CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-668/S004

Trade Name: Lexxel

Generic Name: Enalpril maleate/felodipine

Sponsor: Astra Pharmaceuticals

Approval Date: July 22, 1998

Indications: The treatment of hypertension.
**Reviews / Information Included in this NDA Review.**

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APPLICATION NUMBER:

20-668/S004

APPROVAL LETTER
NDA 20-668/S-004

Astra Pharmaceuticals, L.P.
Attention: Daniel J. Cushing
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

Dear Dr. Cushing:

Please refer to your May 14, 1998 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Lexxel (enalapril maleate/felodipine) Tablets, 5mg/5mg.

We note that this supplement was submitted as a 'Special Supplement - Changes Being Effectuated' under 21 CFR 314.70(c).

This supplemental new drug application provides for final printed labeling revised under ADVERSE REACTIONS to include gynecomastia in the list of adverse reactions associated with the use of felodipine. Your submission stated July 1, 1998 as the implementation date for the change.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final printed labeling included in your May 14, 1998 submission. Accordingly, the supplemental application is approved effective on the date of this letter.

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

If you have any questions, please contact:

Mr. David Roeder
Regulatory Health Project Manager
(301) 594-5313

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
cc:
Archival NDA 20-668
HFD-110/Div. Files.
HFD-110/D.Roeder
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-101/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-95/DDMS (with labeling)
HFD-810/DNDC Division Director
DISTRICT OFFICE

Drafted by: dr/July 14, 1998
Initiated by: F Zieliinski/7/15/98
            K Srinivasachar/7/15/98
            W Link/7/16/98
            A DeFelice/7/16/98
            A Karkowsky/7/16/98
            G Buehier for N Morgenstern/7/17/98
final: sb/7/20/98
filename: 20668S004AP14JUL98.DOC

APPROVAL (AP)

R 7-22-98
APPLICATION NUMBER:

20-668/S004

LABELING
LEXSEL® (Enalapril Maleate-Feldopidine ER)

**TABLETS**

**USE IN PREGNANCY**
When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, LEXSEL should be discontinued as soon as possible. See WARNINGS, Fetal/Natal Mortality and Morbidity.

**DESCRIPTION**
LEXSEL® (Enalapril Maleate-Feldopidine ER) is a combination product consisting of an outer layer of enalapril maleate surrounding a core tablet of extended-release feldopidine. Enalapril maleate is the saltate salt of enalapril, the active ester of a long-acting angiotensin-converting enzyme inhibitor, enalaprilat. Enalapril maleate is chemically described as (S)-1-[(2S)-2-[([(2R)-2-(2-Aminoethyl)-1-aziridinyl]carbonyl]-amino]-3-methyl-3-butenyl]-3-methyl-3-butenyl]-3-oxo-4,4-dihydrophthalazin-1(2H)-one. Its empirical formula is C_{32}H_{47}N_{5}O_{10} and its molecular weight is 610.38. It is a white to off-white, crystalline powder with a molecular weight of 442.53. This sprayable powder is water-soluble in ethyl alcohol, and the solid is insoluble in both.

Feldopidine, a calcium channel blocker, is a dibenzhydrylamine derivative that is chemically described as 2-[[[(tert-butyl)carbonyl]amino]-3-benzhydryl]-1-benzhydryl]-3-oxo-4,4-dihydrophthalazin-1(2H)-one. Its empirical formula is C_{32}H_{47}N_{5}O_{10} and its molecular weight is 610.38.

**CLINICAL PHARMACOLOGY**
Mechanism of Action
The two components of LEXSEL have complementary antihypertensive action. Enalapril is a p-pseudo-1-aminocaproic acid analog. It contains a p-pseudo-1-aminocaproic acid analog. It contains a dipeptide group that is essential for the activity of angiotensin-converting enzyme inhibitors. Enalapril is a p-pseudo-1-aminocaproic acid analog. It contains a dipeptide group that is essential for the activity of angiotensin-converting enzyme inhibitors. Enalapril is a p-pseudo-1-aminocaproic acid analog. It contains a dipeptide group that is essential for the activity of angiotensin-converting enzyme inhibitors.

