

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19834/S009

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

DEC 2 1997

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA 19-834 (S-009, SLR)
Plendil® (Felodipine ER)
Tablets (2.5, 5, and 10 mg)

SUBMISSION DATE: MARCH 27, 1997

ASTRA MERCK INC.

REVIEWER: Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: RESPONSE TO REQUEST FOR INFORMATION

SYNOPSIS:

Felodipine is a calcium channel blocker and the extended release formulation is the subject of approved NDA 19-834 (Plendil® (felodipine ER) Tablets). The food effect study submitted to the NDA showed that co-administration of a standardized breakfast did not affect the pharmacokinetics of Plendil® (felodipine ER) Tablets. The sponsor later submitted an additional food effect study in which Plendil® tablet was co-administrated with a high fat or a carbohydrate rich meal (meal classification according to the sponsor's claims). The sponsor was requested to submit assay validation for the study and has responded to this request.

**SUMMARY
ASSAY**

The assay has been validated over the range of felodipine concentrations observed in the study.

RECOMMENDATION:

The Division of Pharmaceutical Evaluation I has reviewed the sponsor's submission and finds the assay validation satisfactory.

ES/
Emmanuel O. Fadiran, Ph.D. *12/2/97*
Division of Pharmaceutical Evaluation I

FT Initialed by El Tahtawy, Ph.D. *ES/*

cc: NDA 19-834, HFD-110, HFD-860 (Fadiran), CDR (Attn: Barbara Murphy), HFD-340 (Vish). *12/2/97*

JUL 29 1997

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW

NDA 19-834 (SLR009, LBL)

DRUG: Plendil® (felodipine controlled release tablet)

SPONSOR: Astra Merck

TYPE OF SUBMISSION: Labeling Recommendations

DATE OF SUBMISSION: 6/20/97

REVIEWER: Ameeta Parekh, Ph.D.

BACKGROUND: Based on bioavailability studies where Plendil® was coadministered with a light or high calorie meals, (see attached), recommendation was made to the sponsor to state this information in the label. This was stated in **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION** sections addressing the impact of meals on bioavailability (as measured by rate and extent change reflected in AUC and Cmax changes) and instructions for administration based on clinical concerns.

The following two proposals are made by the firm:

RECOMMENDATION:

Regarding sponsor's suggestion on item 1: Since bioavailability is defined as the rate and extent of absorption of the active ingredient, and historically, Cmax and AUC have been used as measures for this parameter, stating that 'pharmacokinetic profile is influenced..' instead of 'bioavailability is influenced..' is confusing. The label should remain the same as previously suggested by the FDA.

Regarding sponsor's suggestion on item 2: Due to the large increase with a heavy meal (as compared to fasting) in Cmax for felodipine, a calcium channel blocker, the primary clinical concern during titration would be attenuated if the drug were to be taken consistently with regards to meals (minutes of meeting, Dr. Lipicky, p.2, attachment). Stating 'Plendil can be taken with or without food', as firm proposes, is misleading. The label should remain the same as previously suggested by the FDA.

IS/
Ameeta Parekh, Ph.D. 7/28/97
Division of Pharmaceutical Evaluation I

FT Initialed by Patrick Marroum, Ph.D. : *IS/* 7/29/97
cc: NDA 16-834, HFD-110(Roeder), HFD-860 (Parekh), CDR (attn Barbara Murphy),
HFD-340 (Vish)

