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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-668/S-003

**Clinical Pharmacology and Biopharmaceutics
Review**

APR - 7 1998

DP

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA ~~20-668~~ (scf-003)
Lexxel (Enalapril maleate/Felodipine ER)
Tablets (5-2.5, 5-5 mg)

SUBMISSION DATES: DECEMBER 19, 1997
APRIL 1, 1998

ASTRA MERCK INC.

REVIEWER: Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: NDA SUPPLEMENT

SYNOPSIS:

Lexxel is a combination tablet consisting of an extended release formulation of felodipine (a calcium channel blocker) and an immediate release formulation of enalapril (an ACE inhibitor). It was approved for the treatment of hypertension in patients for which combination therapy is considered appropriate. The sponsor has submitted a supplement to the NDA to request for the approval of a new strength of the combination tablet (enalapril maleate/felodipine ER, 5-2.5 mg). Two felodipine ER 2.5 mg/enalapril maleate 5 mg combination tablet and the concurrently administered individual tablets are bioequivalent with respect to racemic felodipine, plasma enalaprilat and free and total urinary recovery of enalapril and enalaprilat measured after seven days of daily administration. Acceptable *in vitro* dissolution methods and specifications have been provided for felodipine and enalapril in the new dosage strength Lexxel tablets. No *in vitro in vivo* correlation was attempted. The labeling has been up-dated with the new dosage strength.

RECOMMENDATIONS:

The Division of Pharmaceutical Evaluation I has determined that the sponsor's supplement to NDA 20-668 ^{is acceptable} and recommends the approval of the new strength of Lexxel Tablet.

TSF
Emmanuel O. Fadiran, Ph.D.
Division of Pharmaceutical Evaluation I
4/6/98

FT Initialed by A. Parekh, Ph.D. *TSF* 4/7/98

cc: NDA 20-668, HFD-110, Short (Chemist Team Leader), HFD-860 (Fadiran.), CDR (Attn: Barbara Murphy), HFD-340 (Vish).

BIOEQUIVALENCE STUDY

PROTOCOL STUDY NUMBER: 128

VOLUMES: 11.6 - 11.12

INVESTIGATOR AND LOCATION:



STUDY PERIOD: JANUARY 12 - FEBRUARY 23, 1997.

OBJECTIVES: To assess (i) the bioequivalence of enalapril 5 mg and felodipine ER 2.5 mg administered concurrently and as a combination tablet given once daily for seven days, and (ii) the safety and tolerability of enalapril 5 mg and felodipine ER 2.5 mg administered concurrently and as a combination tablet to healthy volunteers.

TREATMENT/FORMULATIONS:

Treatment A

Two Lexxel[®] (enalapril-felodipine ER) 5-2.5 mg combination Tablet, Lot # AM-108, Formulation # WP-C557.

Treatment B

Two felodipine ER 2.5 mg Tablet, Lot # AM-108, Formulation # H-0788-03-01-04
PLUS

Two enalapril 5 mg Tablet, Lot # AM-108, Formulation # WP-C441.

STUDY DESIGN: Randomized, open-label, multiple-dose, two-period crossover study with 22 healthy male subjects and a washout period of 7 days. Each subject received seven daily doses of Treatments A and B above in a randomized fashion after an overnight fast. Blood samples (9 ml for felodipine; 5 ml for enalaprilat) were collected predose on Day 7 of each treatment at 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 18 and 24 hours post dose. Urine samples for the determination free and total urinary enalaprilat recovery were collected predose on 7 at 0, (pre-dose), 0-2, 2-4, 4-6, 6-8, 8-12, 12-18 and 18-24 hours post dose. Plasma and urine samples were stored at -20°C until analyzed.

ASSAYS:

PLASMA FELODIPINE -

Linearity: Satisfactory. Standard curves from _____ to _____ ng/ml.

Accuracy: Satisfactory. _____ % at _____ ng/ml and _____ % at _____ ng/ml.

Precision: Satisfactory. %CV - _____ % at _____ ng/ml and _____ % at _____

Sensitivity: LOQ - _____ ng/ml.

