CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19834/S002

MEDICAL REVIEW(S)

NOV 29 1993

1 Title and General Information

1.1 Medical Officer's Review

1.1.1 NDA # 19-834/S-002

1.1.2 M.O. Review #

1.1.3 Submission

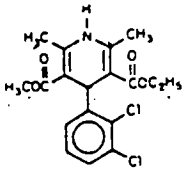
1.1.4 Review completed

1.2 Drug name

1.2.1 Generic name: Felodipine

1.2.2 Proposed trade name: Plendil

1.2.3 Chemical Structure



1.3 Sponsor: Merck Sharp and Dohme

1.4 Pharmacologic Category calcium channel blocker

1.5 Proposed Indication Hypertension

1.6 Dosage Form and Route of Administration 2.5mg extended release tablet

1.7 NDA Drug Classification Type 5 new strength of marketed drug

1.8 Important Related Drugs Felodipine is one of many dihydropyridines of which nifedipine is the prototype.

ABBREVIATIONS(ABBR): ANOVA, analysis of variance; APP, appendix; AUC, area under the curve; BA, Bioavailability; BP Blood pressure; ca, circa; CA, California; Ca, calcium; *CA* cancer; CI,confidence interval; C_{max} maximum concentration; C_{min}, minimum concentration; CR, controlled release; DB, double blind; DFL, degree of fluctuation; (F), fasting; GITS, gastrointestinal therapeutic system; GP, group; GTN, glyceryl trinitrate; IR, immediate release; Kgh,kilogram hour; MR, modified release; (NF), non fasting; OL, open label; OROS, oral osmotic; PBO, placebo; PLL, parallel; RD, randomized; SEC, soft elastic capsule; SR, sustained release; T_{max}, time to maximum concentration.

3 **Material Reviewed** The evidence supporting the bioequivalance of 2.5mg and the approved 5.0mg ER felodipine tablets is presented in a single volume. The question of approvability rests on the data from a single pharmacokinetic study. Other studies included with this submission for ease of reference require no review. Two studies (protocols 003 and 006) from the original NDA are re-examined in support of the evidence of bioequivalence of two 2.5mg and one 5.0mg tablet.

4 **Chemistry/Manufacturing Controls** There has been a minor change (namely in the quantities of exipients) in the formulation of the 2.5mg tablet since the approval of felodipine ER for the treatment of hypertension. The desired extended release of the drug is achieved by finding the optimal mixture of solubilizing agent, binder, lubricant, filler, and felodipine. The 2.5 and 5.0mg tablets vary only by the amount of drug and solubilizing agent. See Chem review for details.

The detailed mechanism of release of the drug from the hydrophilic and hydrophobic components of the gel forming tablet is not completely understood. The coating of the 2.5mg tablet differs ever so slightly from the other tablets. Pharmacokinetic data are necessary in order to determine what effect this subtle difference has on bioavailabity of the drug. Please see bipoharm. review by Dr Patrick Marroum.

Animal Pharmacology/Toxicology NA

6 **Clinical Background**

6.1 Relevant human experience Safety and efficacy of the drug are not in question.

6.2 Important information from related INDs and NDAs Study # 006/16(Hassle protocol 6) demonstrated the superiority of 2.5mg felodipine SR to placebo. A total of 286 patients were enrolled at 16 centers.

Patients were randomized to the four groups to receive PBO, 2.5mg, 5.0mg, or 10mg tablets. Distribution of patients and the demographics and disposition ar tabulated on the following two pages.

Number of Patients Entered by Investigator
(Protocol 6)

Study No.	Investigator	Placebo	Felodipine ER 2.5 mg	Felodipine ER 5.0 mg	Felodipine ER 10.0 mg	Total
006-001	Barker	3	3	4	3	13
006-002	Cohen	5	5	5	5	20
006-003	DiPette	4	3	6	6	19
006-004	Fillingim	5	4	4	5	18
006-005	Goldstein	6	7	7	6	26
006-006	Goodfriend	4	4	6	5	19
006-007	Green	8	7	7	9	31
006-008	Lewin	9	10	10	9	38
006-009	Lucas	4	3	2	2	11
006-010	Miller	3	5	3	4	15
006-011	Sica	4	2	2	3	11
006-012	Synhavsky	4	3	5	4	16
006-013	Velasquez	3	2	1	0	6
006-014	Weber	4	5	4	5	18
006-015	Wochos	0	3	1	1	5
006-016	Wolfson	4	5	5	6	20
Total		70	71	72	73	286