	<u>Study #123</u>	<u>Study V-177</u>	<u>Study V-195</u>				
<u>Study Design</u>	open label, single dose, 2-period crossover 7-day washout	open label single dose 2 period crossover 7-day washout	open label single dose 3-period crossover 7-day washout				
<u>Study Dose</u>	enalapril 5mg/ felodipine ER 5mg	felodipine ER 10 mg	felodipine ER 10 mg				
<u>Patient</u>	18 healthy male mean age: 27 mean weight: 162 lbs	12 healthy male mean age: 27 mean weight: 76kg	14 healthy male mean age: 29 mean weight: 78 kg				
<u>Food</u>	<u>breakfast:</u> 2 eggs, 2 strips of bacon, toast with butter, 2-4 oz of hash brown, a glass of whole milk	<u>breakfast:</u> 2 slices of toast with cheese, 1.5 dL milk with corkflakes, 1.5 dL of orange juice	<u>breakfast:</u> <u>high fat:</u> 3dL standard milk (3% fat) 3 slices toast bread 15 g margarine 1 slice of cheese 1 slice of german sausage 20 g liver paste <u>carbohydrate rich:</u> 2dL orange juice 2dL sour milk (3% fat) 3/4 dL cereals 30 g jam 1 slice of wholemeal bread 1 slice toast bread 10 g margarine 1 slice of cheese 1 slice of ham				
<u>Results:</u>	<u>fed</u> ¹	<u>fast</u> ¹	<u>fed</u> ²	<u>fast</u> ²	<u>carbo</u> ²	<u>high fat</u> ²	<u>fast</u> ²
AUC	10.55	10.20	17.846.01	20.52.56	56	54	53
Cmax	1.32	0.64	2.25.74	5.77	3.69.3	3.69.3	5.72.2
Tmax	5.16	5.45	3.49	4.10	4.7	5.7	4.9
<u>Conclusion</u>	90% CI of AUC and Tmax for S and R felodipine were within the limits of similarity. Cmax for S and R felodipine were increased by high fat food.	Food does not significantly influence on AUC, Cmax or Tmax.	There were no significant differences between the three groups with regard to AUC and Tmax. Cmax was significantly increased after food.				

¹ S felodipine was included. Units for AUC, Cmax and Tmax are ng*hr/mL, ng/mL, and hour respectively.

² Units for AUC, Cmax and Tmax are nmol*h/L, nmol/L and hour respectively.

in ○ are ng/ml

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA 19-834 (S-009, SLR)
 Plendil® (Felodipine ER)
 Tablets (2.5, 5, and 10 mg)

SUBMISSION DATES: SEPT. 19, 1996

ASTRA MERCK INC.

REVIEWER: Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: REVISED LABELING

SYNOPSIS:

Felodipine is a calcium channel blocker and the extended release formulation is the subject of approved NDA 19-834 (Plendil® (felodipine ER) Tablets). The food effect study submitted to the NDA showed that co-administration of a standardized breakfast did not affect the pharmacokinetics of Plendil® (felodipine ER) Tablets. The sponsor has now submitted an additional food effect study in which Plendil® tablet was co-administered with a high fat or a carbohydrate rich meal (meal classification according to the sponsor's claims). The report submitted by the sponsor shows that the report protocol was dated 1-10-88 and the study report was dated 5-9-8.

The results obtained from the study showed that administration of felodipine 10 mg extended release tablet (Plendil®) with food (standardized breakfast) results in (i) no effect on the AUC_{0-24} felodipine, (ii) an increase of 63% in the C_{max} felodipine when administered with a high fat meal or a carbohydrate rich meal, (iii) a delay of 0.8 hour in the T_{max} of felodipine when administered with a high fat meal, (iv) a 0.2 hour faster on-set of the T_{max} of felodipine when administered with a carbohydrate rich meal.

SUMMARY

See appendix.

COMMENT TO THE MEDICAL OFFICER

The mean C_{max} of felodipine increased by about 63% when Plendil® tablet was administered with a high fat meal or a carbohydrate rich meal. Using the established E_{max} pharmacokinetic-pharmacodynamic relationship for racemic felodipine (*P. A. Soons et al (1993) Comparative effects of felodipine, nitrendipine and nifedipine in healthy subjects: concentration-effect relationships of racemic drugs and enantiomers, Eur Clin Pharmacol 44:113-120*), an increase of 63% in the C_{max} will result in a heart rate change of less than 1 bpm and therefore should not be a safety concern. However, examination of individual concentrations reveals that one subject (subject no. 9) had about 3-fold increase in C_{max} (24.1 nmol/L with high fat meal and 8.9 nmol/L under fasted conditions) which will result in a change in heart rate of more than 8 bpm using this established E_{max} model or a drop of about 4 mm Hg in the supine diastolic

blood pressure using the Emax model for blood pressure proposed by the sponsor in the original NDA. If this pharmacodynamic effect is considered clinically meaningful (single dose, 10 mg, normal subjects), appropriate directions should be incorporated in the Dosage and Administration Section of the Labeling.

COMMENTS TO BE SENT TO THE FIRM:

- (1) The sponsor should submit the assay validation over the range of concentrations of felodipine observed in the study.
- (2) The following labeling change should be adopted by the sponsor:

RECOMMENDATION:

The Division of Pharmaceutical Evaluation I has reviewed the sponsor's submission and recommends that the above labeling change be adopted by the sponsor. Please, forward the comments above to the medical officer and the firm respectively.