Specificity: Satisfactory. _____

PLASMA ENALALPRIL AND ENALAPRILAT

Linearity: Satisfactory. Standard curves from _____ ng/ml.

Accuracy: Satisfactory. _____ % at _____ ng/ml and _____ % at _____ ng/ml for enalapril; _____ % at _____ ng/ml and _____ % at _____ ng/ml for enalaprilat.

Precision: Satisfactory. %CV - _____ % at _____ ng/ml and _____ % at _____ ng/ml for enalapril; _____ % at _____ ng/ml and _____ % at _____ ng/ml for enalaprilat.

Specificity: Satisfactory.

Sensitivity: LOQ - _____ ng/ml.

URINE ENALAPRIL AND ENALAPRILAT

Linearity: Satisfactory. Standard curves from _____ ng/ml.

Accuracy: Satisfactory. _____ % at _____ ng/ml and _____ % at _____ ng/ml for enalapril; _____ % at _____ ng/ml and _____ % at _____ ng/ml for enalaprilat.

Precision: Satisfactory. %CV - _____ % at _____ ng/ml and _____ % at _____ ng/ml for enalapril; _____ % at _____ ng/ml and _____ % at _____ ng/ml for enalaprilat.

Specificity: Satisfactory.

Sensitivity: LOQ - _____ ng/ml.

The assays have been validated over the range of concentrations of enalapril and enalaprilat observed in the study.

DATA ANALYSIS: AUC_{0-24} , C_{max} , C_{ss} and T_{max} were calculated.

ANOVA were performed on log-transformed PK parameters and 90% CI from the two one-sided tests were calculated.

TABLE 1
Summary of the Pharmacokinetic Data

Variable	Unit	N	Arithmetic Means (Mean ± S.D.)		Geometric Means		Geometric Mean Ratio	90% Confidence Interval
			Combination Tablet	Co-administered Tablets	Combination Tablet	Co-administered Tablets		
Plasma Enalaprilat								
$AUC_{0-24\text{ hr}}$	ng*hr/mL	22	370.09 ± 67.16	369.15 ± 67.95	364.09	362.71	1.00	(0.94,1.07)
C_{max}	ng/mL	22	44.30 ± 14.36	44.96 ± 12.46	42.11	43.33	0.97	(0.89,1.07)
T_{max}	hours	22	3.42 ± 0.57	3.18 ± 0.66	3.38	3.11	1.09	(1.00,1.18)
Urine Recovery$_{0-24\text{ hr}}$								
Free Enalaprilat	mg	22	2.56 ± 0.49	2.64 ± 0.52	2.51	2.59	0.97	(0.89,1.06)
Total Enalaprilat+Enalapril	mg	22	3.73 ± 0.68	3.87 ± 0.67	3.67	3.82	0.96	(0.88,1.05)
Racemic Felodipine								
$AUC_{0-24\text{ hr}}$	ng*hr/mL	22	19.02 ± 6.87	20.96 ± 8.77	17.85	19.29	0.93	(0.85,1.00)
C_{max}	ng/mL	22	1.20 ± 0.49	1.33 ± 0.57	1.11	1.23	0.90	(0.80,1.02)
T_{max}	hours	22	6.43 ± 4.05	7.14 ± 3.04	5.39	6.51	0.83	(0.65,1.05)

FIGURE 1
Mean (\pm S.D.) of Total Urinary Recovery of Enalapril and Enalaprilat
Over 24-Hour at Day 7 (n=22)