	Placebo	Felodipine ER 2.5 mg	Felodipine ER 5.0 mg	Felodipine ER 10.0 mg	Total
Total Patients	70	71	72	73	286
Sex Male	44(63%)	50(70%)	49(68%)	42(58%)	185(65%)
Female	26(37%)	21(30%)	23(32%)	31(42%)	101(35%)
Age (Years)					
<35	2(3%)	3(4%)	3(4%)	3(4%)	11(4%)
35-44	10(14%)	12(17%)	14(19%)	14(19%)	50(17%)
45-54	21(30%)	18(25%)	18(25%)	13(18%)	70(24%)
55-64	25(36%)	25(35%)	21(29%)	32(44%)	103(36%)
>64	12(17%)	13(18%)	16(22%)	11(15%)	52(18%)
Mean	55.0	54.5	53.6	54.2	54.3
Median	55.5	57.0	55.0	57.0	56.0
Range	32-74	24-75	25-73	28-75	24-75
Racial Origin					
Caucasian	43(61%)	47(66%)	50(69%)	52(71%)	192(67%)
Black	20(29%)	17(24%)	17(24%)	14(19%)	68(24%)
Amer. Indian	0(0%)	1(1%)	0(0%)	0(0%)	1(<1%)
Asian	1(1%)	0(0%)	0(0%)	2(3%)	3(1%)
Hispanic	6(9%)	5(7%)	3(4%)	5(7%)	19(7%)
Mexican	0(0%)	1(1%)	2(3%)	0(0%)	3(1%)
Duration of Disease (Years)					
<1.00	4(6%)	2(3%)	4(6%)	5(7%)	15(5%)
1.00-5.00	21(30%)	18(25%)	24(33%)	23(32%)	86(30%)
5.01-10.00	23(33%)	22(31%)	19(26%)	18(25%)	82(29%)
>10.00	22(31%)	29(41%)	25(35%)	26(36%)	102(36%)
Unknown	0(0%)	0(0%)	0(0%)	1(1%)	1(<1%)
Mean	9.04	11.40	9.96	10.94	10.34
Median	8.00	10.00	8.50	7.50	8.42
Range	0.58-30	0.58-35	0-33	0.17-49	0-49
Stratum (SDBP mmHg)					
Mild I, III (95-105)	50(71%)	54(76%)	56(78%)	54(74%)	214(75%)
Moderate II, IV (106-115)	20(29%)	17(24%)	16(22%)	19(26%)	72(25%)

No significant treatment differences were observed.

Patients Disposition (Protocol 6)

Reason Discontinued	Placebo (n=70)	Felodipine ER 2.5 mg (n=71)	Felodipine ER 5.0 mg (n=72)	Felodipine ER 10.0 mg (n=73)
Completed Study	59(84%)	66(93%)	64(89%)	65(89%)
Discontinued				
Clinical AE	2(3%)	2(3%)	2(3%)	6(8%)
Laboratory AE	0(0%)	0(0%)	0(0%)	0(0%)
Lost to Follow-Up	1(1%)	1(1%)	4(6%)	2(3%)
Protocol Deviation	2(3%)	1(1%)	0(0%)	0(0%)
Therapy Ineffective	6(9%)	1(1%)	1(1%)	0(0%)aa
Patient Withdrew	0(0%)	0(0%)	1(1%)	0(0%)
Total Discontinued	11(16%)	5(7%)	8(11%)	8(11%)

aaSignificantly different from placebo, $p<0.01$.

Data demonstrating the efficacy of the 2.5mg tablet are summarized in the following tables.

A Summary of the Efficacy Results Based on Ranks Using the All-Patients-Treated Approach (Protocol 6)