The prostaglandin system is a family of lipid-derived molecules that play a role in the pathophysiology of arterial hypertension. The ACE inhibitors, including enalapril and feldopidine, block the synthesis of angiotensin II by inhibiting the conversion of angiotensin I to angiotensin II. This results in a decrease in the concentration of angiotensin II, which has vasoconstrictor and pressor effects. The ACE inhibitors increase the concentration of bradykinin, a potent vasodilator, and inhibit the degradation of bradykinin, which reduces the vasoconstrictor effect.

**CONTRAINDICATIONS**
Contraindicated in patients with a prior history of angioedema or hypersensitivity reaction to ACE inhibitors.

**WARNINGS**
Fetal/Natal Mortality and Morbidity

**ADVERSE EFFECTS**
Most of the adverse effects of enalapril and feldopidine are common to other agents in their respective classes. Common adverse effects include nausea, vomiting, diarrhea, abdominal pain, and headache.

**INTERACTIONS**
Enalapril and feldopidine may interact with other medications that affect blood pressure or potassium levels. Patients should be monitored for changes in blood pressure and potassium levels.

**DOSAGE AND ADMINISTRATION**
The recommended dosage for LEXSEL is 10 mg of enalapril maleate and 25 mg of feldopidine Once daily, administered as a single tablet. The dosage may be increased to 20 mg of enalapril maleate and 50 mg of feldopidine once daily if needed.

**OVERDOSAGE**
In the event of an overdose, supportive care should be provided. Activated charcoal may be given to reduce absorption. Hemodialysis or peritoneal dialysis may be considered in patients with severe poisoning.

**PRECAUTIONS**
Antihypertensive effects may be increased in patients with decreased renal function. Cautious use is recommended in patients with a history of angioedema or hypersensitivity to ACE inhibitors.

**NURSING CONSIDERATIONS**
Enalapril and feldopidine should be used with caution in pregnant women or in women who are breast-feeding. Teratogenic effects have been reported with enalapril in animal studies, and feldopidine has not been evaluated in pregnant women. Prenatal monitoring of the fetus should be performed to assess fetal outcome.
Appropriate Antihypertensive Therapy: The Race Against Hypertension

Appropriate antihypertensive therapy is essential in the management of hypertensive patients, and many recent advances in antihypertensive therapy have been made to improve blood pressure control in these patients. Several classes of antihypertensive medications have been shown to be effective in reducing blood pressure and improving long-term cardiovascular outcomes. These include diuretics, ACE inhibitors, ARBs, beta-blockers, calcium channel blockers, and direct renin inhibitors.

Diuretics are the first-line agents for the treatment of hypertension and have been shown to be effective in reducing blood pressure across a wide range of patients. ACE inhibitors and ARBs are also effective in reducing blood pressure and improving cardiovascular outcomes, particularly in patients with left ventricular hypertrophy or diabetes.

Beta-blockers and calcium channel blockers are effective in reducing blood pressure and improving cardiovascular outcomes in patients with hypertension, and are particularly useful in patients with hypertension and concomitant cardiovascular disease.

Direct renin inhibitors are a relatively new class of antihypertensive medications that have shown great promise in reducing blood pressure and improving cardiovascular outcomes in patients with hypertension.

It is important to individualize antihypertensive therapy based on patient characteristics, including age, gender, race, body mass index, and presence of comorbidities. The choice of antihypertensive medication should be based on the patient's overall health status, tolerability, and the presence of any contraindications. Regular follow-up and blood pressure monitoring are important to ensure effective blood pressure control and prevent cardiovascular events.
DOXILE® (Doxil® [pegylated liposomal doxorubicin hydrochloride])

DOXILE® is indicated for the treatment of patients with refractory Kaposi's sarcoma and refractory ovarian cancer. It is indicated for the treatment of patients with advanced ovarian cancer who have failed or are intolerant of standard chemotherapy.

