CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-668/S-003

Chemistry Review(s)

DIVISION OF CARDIO-RENAL DRUGS
Review of Chemistry, Manufacturing and Controls

SEP - 8 1998

NDA # 20-668 S-003 **Review #2** Complete : September 4, 1998

Submission Type	Document Date	CDER Date	Content / Topics Covered
Supplement Amendment	Aug 28, 1998	Aug 31, 1998	Resubmission in response to FDA's Non-approval Letter dated June 19, 1998 (CGMP non-compliance)

Name and Address of Applicant

Astra Merck
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

Daniel J Cushing, Ph.D.
Phone (610) 695-1370
FAX (610) 695-1828

J. Molt, Reg. Pgm. Mgr.
(610) 695-1524

Drug Product Name

Proprietary:	Lexxel Tablets
Nonproprietary:	Enalapril Maleate and Felodipine ER Combination
Code Name:	MK-0421 and MK-0218 ER Combination
Chemical type:	Enalapril is an ACE inhibitor, Felodipine is a calcium channel blocker
Therapeutic Class:	4S

The supplemental application provides for the manufacture of an alternative combination tablet containing 5 mg enalapril maleate and 2.5 mg felodipine.

Pharmacological Category / Indication: Combination of an ACE inhibitor and calcium channel blocker in an extended release tablet for the treatment of hypertension.

Dosage Form: Extended release tablet for oral administration Dispensed: Rx only

Strengths: 5 mg enalapril maleate and 5 mg felodipine (Original, approved 12/27/96)
5 mg enalapril maleate and 2.5 mg felodipine (Supplement S-003)

Chemical name, molecular and structural formula, molecular weight:

I USAN name - Enalapril Maleate

Chemical name: (S)-1-[N-[1-(Ethoxycarbonyl)-3-phenylpropyl]-L-proline,(Z)-2-butenedioate (1:1) salt

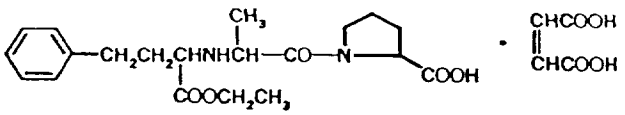
Molecular formula: $C_{24}H_{32}N_2O_9$ Molecular Weight: 492.52

II USAN Name - Felodipine

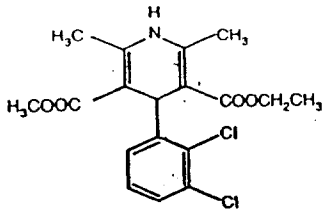
Chemical name: 3,5-pyridinedicarboxylic acid, 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-, ethyl methyl ester, (±)

Molecular formula: $C_{18}H_{19}Cl_2NO_4$ Molecular Weight: 384.26

III Structural Formulae of Drug Substances:



Enalapril Maleate



Felodipine

Supporting Documents:
Astra Merck NDA 20-668 for Lexxel Tablets was approved on December 27, 1996.

Related Documents: Supplement SLR-005 dated Aug 27, 1998 that provides for a revised package insert that contains a new subsection titled "Geriatric Use" that includes available information about the use of Lexxel in elderly patients. (Reference: FDA Final Rule in Federal Register 62, No. 166, August 27, 1997). Perhaps supplements 003 and 005 will be approved at approximately the same time. In any case, the applicant will incorporate all approved labeling changes in the final printed labeling.

Remarks, Comments and Recommendation:
(1) This supplement provides for the manufacture of an alternative combination tablet containing 5 mg enalapril maleate and 2.5 mg felodipine.
(2) **Recommend approval of supplement based on acceptable CGMP Status of all facilities including the Merck-West Point facility. (Please see attached CDER Establishment Evaluation Report dated August 24, 1998)**

/S/ 9/4/98

Florian Zielinski, Review Chemist, New Drug Chemistry I

Distribution:
Original NDA 20-668
HFD 110 Division File
HFD 810 Florian Zielinski
HFD 110 Dave Roeder
Initialed by Kasturi Srinivasachar

/S/ 9-8-98

File name, fwz: NDA 20668 S-003 Rev #2, Lexxel

Redacted 2

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information

for August 24, 1998

Application: NDA 20668/003
Priority: 4S
Org Code: 110
Stamp: 22-DEC-1997 Regulatory Due: 22-JUN-1998
Action Goal:
District Goal: 17-APR-1998
Applicant: ASTRA MERCK
725 CHESTERBROOK BLVD
WAYNE, PA 190875677
Brand Name: LEXXEL (ENLPRIL/FELODPN) TABLETS
Established Name:
Generic Name: ENALAPRIL MALEATE/FELODIPINE ER TABS
Dosage Form: EXT (EXTENDED-RELEASE TABLET
Strength: 5 MG / 2.5 MG COMBO

