CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-834/S004

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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-834/S004

Trade Name: Plendil

Generic Name: Felodipine

Sponsor: Astra Merck

Approval Date: July 25, 1991

Indications: The treatment of hypertension.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-834/S004

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUL 14 1995

NDA 19-834/S-004

Astrå Merck
Attention: Elliott T. Berger, Ph.D.
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

Dear Dr. Berger:

Please refer to your March 20, 1995 supplemental new drug application submitted on March 23, 1995 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plendil (felodipine) Tablets.

We acknowledge receipt of your amendment dated June 1, 1995.

The supplemental application provides for draft labeling revised as follows:

The phrase, "in patients with hypertension" was inserted into the second paragraph of the ——— **Renal/Endocrine Effects** subsection after the words "In clinical trials."

The **PRECAUTIONS: General: Elderly Patients or Patients with Impaired Liver Function** was revised to recommend a starting dose of 2.5 mg in those patients.

The **PRECAUTIONS: Drug Interactions: Digoxin** subsection was revised to read as follows:

> When given concomitantly with Plendil, the pharmacokinetics of digoxin in patients with heart failure were not significantly altered.

The **ADVERSE REACTIONS** section was revised to remove ——— ——— A statement was added to say that, although the antihypertensive effect is increased with 20 mg, there is a disproportionate increase in adverse events.

The **DOSAGE AND ADMINISTRATION** section was revised to recommend a starting dose of 2.5 mg daily in elderly ———

We have completed the review of this supplemental application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, this supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling.

Please submit fifteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 19-834/S-004. Approval of this FPL is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We note that you had proposed that the second paragraph of the **CLINICAL PHARMACOLOGY: Cardiovascular Effects** subsection be revised to read as follows:

A reflex increase in heart rate _____

We beleive that the data that you have submitted are inadequate to allow us to evaluate fully this request. _____

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 contact:

Mr. David Roeder
Regulatory Health Project Manager
(301) 594-5300

Sincerely yours,

R/ 7/14/95

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

Enclosure

cc:
Original NDA
HF-2/MedWatch (with labeling)
HFD-80 (with labeling)
HFD-110
HFD-110/CSO
HFD-240 (with labeling)
HFD-613 (with labeling)
HFD-735/DBarash (with labeling)
HFD-110/DRoeder
sb/6/21/95;6/29/95;7/7/95;7/12/95
R/D: RMittal/6/26/95
RWolters
ADeFelice/6/26/95
AKarkowsky/6/27/95
NMorgenstern/6/29/95;7/10/95

Approval Date: July 25, 1991

APPROVAL
SUPPLEMENT REQUEST

AR 7-12-95

4 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

X § 552(b)(4) Draft Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-834/S004

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 30 1995

NDA 19-834/S-004

Astra Merck
Attention: Elliott T. Berger, Ph.D.
725 Chesterbrook Blvd
Wayne, PA 19087-5677

Dear Dr. Berger:

Please refer to your March 20, 1995 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plendil (felodipine) Tablets, 2.5, 5 and 10 mg.

The supplemental application provides for draft labeling revised as follows:

The second paragraph of the **CLINICAL PHARMACOLOGY: Cardiovascular Effects** subsection was revised to reflect updated information concerning the effect of felodipine on heart rate.

The phrase, "in patients with hypertension" was inserted into the second paragraph of the **Renal/Endocrine Effects** subsection after the words "In clinical trials."

The **PRECAUTIONS: General: Elderly Patients or Patients with Impaired Liver Function** was revised to recommend a starting dose of 2.5 mg in those patients.

The **PRECAUTIONS: Drug Interactions: Digoxin** subsection was revised to reflect updated information on the interaction between felodipine and digoxin.

The **ADVERSE REACTIONS** section was revised to remove [redacted] A statement was added to say that, although the antihypertensive effect is increased with 20 mg, there is a disproportionate increase in adverse events.