					BASELINE		VALUE		CHANGE		COMPARISON		
CODE	WEEK	TREATMENT		N	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.	VS. B	VS. C	VS. D
SYSTOLIC BP	WEEK 4	PLACEBO	(A)	68	154.4	14.8	148.5	18.0	-5.9	14.3	0.325	0.035	<0.001
		FEL 2.5	(B)	71	151.4	16.5	144.2	18.9	-7.3	15.7	--	0.345	0.019
		FEL 5.0	(C)	72	147.9	13.4	139.1	12.5	-8.8	12.4			0.225
		FEL 10.0	(D)	70	153.8	15.5	140.0	13.4	-13.7	12.8			
BETWEEN GROUP TEST RESULTS FOR CHANGE						TREATMENT	**	0.0068					
						STUDY	NS	0.1627					
						BASELINE	**	0.0001					
INTERACTION BETWEEN TREATMENT AND STUDY							NS	0.4412					
INTERACTION BETWEEN BASELINE AND STUDY							NS	0.4575					
INTERACTION BETWEEN BASELINE AND TREATMENT							NS	0.4651					
INTERACTION BETWEEN BASELINE, STUDY AND TREATMENT							NS	0.4342					
	WEEK 8	PLACEBO	(A)	68	154.4	14.8	149.5	18.3	-4.9	14.6	0.156	0.008	<0.001
		FEL 2.5	(B)	71	151.4	16.5	144.4	18.7	-7.0	15.0		0.193	<0.001
		FEL 5.0	(C)	72	147.9	13.4	139.2	12.0	-8.8	12.4			0.051
		FEL 10.0	(D)	70	153.8	15.5	138.9	13.4	-14.8	13.1			--
BETWEEN GROUP TEST RESULTS FOR CHANGE						TREATMENT	**	0.0001					
						STUDY	NS	0.4904					
						BASELINE	**	0.0001					
INTERACTION BETWEEN TREATMENT AND STUDY							NS	0.3665					
INTERACTION BETWEEN BASELINE AND STUDY							NS	0.2376					
INTERACTION BETWEEN BASELINE AND TREATMENT							NS	0.7410					
INTERACTION BETWEEN BASELINE, STUDY AND TREATMENT							NS	0.3849					
DIASTOLIC BP	WEEK 4	PLACEBO	(A)	68	101.0	5.4	95.1	9.0	-5.8	6.7	0.116	0.002	<0.001
		FEL 2.5	(B)	71	100.6	5.3	93.0	8.2	-7.6	6.8	--	0.128	0.007
		FEL 5.0	(C)	72	100.6	4.8	91.2	7.1	-9.3	6.5	--	--	0.216
		FEL 10.0	(D)	70	101.2	5.0	90.4	7.1	-10.8	6.8	--	--	--
BETWEEN GROUP TEST RESULTS FOR CHANGE						TREATMENT	**	0.0001					
						STUDY	**	0.0039					
						BASELINE	*	0.0207					
INTERACTION BETWEEN TREATMENT AND STUDY							*	0.0213					
INTERACTION BETWEEN BASELINE AND STUDY							NS	0.1851					
INTERACTION BETWEEN BASELINE AND TREATMENT							NS	0.0978					
INTERACTION BETWEEN BASELINE, STUDY AND TREATMENT							*	0.0186					
	WEEK 8	PLACEBO	(A)	68	101.0	5.4	95.7	9.5	-5.3	7.6	0.016	<0.001	<0.001
		FEL 2.5	(B)	71	100.6	5.3	92.7	7.8	-7.8	6.0		0.123	0.001
		FEL 5.0	(C)	72	100.6	4.8	91.0	7.1	-9.5	5.9			0.006
		FEL 10.0	(D)	70	101.2	5.0	89.9	7.6	-11.3	7.2			
BETWEEN GROUP TEST RESULTS FOR CHANGE						TREATMENT	**	0.0001					
						STUDY	**	0.0001					
						BASELINE	**	0.0033					
INTERACTION BETWEEN TREATMENT AND STUDY							NS	0.2256					
INTERACTION BETWEEN BASELINE AND STUDY							NS	0.5478					
INTERACTION BETWEEN BASELINE AND TREATMENT							NS	0.7111					
INTERACTION BETWEEN BASELINE, STUDY AND TREATMENT							NS	0.2389					

NS -- NOT STATISTICALLY SIGNIFICANT
* -- TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, P<=0.05
** -- TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, P<=0.01
ANALYSIS BASED ON RANKS

A Summary of the Efficacy Results Based on Ranks Using the Per-Protocol Approach (Protocol 6)

PARAMETER	WEEK	TREATMENT		N	BASELINE VALUE MEAN	BASELINE VALUE S.D.	VALUE MEAN	VALUE S.D.	CHANGE MEAN	CHANGE S.D.	COMPARISON VS B	COMPARISON VS C	COMPARISON VS D
SYSTOLIC BP	WEEK 8	PLACEBO	(A)	56	152.0	12.8	146.6	14.9	-5.4	15.0	NS	*	**
		FEL 2.5	(B)	64	151.8	16.7	142.8	17.2	-8.9	13.0	**	NS	*
		FEL 5.0	(C)	62	147.8	12.8	139.5	12.1	-8.3	12.3	**	**	**
		FEL 10.0	(D)	60	153.1	15.2	138.8	12.7	-15.1	12.4	**	**	**
DIASTOLIC BP													
	WEEK 8	PLACEBO	(A)	56	99.1	4.6	94.0	8.0	-5.8	7.4	*	**	**
		FEL 2.5	(B)	64	100.1	5.2	92.2	7.1	-8.4	5.6	**	NS	*
		FEL 5.0	(C)	62	100.1	4.4	90.6	6.6	-9.5	5.6			NS
		FEL 10.0	(D)	60	101.1	5.2	89.8	7.7	-11.5	7.2	**	**	**

NS -- NOT STATISTICALLY SIGNIFICANT
* -- TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, P<0.05
** -- TREATMENT DIFFERENCE STATISTICALLY SIGNIFICANT, P<0.01
ANALYSIS BASED ON RANKS

Trough to Peak Blood Pressure Ratios at Week 8 (Protocol 6)