FDA Contacts:

D. ROEDER	(HFD-110)	301-594-5300	, Project Manager
F. ZIELINSKI	(HFD-110)	301-594-5300	, Review Chemist
J. SHORT	(HFD-110)	301-594-5300	, Team Leader

Overall Recommendation:

ACCEPTABLE on 20-AUG-1998 by S. ADAMS (HFD-320) 301-594-0095

Establishment: 9610565
ASTRA PRODUCTION CHEMICALS
STRANGNASVAGEN 20
SODERTALJE, , SW
DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 30-APR-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities:

Establishment: 1036761
MERCK AND CO INC
4633 MERCK RD
WILSON, NC 27893
DMF No:
AADA No:

Profile: TTR OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 27-JAN-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Responsibilities:

Establishment: 2510592
MERCK AND CO INC
SUMNEYTOWN PIKE
WEST POINT, PA 194860004
DMF No:
AADA No:

Profile: TTR OAI Status: OAI ALERT
Last Milestone: OC RECOMMENDATION
Responsibilities:

Milestone Date **20-AUG-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
FIRM RESPONSE TO DEFIC. ADEQ

Establishment: **2623436**
MERCK MANUFACTURING DIV ME
RD 2, KM 56.7
BARCELONETA, PR 00617

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **27-JAN-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:

Establishment:

DMF No:
AADA No:

Profile: **TTR** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **27-JAN-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:

JUN 19 1998

DIVISION OF CARDIO-RENAL DRUGS
Review of Chemistry, Manufacturing and Controls

NDA # 20-668 S-003 Complete : June 18, 1998

Submission Type	Document Date	CDER Date	Content / Topics Covered
Supplement SCF	Dec 19, 1997	Dec 22, 1997	New Combination of enalapril (5 mg) and felodipine (2.5 mg) ER Tablet
Amendment BC	April 16, 1998	April 17, 1998	month stability data update

Name and Address of Applicant

Astra Merck
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

Daniel J Cushing, Ph.D.
Phone (610) 695-1370
FAX (610) 695-1828

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Drug Product Name

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5 mg enalapril maleate and 2.5 mg felodipine (Supplement S-003)

Chemical name, molecular and structural formula, molecular weight:

I USAN name - Enalapril Maleate

Chemical name: (S)-1-[N-[1-(Ethoxycarbonyl)-3-phenylpropyl]-L-proline,(Z)-2-butenedioate (1:1) salt

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Chemical name: 3,5-pyridinedicarboxylic acid, 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-, ethyl methyl ester, (±)

Molecular formula: $C_{18}H_{19}Cl_2NO_4$ Molecular Weight: 384.26

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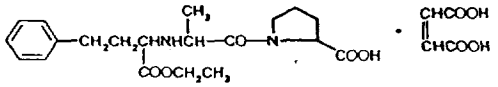
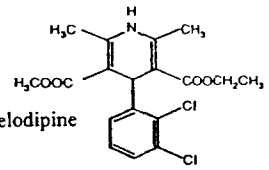


Enalapril Maleate



Felodipine

Supporting Documents:
Astra Merck NDA 20-668 for Lexxel Tablets was approved on December 27, 1996.

Related Documents: CMC Review #5 dated April 9, 1997 of the amendment dated March 26, 1997 is an evaluation of [redacted]-month stability data for the 5-5 combination tablet. Conclusions noted include:

(1) Stability is not dependent on the container/closure tested (blister, pouch, [redacted] bottles filled with either 1000, 100, 30 or 4 tablets)
(2) Extrapolation of data from [redacted] months indicates that all container/closures tested will maintain the tablets within specifications for assay, impurities and dissolution rate until the proposed expiration date [redacted] years).

Consults:

(1) EES: District Office Recommendation for the Merck Facility at West Point (CFN # 2510592) dated April 1, 1998 is "Withhold" because development data are insufficient and lab controls are inadequate. A follow-up E-mail from Ms Debbie Pagano dated June 12, 1998 (attached) states that Merck West Point will receive a **Warning Letter** during the week of June 15, 1998 because they did not provide a satisfactory response to CGMP observations. The recommendation is "**Withhold Approval of All Pending Supplements.**" The probability of a satisfactory response arriving before the PDUFA due date is small.
(2) Biopharmaceutics: Bioequivalence to concurrently administered individual tablets was demonstrated. Acceptable *in vitro* dissolution methods and specifications were provided for felodipine and enalapril in the new dosage strength Lexxel Tablets. No *in vivo-in vitro* correlation was attempted. The Division recommends approval in the Biopharmaceutics Review dated April 7, 1998.