The **DOSAGE AND ADMINISTRATION** section was revised to recommend a starting dose of 2.5 mg daily in elderly and [redacted]

We have completed the review of this supplemental application as submitted with draft labeling and it is approvable. Before this supplement may be approved, however, it will be necessary for you to submit final printed labeling (FPL). The labeling should be identical in content to the submitted draft. In addition, all previous revisions as reflected in the most recently approved package insert must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the FPL may be required.

Please submit fifteen copies of the printed labeling ten of which are individually mounted on heavy weight paper or similar material.

Within 10 days after the date of this letter, you are required to amend this supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw this supplemental application.

These changes may not be implemented until you have been notified in writing that this supplemental application is approved.

Should you have any questions, please contact:

Mr. David Roeder
Regulatory Health Project Manager
Telephone: (301) 594-5300

Sincerely yours,

5/30/95

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

cc:
Original NDA
HFC-130/JAllen
HFD-80
HFD-110
HFD-110/CSO
HFD-110/DRoeder
sb/5/16/95;5/30/95
R/D: RMittal
RWolters/5/24/95
ADeFelice/5/25/95
AKarkowsky/5/30/95
NMorgenstern/5/30/95

Approval Date: July 26, 1991

APPROVABLE

AR 5-30-95

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-834/S004

LABELING

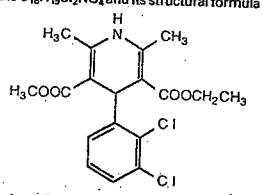
ASTRA MERCK
Wayne, PA 19087, USA

TABLETS

PLENDIL®
(FELODIPINE)
EXTENDED-RELEASE TABLETS

DESCRIPTION

PLENDIL* (Felodipine) is a calcium antagonist (calcium channel blocker). Felodipine is a dihydropyridine derivative that is chemically described as ± ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate. Its empirical formula is $C_{18}H_{19}Cl_2NO_4$ and its structural formula is:



Felodipine is a slightly yellowish, crystalline powder with a molecular weight of 384.26. It is insoluble in water and is freely soluble in dichloromethane and ethanol. Felodipine is a racemic mixture.

Tablets PLENDIL provide extended release of felodipine. They are available as tablets containing 2.5 mg, 5 mg or 10 mg of felodipine for oral administration. In addition to the active ingredient felodipine, the tablets contain the following inactive ingredients: Tablets PLENDIL 2.5 mg — hydroxypropyl cellulose, lactose, FD&C Blue 2, sodium stearyl fumarate, titanium dioxide, yellow iron oxide and other ingredients. Tablets PLENDIL 5 mg and 10 mg — cellulose, red and yellow oxide, lactose, polyethylene glycol, sodium stearyl fumarate, titanium dioxide and other ingredients.

CLINICAL PHARMACOLOGY

Mechanism of Action

Felodipine is a member of the dihydropyridine class of calcium channel antagonists (calcium channel blockers). It reversibly competes with nitrendipine and/or other calcium channel blockers for dihydropyridine binding sites, blocks voltage-dependent Ca^{++} currents in vascular smooth muscle and cultured rabbit atrial cells and blocks potassium-induced contracture of the rat portal vein.

In vitro studies show that the effects of felodipine on contractile processes are selective, with greater effects on vascular smooth muscle than cardiac muscle. Negative inotropic effects can be detected *in vitro*, but such effects have not been seen in intact animals.

The effect of felodipine on blood pressure is principally a consequence of a dose-related decrease of peripheral vascular resistance in man, with a modest reflex increase in heart rate (see *Cardiovascular Effects*). With the exception of a mild diuretic effect seen in several animal species and man, the effects of felodipine are accounted for by its effects on peripheral vascular resistance.

Pharmacokinetics and Metabolism

Following oral administration, felodipine is almost completely absorbed and undergoes extensive first-pass metabolism. The systemic bioavailability of PLENDIL is approximately 20 percent. Mean peak concentrations following the administration of PLENDIL are reached in 2.5 to 5 hours. Both peak plasma concentration and the area under the plasma concentration time curve (AUC) increase linearly with doses up to 20 mg. Felodipine is greater than 99 percent bound to plasma proteins.

