceptable overall compliance recommendation for establishments involved in the manufacture of Emend (aprepitant) capsules. Per the letter dated December 27, 2002, Merck withdrew the [redacted] from consideration as a packaging site. Today, the EER for this site was also withdrawn from EES. All of the remaining sites were Acceptable.

APPEARS THIS WAY
ON ORIGINAL

METHODS VALIDATION

See CMC Review #1 dated March 13, 2003

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Place
3/25/03 12:09:52 PM
CHEMIST

Liang Zhou
3/25/03 01:35:50 PM
CHEMIST