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APPLICATION NUMBER:

20-668/S004

CHEMISTRY REVIEW(S)
DIVISION OF CARDIO-RENAL DRUGS
Review of Chemistry, Manufacturing and Controls

NDA # 20-668 S-004
Complete: May 20, 1998

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<td>Supplement SLR</td>
<td>May 14, 1998</td>
<td>May 15, 1998</td>
<td>Revisions of “Adverse Reactions” section of approved Package Insert; CBE effective 7/1/98</td>
</tr>
</tbody>
</table>

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

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 revision of the package insert for Lexxel effective on or about July 1, 1998. Specifically, gynecomastia is added to the list of adverse events. Editorial corrections are also made throughout the Package Insert.

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
Dispensed: Rx only
Strength: 5 mg enalapril maleate and 5 mg felodipine (Original, approved 12/27/96)

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_{26}H_{32}N_{2}O_{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_{11}H_{16}Cl_{2}NO_{4} Molecular Weight: 384.26
III Structural Formulae of Drug Substances:

Enalapril Maleate

Felodipine

Supporting Documents:
(1) Astra Merck NDA 20-668 for Lexcel Tablets was approved on December 27, 1996.
(2) Revision of Package Insert via Supplement S-002 was approved March 3, 1998.

Consults: None

Telephone conversation on May 20, 1998  Judy Molt (Astra Merck) stated that page 2 of the annotated version of the text contains a typographical error due to cutting and pasting. The sentence about “ink” should end with “ammonium hydroxide.” The final printed copy is correct.

Remarks, Comments and Recommendation:
Recommend approval of CBE supplement.

Florian Zielinski, Review Chemist, New Drug Chemistry I

Distribution:
Original NDA 20-668 S-004
HFD 110 Division File
HFD 810 Florian Zielinski
HFD 110 Dave Roeder
Initialed by Kasturi Srinivasachar

File name: NDA 20668 S-004 Lexcel
NDA 20-668/S-004

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

Dear Dr. Cushing:

Please refer to your May 14, 1998 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 November 14, 1998.

The supplemental application provides for revision of the package insert for Lexxel effective on or about July 1, 1998. Specifically, gynecomastia is added to the list of adverse events. Editorial corrections are also made throughout the Package Insert.

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,

Kasturi Srinivasachar, Ph.D.
Chemistry Team Leader, DNDC I
Division of Cardio-Renal Drug Products (HFD-110)
Office of Drug Evaluation I
Center for Drug Evaluation and Research
cc: Original NDA 20-668/S-004  
HFD-110 Division File  
HFD-110 Project Manager, Dave Roeder  
HFD-810 Review Chemist, Florian Zielinski, 5/20/98  
HFD-92 DDM-DIAB  
DISTRICT OFFICE  
HFD-810, DNDC I Division Director, Charles Hoiberg

Drafted by: FWZ/May 20, 1998/NDA 20668 S-004  
Initialed by: Kasturi Srinivasachar  
Final:

Approval Date: December 27, 1996

APPROVED
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-668/S004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
RHPM Review of Final Printed Labeling

Application: NDA 20-668/S-004
- Lexxel (enalapril maleate/felodipine) Tablets

Sponsor: Astra Merck

Supplement Date: May 14, 1998

Type of Supplement: Special Supplement: Changes Being Effected

Review

The sponsor revise the package insert to add gynecomastia to the list of adverse reactions associated with the use of felodipine. We had requested this change for all calcium channel blockers in a letter dated September 24, 1996. In addition to that, the sponsor made a number of minor editorial changes. No other changes were made to the package insert.

Recommendation

I recommend that this supplemental application be approved.

David Roeder
Regulatory Health Project Manager

dr/7-10-98

cc: NDA 20-668
- HFD-110
- HFD-110/DRoeder/SBenton