DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-668/S-008

AstraZeneca LP
Attention: Cindy M. Lancaster, MS, MBA
Director, Regulatory Affairs
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

18 SEP 2001

Dear Ms. Lancaster:

Please refer to your supplemental new drug application dated January 12, 2001, received January 16, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LEXXEL Tablets (enalapril maleate - felodipine ER).

This "Changes Being Effected" supplemental new drug application provides for final printed labeling revised as follows:

PRECAUTIONS, Drug Interactions section – Added the following subsection regarding CYP3A4 inhibitors after the "*Lithium*" subsection for consistency with the PLENDIL labeling:

> *CYP3A4 Inhibitors* – Co-administration of CYP3A4 inhibitors (eg, ketoconazole, itraconalzole, erythromycin, grapefruit juice, cimetidine) with felodipine may lead to several-fold increases in the plasma levels of felodipine, either due to an increase in bioavailability or due to a decrease in metabolism. These increases in concentration may lead to increased effects, (lower blood pressure and increased heart rate). These effects have been observed with co-administration of itraconazole (a potent CYP3A4 inhibitor). Caution should be used when CYP3A4 inhibitors are co-administered with felodipine. A conservative approach to dosing felodipine should be taken. The following non-specific interactions have been reported:
> *Itraconazole* – Co-administration of another extended release formulation of felodipine with itraconazole resulted in approximately 8-fold increase in the AUC, more than 6-fold increase in the C_{max} and 2-fold prolongation in the half-life of felodipine.
> *Erythromycin* – Co-administration of felodipine (PLENDIL) with erythromycin resulted in approximately 2.5-fold increase in the AUC and C_{max}, and about 2-fold prolongation in the half-life of felodipine.
> *Grapefruit juice* – Co-administration of felodipine with grapefruit juice resulted in more than 2-fold increase in the AUC and C_{max}, but no prolongation in the half-life of felodipine.

PRECAUTIONS, Drug Interactions section – The following text was changed from:

> *Cimetidine* – In healthy subjects, pharmacokinetic studies showed an approximately 50% increase in the area under the plasma concentration time curve (AUC) as well as the C_{max} of felodipine when given concomitantly with cimetidine. It is anticipated that a clinically significant interaction may occur in some hypertensive patients.

to

> *Cimetidine* – Co-administration of felodipine with cimetidine (a non-specific CYP-450 inhibitor) resulted in an increase of approximately 50% in the AUC and the C_{max} of felodipine.

PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility section, last paragraph – The paragraph was changed from:

> A fertility study in which male and female rats were administered doses of 3.8, 9.6, or 26.9 mg/kg/day showed….

to

> A fertility study in which male and female rats were administered doses of 3.8, 9.6, or 26.9 mg/kg/day (up to 24 times† the maximum recommended human dose on a mg/m^2 basis) showed….

PRECAUTIONS, Pregnancy section –

Teratogenic Effects subsection – The first sentence was changed from:

> Studies in pregnant rabbits administered doses of felodipine 0.46, 1.2, 2.3, and 4.6 mg/kg/day showed…

to

> Studies in pregnant rabbits administered doses of felodipine 0.46, 1.2, 2.3, and 4.6 mg/kg/day (from 0.8 to 8 times† the maximum recommended human dose on a mg/m^2 basis) showed….

Nonteratogenic Effects subsection – The first sentence was changed from:

> Significant enlargement of the mammary glands, in excess of the normal enlargement for pregnant rabbits, was found with doses greater than or equal to 1.2 mg/kg/day (1.4 times…

to

> Significant enlargement of the mammary glands, in excess of the normal enlargement for pregnant rabbits, was found with doses greater than or equal to 1.2 mg/kg/day (2.1 times…

ADVERSE REACTIONS section – **Felodipine as an Extended-Release Formulation** subsection changed from:

> ***Skin***: Contusion, erythema, urticaria;

to

> ***Skin***: Angioedema, contusion, erythema, urticaria, leukocytoclastic vasculitis;

Changed address and company information from

> Manufactured by:
> Merck & Co., Inc., West Point PA 19486

To

> LEXXEL is a trademark of the AstraZeneca group
> © AstraZeneca 2000
> Manufactured for: Astra Zeneca LP, Wilmington, DE 19850
> By: Merck & Co., Whitehouse Station, NJ 08889, USA

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the submitted final printed labeling. 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 call

John Guzman
Regulatory Health Project Manager
(301) 594-5312.

Sincerely,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research