	TREATMENT	N	BASELINE TROUGH	BASELINE PEAK	VALUE TROUGH	VALUE PEAK	CHANGE TROUGH	CHANGE PEAK	TROUGH:PEAK RATIO UNADJUSTED	TROUGH:PEAK RATIO MINUS PBO[1]
All-Patients-Treated Approach										
Sitting Diastolic Blood Pressure	PLACEBO	65	100.5	98.9	94.8	93.2	-5.7	-5.7	100 %	--
	FEL 2.5	68	100.5	99.0	92.4	88.6	-8.2	-10.4	79 %	53 %
	FEL 5.0	69	100.3	98.6	90.8	86.9	-9.4	-12.0	78 %	59 %
	FEL 10.0	67	101.3	99.6	89.6	83.1	-11.7	-16.5	71 %	56 %
Sitting Systolic Blood Pressure	PLACEBO	65	153.6	151.8	147.9	142.5	-5.7	-3.4	167 %	--
	FEL 2.5	68	151.8	150.5	143.4	137.7	-8.4	-12.8	66 %	29 %
	FEL 5.0	69	147.2	147.1	139.1	134.2	-8.1	-12.9	63 %	25 %
	FEL 10.0	67	154.1	153.0	138.5	131.6	-15.7	-21.4	73 %	56 %
Per-Protocol Approach										
Sitting Diastolic Blood Pressure	PLACEBO	(A) 51	99.8	99.1	94.2	92.3	-5.6	-6.8	82	--
	FEL 2.5	(B) 63	100.6	99.0	92.2	88.4	-8.4	-10.5	80	76
	FEL 5.0	(C) 58	100.3	98.5	90.9	86.5	-9.4	-12.1	78	72
	FEL 10.0	(D) 56	101.3	99.3	89.7	83.0	-11.6	-16.2	72	64
Sitting Systolic Blood Pressure	PLACEBO	(A) 51	151.9	150.4	145.3	145.3	-6.6	-5.1	129	--
	FEL 2.5	(B) 63	151.7	150.7	142.7	137.4	-9.0	-13.3	68	29
	FEL 5.0	(C) 58	148.0	147.5	139.8	134.6	-8.2	-12.9	64	21
	FEL 10.0	(D) 56	154.1	152.3	139.1	131.4	-15.0	-20.9	72	53

[1] The trough to peak ratio is computed after subtracting the placebo effect.

A Summary of the Subgroup Analysis Results at Week 8
Based on Ranks Using the All-Patients-Treated Approach
(Protocol 6)