[Signature]
Emmanuel O. Fadiran, Ph.D.
Division of Pharmaceutical Evaluation I

2/5/97

FT Initialed by A. Parekh, Ph.D. ----- *[Signature]*

2/5/97

cc: NDA 19-834, HFD-110, HFD-860 (Fadiran, Malinowski), Review Files (Mira Millison, HFD-850, WOC2 3070), HFD-340 (Vish).

APPENDIX

FOOD EFFECT STUDY

PROTOCOL NUMBER: V-195

INVESTIGATOR AND LOCATION:

STUDY PERIOD: Not specified BUT protocol was dated 3-10-86 and final report dated 5-9-88

OBJECTIVES: To determine the effects of fasting, high fat and carbohydrate rich food intake on absorption, elimination and hemodynamic parameters after single 10 mg dose extended release felodipine.

FORMULATION: Felodipine 10mg extended release tablets, Batch no H 573-4-3

STUDY DESIGN: Randomized, open, three-period crossover study with 14 healthy male subjects and a washout period of 7 days. Subjects received a single Felodipine 10mg extended release tablet on three occasions (once under fasting conditions - Treatment A, and then together with a high fat meal - Treatment B or a carbohydrate rich meal - Treatment C). Subjects fasted for 10 hours prior to dosing. The fed group were dosed immediately following the ingestion of the standardized breakfast and then fasted for four hours while the fasted group remained fasting for four hours post dose. Blood samples (5 ml) were collected predose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, and 24 hours post dose and plasma samples were stored at -20°C until analyzed.

The standardized breakfasts consisted of :

High fat meal

- 300 ml standard meal (3% fat)
- 2 slices toast bread
- 15 g margarine
- 1 slice of cheese
- 1 slice of german sausage of salami type
- 20 g liver paste

Total energy = 646 Kcal

Carbohydrate rich meal

- 200 ml orange juice
- 200 ml sour milk (3% fat)
- 75 ml cereals
- 1 slice roast bread
- 30 g jam
- 1 slice wholemeal bread
- 10 g margarine
- 1 slice of cheese
- 1 slice of ham

Total energy = 641 Kcal

ASSAY:

- Linearity:
- Accuracy:
- Precision:
- Sensitivity:
- Specificity:

The sponsor has been requested to submit the assay validation over the range of concentrations observed in the study.

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

RESULTS: The results obtained from the study are summarized in Table 1 while Fig. 1 shows the mean plasma concentration-time profiles..

Table 1. Effects of Food on the Pharmacokinetic Parameters of Plendil® Tablets

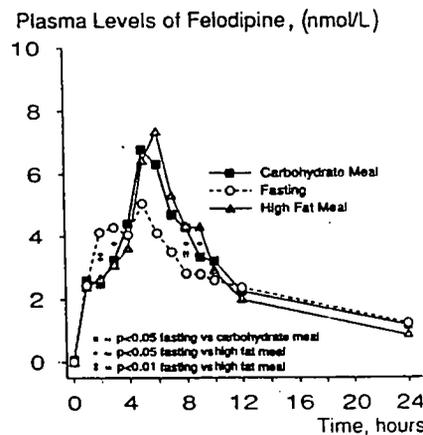
PK PARAMETER	FASTED (Treatment A) ^a	FED [#] (Treatment B) ^a	FED [*] (Treatment C) ^a
AUC_{0-24} (h*nmol/l)	59 (27)	62 (24)	58 (25)
C_{max} (nmol/l)	5.7 (3.2)	9.3 (5.6)	9.3 (5.3)
T_{max} (h)	4.93 (2.46)	4.71 (2.13)	5.71 (1.98)

^aMean (Standard Deviation)

[#]Carbohydrate rich breakfast

^{*}High fat breakfast

Fig. 1: Mean Plasma Concentration-Time Profiles



CONCLUSIONS: Administration of felodipine 10 mg extended release tablet (Plendil®) with food (standardized breakfast) results in (i) no effect on the AUC_{0-24} felodipine, (ii) an increase of 63% in the C_{max} felodipine when administered with a high fat meal or a carbohydrate rich meal, (iii) a delay of 0.8 hour in the T_{max} of felodipine when administered with a high fat meal, (vi) a 0.2 hour faster on-set of the T_{max} of felodipine when administered with a carbohydrate rich meal.