CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

NDA 20-668/S-001

Trade Name: Lexxel

Generic Name(s): (Enalapril maleate/felodipine)

Sponsor: Astra Merck

Agent:

Approval Date: July 2, 1997

Indication: The treatment of hypertension.

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APPLICATION NUMBER:

20-668/S-001

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APPLICATION NUMBER

20-668/S-001

Approval Letter(s)

NDA 20-668/S-001 JUL 2 1997

Astra Merck Inc.
Attention: Daniel J. Cushing, Ph.D.
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

Dear Dr. Cushing:

Please refer to your June 16, 1997 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lexxel (enalapril maleate-felodipine ER) Tablets, 5-5 mg.

The user fee goal date is December 17, 1997.

The supplemental application provides for:

(1) an increase, from 4 to 7, in the number of tablets placed into the primary package, a 30 mL HDPE bottle, and

(2) [redacted]

We have completed review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Sincerely Yours,

7/2/97

Robert J. Wolters, Ph.D.
Chemistry Team Leader, DNDCI
Division of Cardio-Renal Drug Products (HFD-110)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Appears This Way
On Original

cc: NDA 20-668
DISTRICT OFFICE
HFD-92
HFD-110/FZielinski/ Florian Zielinski July 2, 1997
HFD-110/CSO
HFD-232
HFD-810/New Drug Chemistry Division Director
cg/06-25-97

Approval Date: December 27, 1996

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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-668/S-001

Chemistry Review(s)

JUN 20 1997

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

NDA # 20-668 S-001 Review # 6 Complete : June 19, 1997

Submission Type	Document Date	CDER Date	Content / Topics Covered
Supplement, SCM	June 16, 1997	June 17, 1997	Alternative site for secondary packaging of physicians' samples **and** an increase in the count in the bottle from 4 to 7 tablets.

Name and Address of Applicant

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

Daniel J Cushing, PhD
Phone (610) 695-1370
FAX (610) 695-1828

Judith 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

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

Dosage Form: Extended release tablet for oral administration

Strength: 5 mg enalapril maleate and 5 mg felodipine Dispensed: Rx only

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

REVIEW NOTES, NDA 20-668 Supplement S-001 dated June 16, 1997

Dosage Form: No changes reported.

Packaging Changes:
The six different "container/closures" described in Original NDA are:

(a) Al foil blister pack
(b) Al foil strip pouch
(c) 24 oz HDPE bottle containing 1000 tablets
(d) 30 mL HDPE bottle containing 4 tablets
(e) 75 mL HDPE bottle containing 30 tablets
(f) 75 mL HDPE bottle containing 100 tablets

This Supplement states that an additional primary package will be manufactured, specifically, a 30 mL HDPE bottle containing 7 rather than 4 tablets. (This is the only change in the primary package). The container-closure is fully described in the approved NDA. Briefly, the HDPE bottle contains a _____ The _____ It includes _____

Furthermore, this primary package will be incorporated into a secondary package at an alternative site: _____
Secondary packaging operations are not expected to impact on the primary packaging or its contents.

The secondary packaging is called _____ A single unit consists of:

7 tablets in a 30 mL HDPE bottle, labeled with lot number and expiration date
1 personalized physician prescription blank
patient information literature
multi-colored cardboard backer card, 9 x 4 5/16 inches

The backer card is _____ to the _____. The temperature in the primary container does not exceed _____ typically.

12 packages will be placed into a display tray.

All printed patient information will be submitted to DDMAC at time of first use.

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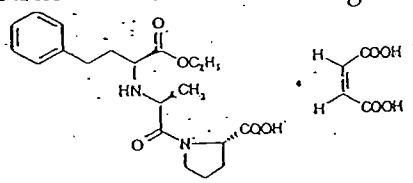
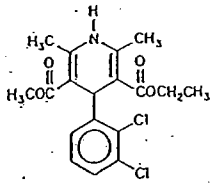
III Structural Formulae of Drug Substances:



Enalapril Maleate



Felodipine

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

Related Documents: CMC Review #5 dated April 9, 1997 of the amendment dated March 26, 1997 is an evaluation of 18 month stability data. Conclusions noted include:

1. Stability is not dependent on the container/closure tested (blister, pouch, HDPE bottles filled with either 1000, 100, 30 or 4 tablets)
2. Extrapolation of data from 18 to 24 months indicates that all container/closures tested will maintain the tablets within specifications for assay, impurities and dissolution rate until the expiration date (2 years).

Consults: None

Remarks, Comments and Recommendation:
This Supplement states that an additional primary package will be manufactured, specifically, a 30 mL HDPE bottle containing 7 tablets. The bottle also contains a [redacted] The [redacted] The [redacted]

Furthermore, this primary package will be incorporated into a secondary package at an alternative site: [redacted]
Secondary packaging operations are not expected to impact on the primary packaging or its contents.

Recommend approval of supplement.

Florian Zielinski 6/19/97

Florian Zielinski, Review Chemist, New Drug Chemistry I

Distribution:
Original NDA 20-668
HFD 110 Division File
HFD 110 Florian Zielinski
HFD 110 Dave Roeder
Initialed by RJ Wolters

6/20/97

File name, fwz : NDA 20668 LEXXEL Review #6