Subgroup		Treatment	N	Baseline Mean	Baseline S.D.	Value Mean	Value S.D.	Change Mean	Change S.D.	Comparison vs 2.5	Comparison vs 5.0	Comparison vs 10
Blacks	Diastolic BP (mmHg)	Placebo	19	101.3	6.1	96.7	10.4	-4.5	7.8	NS	NS	**
		FEL 2.5	17	100.6	5.9	91.5	6.8	-9.2	4.4	--	NS	NS
		FEL 5.0	17	100.9	5.2	93.3	7.9	-7.6	7.2	--	--	NS
		FEL 10.0	13	100.1	4.5	88.6	7.5	-11.5	7.2	--	--	--
	Systolic BP (mmHg)	Placebo	19	151.8	12.0	148.5	14.8	-3.3	10.1	NS	*	**
		FEL 2.5	17	146.8	19.9	140.1	16.7	-6.8	9.7	--	NS	**
		FEL 5.0	17	146.1	12.7	138.1	13.4	-8.0	12.9	--	--	NS
		FEL 10.0	13	156.8	18.4	138.2	17.5	-18.5	11.0	--	--	--
Non-Blacks	Diastolic BP (mmHg)	Placebo	49	100.8	5.1	95.3	9.1	-5.6	7.6	NS	**	**
		FEL 2.5	54	100.6	5.2	93.1	8.1	-7.4	6.4	--	NS	**
		FEL 5.0	55	100.4	4.7	90.3	6.7	-10.1	5.4	--	--	NS
		FEL 10.0	57	101.4	5.2	90.1	7.7	-11.3	7.3	--	--	--
	Systolic BP (mmHg)	Placebo	49	155.5	15.8	149.9	19.6	-5.6	16.1	NS	*	**
		FEL 2.5	54	152.9	15.2	145.7	19.2	-7.1	16.4	--	NS	**
		FEL 5.0	55	148.5	13.7	139.5	11.6	-9.0	12.3	--	--	NS
		FEL 10.0	57	153.1	14.9	139.1	12.5	-14.0	13.5	--	--	--
Elderly (≥65)	Diastolic BP (mmHg)	Placebo	11	100.4	4.6	94.7	9.0	-5.6	8.0	NS	*	**
		FEL 2.5	13	98.6	4.2	92.6	5.9	-6.0	4.3	*	**	**
		FEL 5.0	16	99.8	4.7	88.1	7.0	11.8	6.2	--	--	NS
		FEL 10.0	11	99.8	6.0	85.2	6.6	-14.6	7.1	--	--	*
	Systolic BP (mmHg)	Placebo	11	162.2	20.9	165.8	26.6	3.6	17.1	NS	*	**
		FEL 2.5	13	159.7	19.3	151.2	15.4	-8.5	11.4	--	NS	*
		FEL 5.0	16	157.8	13.0	142.4	14.5	-15.4	11.1	--	--	NS
		FEL 10.0	11	155.3	21.7	137.2	18.4	-18.1	15.9	--	--	--
Non-elderly (<65)	Diastolic BP (mmHg)	Placebo	57	101.1	5.5	95.9	9.6	-5.2	7.6	*	**	**
		FEL 2.5	58	101.0	5.5	92.8	8.2	-8.3	6.3	--	NS	*
		FEL 5.0	56	100.8	4.8	91.9	6.9	-8.9	5.7	--	--	NS
		FEL 10.0	59	101.4	4.9	90.7	7.5	-10.7	7.2	--	--	--
	Systolic BP (mmHg)	Placebo	57	152.9	13.1	146.4	14.6	-6.6	13.6	NS	NS	**
		FEL 2.5	58	149.6	15.4	142.8	19.1	-6.7	15.8	--	NS	*
		FEL 5.0	56	145.1	12.3	138.2	11.1	-6.9	12.2	--	--	NS
		FEL 10.0	59	153.5	14.3	139.2	12.4	-14.2	12.6	--	--	--
Moderate Hypertension (>105)	Diastolic BP (mmHg)	Placebo	18	108.7	2.6	103.3	10.0	-5.3	8.8	NS	*	**
		FEL 2.5	17	109.0	2.4	101.6	7.6	-7.4	7.2	--	NS	**
		FEL 5.0	16	108.1	2.0	97.3	7.9	-10.8	7.4	--	--	NS
		FEL 10.0	19	108.2	2.4	93.4	8.1	-14.8	8.5	--	--	--
	Systolic BP (mmHg)	Placebo	18	167.6	15.0	162.7	20.8	-4.9	16.5	NS	NS	**
		FEL 2.5	17	165.2	19.4	160.2	22.7	-5.0	20.8	--	NS	**
		FEL 5.0	16	155.9	15.5	145.0	10.4	-10.9	15.0	-	--	NS
		FEL 10.0	19	162.4	15.6	142.9	13.2	-19.5	17.1	-	--	-
Mild Hypertension (≤105)	Diastolic BP (mmHg)	Placebo	50	98.2	2.7	92.9	7.6	-5.3	7.2	*	**	**
		FEL 2.5	54	97.9	2.4	89.9	5.5	-8.0	5.7	--	NS	NS
		FEL 5.0	56	98.4	2.7	89.3	5.7	-9.1	5.5	--	--	NS
		FEL 10.0	51	98.5	2.7	88.5	7.1	-10.0	6.3	--	--	--
	Systolic BP (mmHg)	Placebo	50	149.7	11.7	144.8	14.9	-4.9	14.1	NS	NS	**
		FEL 2.5	54	147.1	13.0	139.4	14.2	-7.7	12.8	--	NS	**
		FEL 5.0	56	145.7	12.0	137.5	12.0	-8.2	11.6	--	--	*
		FEL 10.0	51	150.5	14.3	137.4	13.3	-13.1	11.0	--	--	--

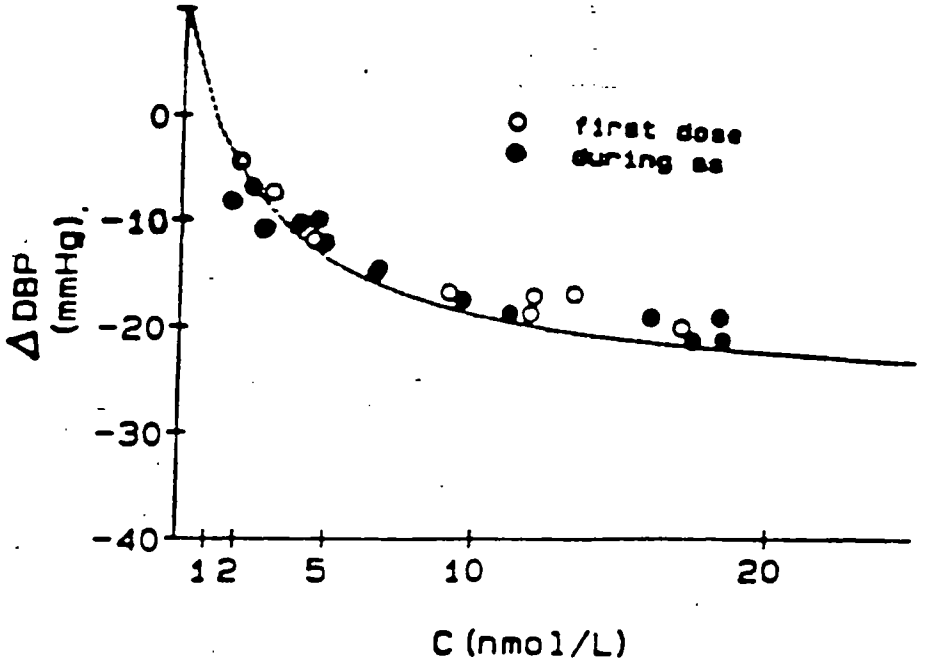
These data demonstrate an effect of the 2.5 mg dose on blood pressure. See Statistical Review NDA 19-834 Vol.1.1A.

