CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 19834/S002

BIOEQUIVALENCE REVIEW(S)

JUN 20 1994

NDA:19-834.
SE2(002).
Felodipine Er 2.5 mg tablets
Plendil 2.5, 5, 10 mg.
Merck Research Laboratories

Submission Date: July 28, 1993.

Reviewer: Patrick J Marroum.

Type of submission: Bioequivalence study to support an efficacy supplement.

Background:

Felodipine is a calcium channel blocker of the dihydropyridine type and is approved for the treatment of hypertension. Currently, 2 strengths of the extended release tablets (Plendil^{R}) the 5 and 10 mg are marketed by Merck. The sponsor is seeking approval of a new lower strength of 2.5 mg ER tablets. A bioequivalency study between 2x2.5 mg tablets and 1x5 mg ER tablet is submitted with this supplement in support of the approval of the 2.5 mg strength.

Results:

The study comparing the 2 strengths 1x5 mg vs 2x2.5 mg ER tablets showed that they are bioequivalent based on the comparison of AUC and CMAX for the parent drug.
The main pharmacokinetic parameters are summarized as follows:

	CMAX	CMAX	CMAX	AUC	AUC	AUC
	2x2.5 mg	5 mg	Ratio 90 % CI	2x2.5 mg	5 mg	Ratio 90 % CI
Felodipine	4.2 nmol/l	4.7 nmol/l	0.8-1.02	45 nmol.h/l	47 nmol.h/l	0.88-1.05

Additionally, the 2.5 mg ER tablets passed the dissolution specifications set for the 5 and 10 mg tablets and thus the same dissolution specification are recommended for this strength.

A copy of the updated package insert as well as the compositional formula for the 2.5 mg ER tablet is included in Appendix II.

Labelling comments:

-The sponsor should list all the ingredients that form the 2.5, 5 and 10 mg ER tablets and not give only a partial listing (the updated label has only a partial listing of the ingredients).

-A statement in the Pharmacokinetics and Metabolism section saying that at steady-state 2x2.5 mg ER tablets were found to be bioequivalent to 1x5 mg tablet should be included.

Recommendation:

This study is acceptable for meeting the Division of Biopharmaceutics requirements and shows that the 2x2.5 mg ER Plendil tablets are bioequivalent to 1x5 mg ER Tablets. Based on the result of this study, the sponsor satisfies the Division of Biopharmaceutics requirements for approval of this supplement. The newly updated package insert was reviewed by the Division of Biopharmaceutics and found acceptable provided the above labelling comments are taken into consideration. Furthermore the same dissolution specifications as the 5 and 10 mg ER tablets are recommended for this new 2.5 mg strength.

/S/

Patrick J Marroum Ph.D 6/17/94

RD/FT initialed by A Parekh /S/ 6/20/94

cc: NDA 19-834, HFD 110, HFD 426 (Marroum), Chron, Fleischer , Drug, FOI (HFD 19), HFD 340 (Vishwanathan).

A comparative study on the relative bioavailability of 2.5 and 5 mg ER tablets of felodipine.

Study: V-014.

Investigators:

Clinical:

Objectives:

To evaluate the relative bioavailability of 2.5 mg tablets ER formulation, in steady state. As a reference, a 5 mg ER tablet was used.

Formulation:

Treatment A: 2x2.5 mg felodipine ER tablets, batch #H788-1-1 containing 2.53 mg of the active drug.

Treatment B: 5 mg felodipine ER tablets, batch# H708-2-3 containing 5.1 mg of the active drug.

Study Design:

The study was accomplished in 2 treatments administered in a 2 way, complete randomized crossover steady-state design in 20 healthy male subjects between the ages of 20 and 32 years. The study included 2 study periods lasting for 8 days each and a washout period of about one week in between. The subjects were assigned at random to take either the 2.5 mg or the 5 mg tablet treatments. The 2 treatments were taken at home for 5 days (days 1 to 5 and 9 to 13) and at the laboratory on day 6,7, 14 and 15. Days 7 and 15 were full sampling days. On days 6, 8, 14 and 16 sampling of blood for the 24 hour analysis of felodipine was done. The tablets were taken at about 8 hours in the morning at 24 hour intervals. Food was provided 4, 8,and 12 hours after the dose of felodipine. Blood samples were collected on 0, 0.5, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14 and 24 hours post dose administration.

Assay:

Data Analysis:

Model independent techniques were used to calculate the felodipine pharmacokinetic parameters. CMAX, CMIN and TMAX were extracted from the raw data. The AUC values were calculated by trapezoidal rule. 90 % confidence intervals were constructed around the log transformed AUC and CMAX.

Results:

Table 1 gives the mean pharmacokinetic parameters for both treatments while Figure 1 shows the mean plasma profile for both treatments. Table 2 gives the 90 % confidence intervals of the log transformed parameter parameters of interest.
From the above results, it can be seen that 2x2.5 mg ER tablets are bioequivalent to 1x5 mg ER tablets.