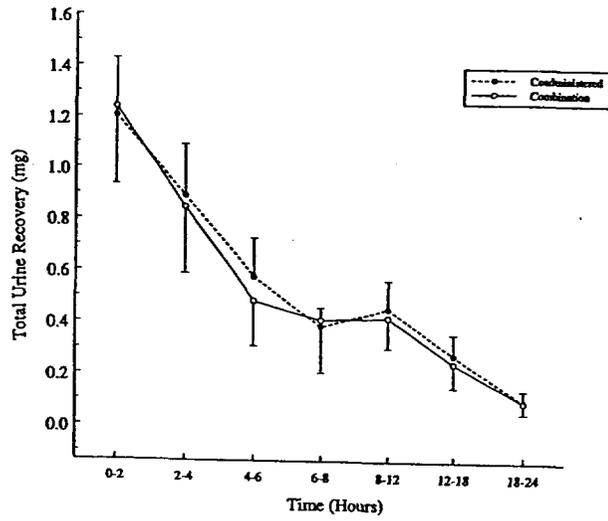


FIGURE 2
Mean (\pm S.D.) of Plasma Enalaprilat Concentration Over 24-Hour at Day 7 (n=22)

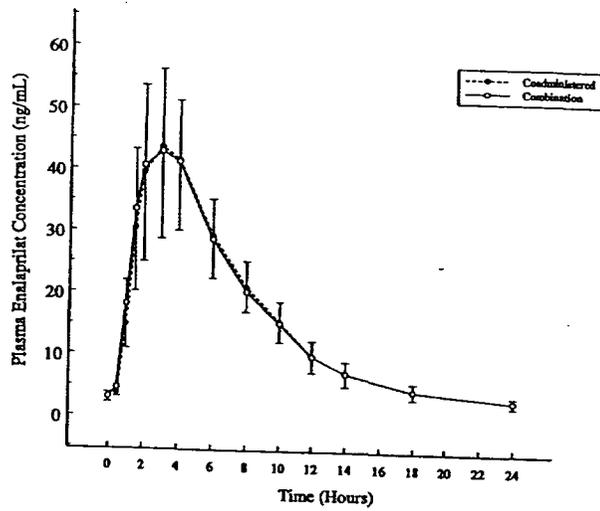
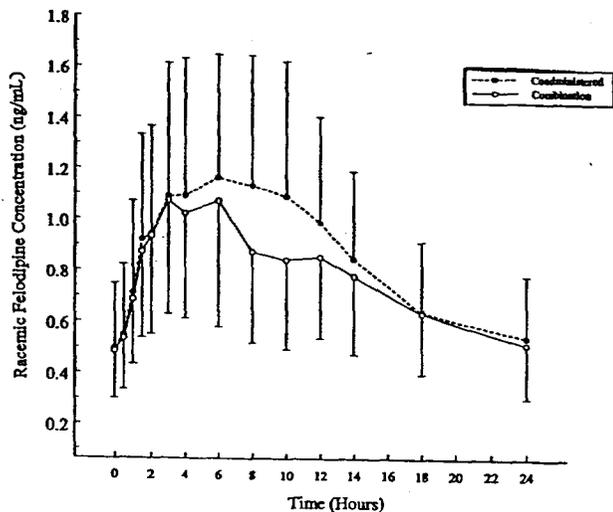


FIGURE 3
Mean (\pm S.D.) of Racemic Felodipine Concentration Over 24-Hour at Day 7 (n=22)



CONCLUSION: The data obtained from the study shows that Lexxel[®] (enalapril-felodipine ER) 5-2.5 mg combination Tablet and the concurrently administered individual tablets are bioequivalent.

**APPEARS THIS WAY
ON ORIGINAL**

TABLE 1: COMPOSITION OF THE FORMULATION

Qualitative and Quantitative Composition

<u>Core Tablets</u>	<u>mg/Tablet</u>
Felodipine	2.50
Propyl Gallate NF	
Polyoxy 40 Hydrogenated Castor Oil NF	
Lactose Anhydrous NF	
Aluminum Silicate	
Sodium Stearyl Fumarate NF	
Enalapril Maleate USP ^s	5.00
Carnauba Wax NF	

DRUG PRODUCT DISSOLUTION TESTING

DISSOLUTION DATA

Enalapril-Felodipine 5-2.5 mg

0218ASRT002B

Temperature ini

Lot no.