6.3 Foreign experience NA

6.4 Human Pharmacology

6.4.1 Pharmacokinetics The pharmacokinetic data of interest are the bioequivalence of the 1.25 and 2.5mg, the 2.5 and 5mg ER tablets. Plasma levels necessary to establish a dose proportionality for the 2.5 mg dose are lacking. It is not therefor feasible to apply the hyperbolic curve fitting model as for the 10mg dose. The curve derived from the relationship

$$E = \frac{Emax(C-Cmin)}{EC50)+(C-Cmin)}$$ is taken from biopharm review by Dr.Teng.



For the 2.5mg dose this curve would be shifted far to the left and the value of E close to zero. Extrapolation from values for the 10 mg dose assuming linearity of dose proportionality is not permissible. This model does little to support the case for the 2.5mg sustained release tablet.

6.4.2 Pharmacodynamics

Study 003/16 was a dose response study of 1.25, 2.5, 5.0 and 10mg bid felodipine in mild to moderate hypertension. All doses beat placebo, and reduction in DBP increased *pari passu* with dose. The response to the 1.25 mg dose was most impressive in elderly with mild hypertension.

In a third study the 2.5 mg dose did not beat placebo and there was no difference between the effects of the 5.0 and 10.0 mg bid doses on trough or peak diastolic blood pressures. Moreover in this study the t/p was <1/2 for the 5.0 and 10.0 mg bid doses.

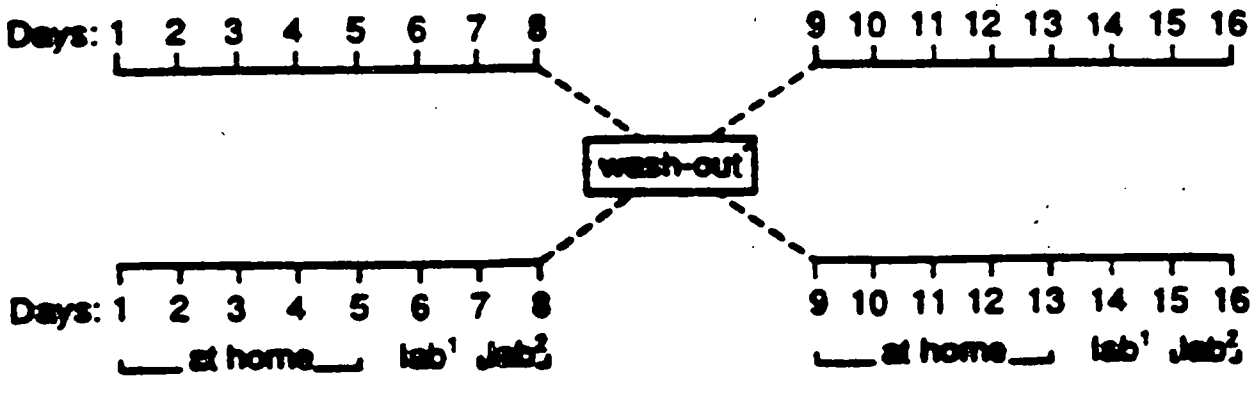
7 Description of Clinical Data Sources NA

8 Clinical Studies

8.1 Trial # V-014 A comparative study on the relative bioavailability of 2.5 and 5.0 mmg felodipine tablets.

8.1.1 Objective: Evaluation of the 2.5mg formulation at steady state with reference to the 5.0mg tablet.

8.1.2 Design The study was a two way crossover randomized comparison of two (2) 2.5mg tablets with one(1) 5mg tablet at steady state. The crossover design is displayed in the diagram.



¹ Days 6 and 14: 24-hour sample 8 a.m. (trough I) + felodipine dose at the lab
² Days 7 and 15: 24-hour sample 8 a.m. (trough II) + felodipine dose at the lab + full sampling day (0-14h): cont. on days 8 and 16 with 24-hour samples (trough III)
* wash-out period of 1 week

8.1.3 Protocol

8.1.3.1 Population, procedures Twenty healthy men aged 20-24 years selected according to the inclusion and exclusion are as given in the original NDA. The subjects were evaluated by medical history, physical examination,laboratory test and ecg, and all were considered to be healthy. Their physical characteristics are summarized in the table.