Remarks, Comments and Recommendation:

(1) This supplement provides for the manufacture of an alternative combination tablet containing 5 mg enalapril maleate and 2.5 mg felodipine.
(2) Request for categorical exclusion from the requirement to prepare an Environmental Assessment is granted.
(3) Evaluation of [redacted] month stability data (average assay, degradation, dissolution) confirm that all tablets in all containers meet specifications at all time points
(4) **Recommend non-approval of supplement based on unacceptable CGMP Status of Merck-West Point facility.**

S June 18, 1998

Florian Zielinski, Review Chemist, New Drug Chemistry I

Distribution:
Original NDA 20-668
HFD 110 Division File
HFD 810 Florian Zielinski
HFD 110 Dave Roeder
Initialed by Kasturi Srinivasachar

S 6-18-98

File name, fwz: NDA 20668 S-003 Lexxel

E L E C T R O N I C M A I L M E S S A G E

Date: 12-Jun-1998 10:06am EDT
From: Florian Zielinski
ZIELINSKIF
Dept: HFD-110 WOC2 5085
Tel No: 301-594-5300 FAX 301-594-5494

TO: EES Questions (EESQUESTIONS)
TO: Kasturi Srinivasachar (SRINIVASACHA)
TO: dpagano (dpagano@ora.fda.gov@internet)

Subject: NDA 20-668 S-003

The PDUFA Due date for this supplement is rapidly approaching. Action is due June 22,1998. Is there a chance that CGMP issues pertaining to Merck, West Point will be resolved in time -- or -- should I prepare a Non-Approval Letter to be sent on 6/22/98 ??

I need to get the letter and a completed CMC Review to the Division TIA by COB Thursday June 18 !!!

Thanks for the help. If you need to call me, it's (301) 594-5348 at work or (301) 838-0214 at home in the evening or early morning.

Florian

E L E C T R O N I C M A I L M E S S A G E

Date: 12-Jun-1998 10:25am EDT
From: dpagano
dpagano@ora.fda.gov
Dept:
Tel No:

TO: ZIELINSKIF (ZIELINSKIF@A1)

Subject: Re: NDA 20-668 S-003

Hi Florian:

The Warning Letter is scheduled to go out early next week. The firms response to the GMP observations are not satisfactory and will be addressed in the Warning Letter. I don't see a satisfactory response coming in, in enough time for your PDUFA date.

At the present time, we are recommending withhold for all pending supplements and applications.

Debbie

for June 15, 1998

Application: **NDA 20668/003**
Priority: **4S** Org Code: **110**
Stamp: **22-DEC-1997** Regulatory Due: **22-JUN-1998**
Action Goal: District Goal: **17-APR-1998**
Applicant: **ASTRA MERCK**
725 CHESTERBROOK BLVD
WAYNE, PA 190875677
Brand Name: **LEXXEL (ENLPRIL/FELODPN) TABLETS**
Established Name:
Generic Name: **ENALAPRIL MALEATE/FELODIPINE ER TABS**
Dosage Form: **EXT (EXTENDED-RELEASE TABLET**
Strength: **5 MG / 2.5 MG COMBO**

FDA Contacts:

D. ROEDER	**(HFD-110)**	**301-594-5300**	**, Project Manager**
F. ZIELINSKI	**(HFD-110)**	**301-594-5300**	**, Review Chemist**
J. SHORT	**(HFD-110)**	**301-594-5300**	**, Team Leader**

Overall Recommendation:

Establishment: **9610565**
ASTRA PRODUCTION CHEMICALS
STRANGNASVAGEN 20
SODERTALJE, , SW
DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **30-APR-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities:

Establishment: **1036761**
MERCK AND CO INC
4633 MERCK RD
WILSON, NC 27893
DMF No:
AADA No:

Profile: **TTR** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **27-JAN-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities:

Establishment: **2510592**
MERCK AND CO INC
SUMNEYTOWN PIKE
WEST POINT, PA 194860004
DMF No:
AADA No:

Profile: **TTR** OAI Status: **POTENTIAL OAI**
Last Milestone: **DO RECOMMENDATION**
Milestone Date **01-APR-1998**
Responsibilities:

Decision: **WITHHOLD**
Reason: **INADEQUATE LAB CONTROLS**
INSUFFICIENT DEVELOPMENT DA

Establishment: **2623436**
MERCK MANUFACTURING DIV ME
RD 2, KM 56.7
BARCELONETA, PR 00617

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **27-JAN-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:

Establishment:

DMF No:
AADA No:

Profile: **TTR** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **27-JAN-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:

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