001

% Relative Humidity ini

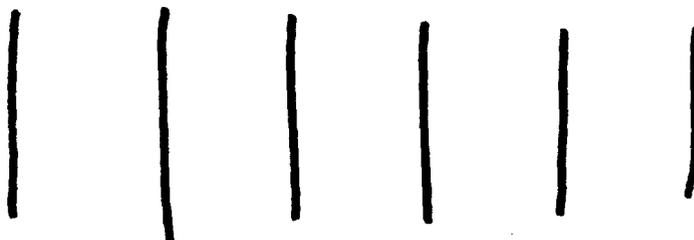
Batch Size

Study Start Date ini

Date of Mfg.

2-Nov-96

Time (weeks)	Enalapril Dissolution (% label)	Felodipine Dissolution (% label)
0		



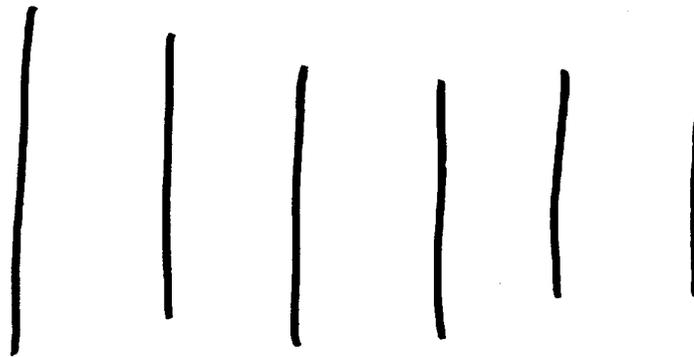
Mean 102 103 103 20 69 99

Enalapril-Felodipine 5-2.5 mg
0218ASRT002B

Temperature ini
% Relative Humidity ini
Study Start Date ini

Lot no. 002
Batch Size
Date of Mfg. 2-Nov-96

Time (weeks)	Enalapril Dissolution (% label)	Felodipine Dissolution (% label)
<u>0</u>		



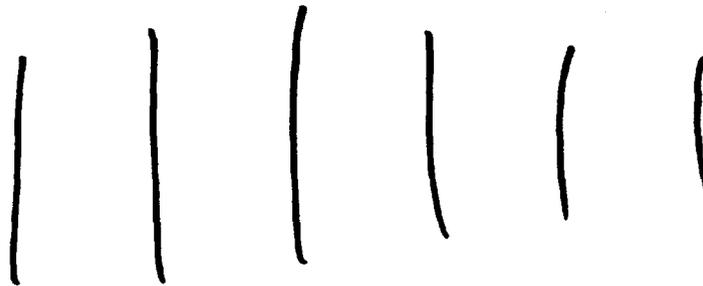
Mean	102	102	102	20	68	99
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Enalapril-Felodipine 5-2.5 mg
0218ASRT002B

Temperature ini
% Relative Humidity ini
Study Start Date ini

Lot no. 003
Batch Size _____
Date of Mfg. 24-Oct-96

Time (weeks)	Enalapril Dissolution (% label)	Felodipine Dissolution (% label)
0		



Mean 103 103 103 19 67 99

PROPOSED DISSOLUTION METHODS AND AND SPECIFICATIONS

Based on the dissolution data above the sponsor has proposed the following dissolution methods and specifications:

Dosage Form, Strengths: Film coated tablet, felodipine ER/enalapril 2.5-5 mg

Dissolution Medium: 500 ml 0.1 M phosphate buffer solution pH6.5 containing 1.0% sodium lauryl sulfate at 37°C

Apparatus: USP Apparatus II at 50 rpm

Sampling Times: 15, 30, 45 and 60 minutes (for enalapril)
2, 6, and 10 hours (for felodipine)

Recommended Dissolution Specification for enalapril: Q= 100% in 30 minutes.

COMMENTS: This dissolution specification is acceptable for the enalapril component of the formulation.

Recommended Dissolution Specifications for felodipine: Mean of 6 tablets at each interval

Time (h)	Cumulative % Released

COMMENTS: These dissolution specifications are acceptable for the felodipine component of the formulation.

**APPEARS THIS WAY
ON ORIGINAL**

19 pages redacted from this section of
the approval package consisted of draft labeling