Individual subject data at the time of the pretreatment period and the treatment sequence during the study, n=20

Subject	Age (years)	Weight (kg)	Height (cm)	Supine SBP (mmHg)	Supine DBP (mmHg)	Supine HR (beats/min)	Standing SBP (mmHg)	Standing DBP (mmHg)	Standing HR (beats/min)	Treatment sequence*
1										1, 2
2										2, 1
3										1, 2
4										2, 1
5										1, 2
6										2, 1
7										2, 1
8										1, 2
9										1, 2
10										2, 1
11										2, 1
12										1, 2
13										1, 2
14										2, 1
15										2, 1
16										1, 2
17										2, 1
18										1, 2
19										1, 2
20										2, 1
Mean:	24	76.1	185.4	123	68	65	125	86	81	
SD:	3	6.2	6.7	9	7	14	10	7	14	
Min:										
Max:										

* 1 = 2x2.5 mg
2 = 1x5 mg

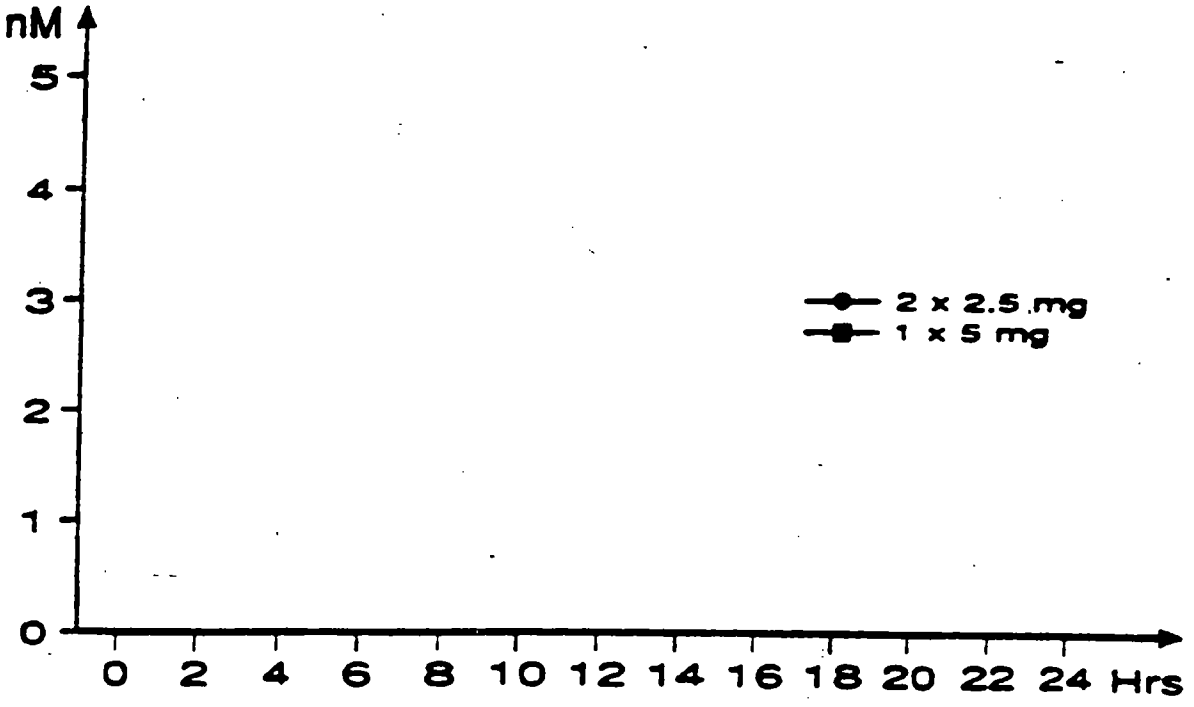
Indwelling catheters were inserted in antecubital vein of each subject for blood sampling on days 6,7,14,and 15 of the study at intervals of 0.5, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, and 24 hours after medication.

8.1.3.2 Endpoints: The pharmacokinetic measurements C_{min},$C_{,max}$, T_{max}, and AUC for the two formulations at steady state.

8.1.3.3 Statistical considerations

Peak and trough Cmax Cm,tmax were determined for each subject were treated (except for tmax) by parametric analysis. Proper attention was given to period and carryover effects.

8.1.4 Results The pharmacokinetics of the two formulations is graphically displayed in the curve.



Except for a slight difference in C_{max} the two cures are superimposable.
The pharmacokinetic data for the two formulations, 2.5x2 and 5mg tablet are summarized tabular form on the next page.