Dissolution:

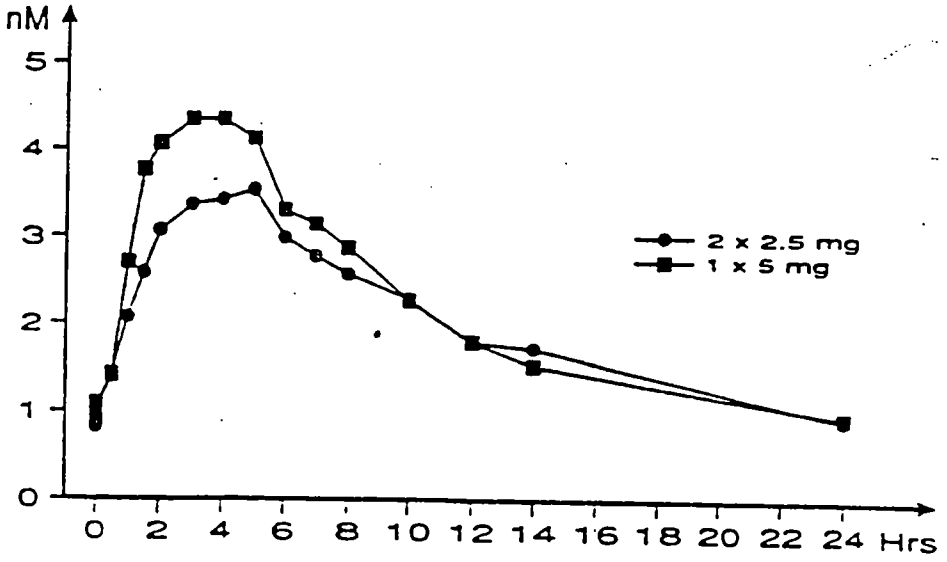
The dissolution method used ml of phosphate buffer pH 6.5 with % sodium lauryl sulphate. The apparatus was a USP type II apparatus at a paddle speed of 50 rpm.
The dissolution specifications set in the original submission were as follows:

Time	% Dissolved
2 hours	
6 hours	
10 hours	

Table 3 gives the individual as well as the mean % dissolved at 2, 6 and 10 hours and shows that the above dissolution specifications are also suitable for the new 2.5 mg ER tablet strength.

FIGURE 1

Mean plasma concentrations of felodipine after 2x2.5 and 1x5 mg felodipine ER tablets, n=20.



Note: The Cmax values in Table 2 appear higher than the mean plasma profile Cmax in Fig. 1. This is because the values in Table 2 are average of individual Cmax values.

Table 8

A summary of the pharmacokinetic variables for 2x2.5 mg and 1x5 mg felodipine ER tablets. Values are presented as mean (SD), n = 20.

Felodipine Formulation	C_{max} (nmol/L)	C_{min} (nmol/L)	AUC (nmol·h/L)	t_{max} (h)
2x2.5 mg	4.3(1.1)	0.9(0.5)	47(15)	4.5(2.1)
1x5 mg	5.2(2.5)	1.0(0.6)	52(24)	3.8(1.9)

Table 9

Geometric means and 90% confidence limits for C_{max}, C_{min} and AUC ratios. Medians and 90 % confidence limit for the median difference in t_{max}. n=20.

	Geometric means		Lower limit	Ratio	Upper limit	Significance level
	2x2.5mg	1x5mg				
C_{max} (nmol/L)	4.2	4.7	0.80	0.90	1.02	ns
C_{min} (nmol/L)	0.8	0.8	0.78	0.96	1.18	ns
AUC (nmol·h/L)	45	47	0.88	0.96	1.05	ns
t_{max} (h)	4.5*	4.0*	-0.5	1.0**	2.0	ns

* medians

** median difference

The analysis showed no significant differences in studied variables C_{max}, C_{min}, AUC and t_{max} between the two treatments.

Table 3 Tablets PLENDIL
Drug Release -
Ruggedness

Sample	Time	% Felodipine Released			
		Analyst #1		Analyst #2	
Tablets PLENDIL 2.5 mg Lot CO218-SRT-001-D006	2 Hours	16	18	18	15
		16	16	17	14
		15	15	16	16
		18	16	20	16
		15	17	17	17
		20	19	17	16
	Average	16.8%		16.6%	
	6 Hours	53	54	60	49
		51	49	52	51
		51	48	49	54
		58	46	61	53
		51	50	53	56
		62	55	54	52
	Average	52.3%		53.7%	
	10 Hours	85	85	92	77
		83	77	82	84
		82	79	78	88
		88	76	92	85
		84	80	87	87
		93	88	90	85
	Average	83.3%		85.6%	