Felodipine Cmax(nmol/L), Cmin(nmol/L), AUC(nmol·h/L), tmax(h) and frel(%), n=20

Subj. no.	2 x 2.5mg				1 x 5 mg				
	Cmax	Cmin	AUC*	tmax	Cmax	Cmin	AUC*	tmax	frel
1	4.2	0.9	55.6	5.0	4.8	0.8	53.2	4.0	105
2	4.2	0.2	30.7	5.0	3.3	0.2	23.5	1.5	131
3	6.6	1.0	63.0	5.0	8.8	1.2	74.3	3.0	85
4	5.3	1.5	62.2	5.0	8.3	2.2	73.6	4.0	85
5	3.7	1.1	53.0	2.0	4.9	1.3	67.8	10.0	78
6	3.0	1.1	46.7	7.0	2.7	1.0	38.1	3.0	123
7	5.3	1.1	51.7	10.0	8.2	0.8	50.5	1.5	102
8	3.8	0.9	48.7	8.0	3.5	1.0	41.9	4.0	116
9	4.0	0.2	33.1	3.0	4.6	0.8	46.5	5.0	71
10	3.4	0.6	36.4	3.0	1.6	0.2	20.9	4.0	174
11	4.7	0.8	44.8	4.0	4.3	1.0	51.3	1.0	87
12	7.1	2.3	91.7	2.0	12.0	2.7	136.2	2.0	67
13	2.6	0.5	33.0	2.0	4.0	0.4	38.3	5.0	86
14	3.9	0.7	34.0	3.0	4.5	1.0	43.7	5.0	78
15	3.8	0.5	31.7	5.0	3.1	0.9	35.6	3.0	89
16	3.0	0.9	32.2	3.0	4.3	0.8	46.5	4.0	69
17	4.2	0.7	43.0	4.0	5.4	0.6	38.7	3.0	111
18	4.0	1.2	50.8	5.0	7.1	1.2	63.6	3.0	80
19	5.0	1.2	53.7	3.0	4.3	0.8	42.1	4.0	128
20	5.1	1.0	49.8	5.0	3.9	1.0	43.3	5.0	115
Mean	4.3	0.9	47.3	4.5	5.2	1.0	51.5	3.8	99
SD	1.1	0.5	14.7	2.1	2.5	0.6	24.5	1.9	27
SEM	0.3	0.1	3.3	0.5	0.6	0.1	5.5	0.4	6
GM									96

*) the AUC-values are corrected for dose

8.1.4.2 Efficacy endpoint outcomes *Vide supra*

8.1.4.3 Safety comparisons NA

9 Overview of Efficacy NA

10 Overview of Safety

Safety was monitored by physical examination, ecg, and standard laboratory tests. There was no evidence of disease on physical examination in any subject and no ecg abnormalities. Transient elevations of S-ASAT and S-ALAT in one subject.

10.1 Significant/Potentially Significant Events

10.1.1 Deaths There were no deaths

10.1.2 Other Significant/Potentially Significant Events

There were no serious or unexpected ADRs. ADRs are summarized in the tables.

No. of individuals with the most common adverse experiences.

Symptom	2x2.5 mg	1x5 mg
Headache	7	13
Flush	2	-
Increased diuresis	-	2
Total No. of individuals with AE's	13	16

10.2 Other Safety Findings NA

11 Labeling Review See original NDA. Items in labeling listed below need no modification save for inclusion of the 2.5mg dose.

11.1 Description
11.2 Clinical Pharmacology
11.3 Indications and Usage
11.4 Contraindications
11.5 Warnings
11.6 Precautions
- **11.6.1 General**
- **11.6.2 Information for patients**
- **11.6.3 Laboratory tests**
- **11.6.4 Drug Interactions**
- **11.6.5 Carcinogenesis, mutagenesis, impairment of fertility**
- **11.6.6 Pregnancy**
- **11.6.7 Labor and delivery**
- **11.6.8 Nursing mothers**
- **11.6.9 Pediatric use**

11.7 Adverse Reactions
11.8 Drug Abuse and Dependence
11.9 Overdosage
11.10 Dosage and Administration
11.11 How Supplied

12 Conclusions

Equivalaence of the 2.5mg and 5mg tablets by in vitro measurements appears well established. The conclusion that the 2.5mg ER tablet is an acceptable formulation rests on two clinical studies and evidence that the 2.5 and 5.0mg tablets ar bioequivalent. The two studies reviewed (003 and 006) showed this dose to be superior to placebo. The case is weakened by another study in which none of the doses appeared effective. In the original submission it was concluded that 5.0mg was the most reasonable starting dose, studies 003 and 006 not withstanding. This conclusion is probably correct where mean values are the criteria of efficacy, but in practical application clinicians would prefer to begin treatment with the lowest possible dose. Since there is some evidence though indirect that 2.5 mg ER tablet is an effective dose, it is desirable to have the dose available. The dose doubtless is ineffective for many patients. However, in some patients e.g. older patients, patients with liver disease, the smaller dose would be particularly desriable.

The pharmacokinetic data reviewed demonstrate beyond peradventure of cavil the bioequivalence of two 2.5mg tablets and one 5.0mg tablet.

13 Recommendations Approval is recommended.

/S/

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cc **org**
HFD-110
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References

1 LB Shelmer and Beal,SL. Pharmacokinetic parameter estimates from several least square procedures; superiority of extended least squares. J Pharmacokinetics an Pharmacodynamics 13: 185, 1985.