Following intravenous administration, the plasma concentration of felodipine declined triexponentially with mean disposition half-lives of 4.8 minutes, 1.5 hours and 9.1 hours. The mean contributions of the three individual phases to the overall AUC were 15, 40 and 45 percent, respectively, in the order of increasing $t_{½}$.

Following oral administration of the immediate-release formulation, the plasma level of felodipine also declined polyexponentially with a mean terminal $t_{½}$ of 11 to 16 hours. The mean peak and trough steady-state plasma concentrations achieved after 10 mg of the immediate-release formulation given once a day to normal volunteers, were 20 and 0.5 nmol/L, respectively. The trough plasma concentration of felodipine in most individuals was substantially below the concentration needed to effect a half-maximal decline in blood pressure (EC_{50}) (4-6 nmol/L for felodipine), thus precluding once a day dosing with the immediate-release formulation.

Following administration of a 10-mg dose of PLENDIL, the extended-release formulation, to young, healthy volunteers, mean peak and trough steady-state plasma concentrations of felodipine were 7 and 2 nmol/L, respectively. Corresponding values in hypertensive patients (mean age 64) after a 20-mg dose of PLENDIL were 23 and 7 nmol/L. Since the EC_{50} for felodipine is 4 to 6 nmol/L, a 5 to 10-mg dose of PLENDIL in some patients, and a 20-mg dose in others, would be expected to provide an antihypertensive effect that persists for 24 hours (see *Cardiovascular Effects* below and DOSAGE AND ADMINISTRATION).

The systemic plasma clearance of felodipine in young healthy subjects is about 0.8 L/min and the apparent volume of distribution is about 10 L/kg.

Following an oral or intravenous dose of ^{14}C-labeled felodipine in man, about 70 percent of the dose of radioactivity was recovered in urine and 10 percent in the feces. A negligible amount of intact felodipine is recovered in the urine and feces (<0.5%). Six metabolites, which account for 23 percent of the oral dose, have been identified; none has significant vasodilating activity.

Following administration of PLENDIL to hypertensive patients, mean peak plasma concentrations at steady state are about 20 percent higher than after a single dose. Blood pressure response is correlated with plasma concentrations of felodipine.

The bioavailability of PLENDIL is not influenced by the presence of food in the gastrointestinal tract. In a study of six patients, the bioavailability of felodipine was increased more than two-fold when taken with doubly concentrated grapefruit juice, compared to when taken with water or orange juice. A similar finding has been seen with some other dihydropyridine calcium antagonists, but to a lesser extent than that seen with felodipine.

Age Effects: Plasma concentrations of felodipine, after a single dose and at steady state, increase with age. Mean clearance of felodipine in elderly hypertensives (mean age 74) was only 45 percent of that of young volunteers (mean age 26). At steady state mean AUC for young patients was 39 percent of that for the elderly. Data for intermediate age ranges suggest that the AUCs fall between the extremes of the young and the elderly.

Hepatic Dysfunction: In patients with hepatic disease, the clearance of felodipine was reduced to about 60 percent of that seen in normal young volunteers.

Renal impairment does not alter the plasma concentration profile of felodipine; although higher concentrations of the metabolites are present in the plasma due to decreased urinary excretion, these are inactive.

Animal studies have demonstrated that felodipine crosses the blood-brain barrier and the placenta.

Cardiovascular Effects

Following administration of PLENDIL, a reduction in blood pressure generally occurs within two to five hours. During chronic administration, substantial blood pressure control lasts for 24 hours, with trough reductions in diastolic blood pressure approximately 40-50 percent of peak reductions. The antihypertensive effect is dose-dependent and correlates with the plasma concentration of felodipine.

A reflex increase in heart rate frequently occurs during the first week of therapy; this increase attenuates over time. Heart rate increases of 5-10 beats per minute may be seen during chronic dosing. The increase is inhibited by beta-blocking agents.

The P-R interval of the ECG is not affected by felodipine when administered alone or in combination with a beta-blocking agent. Felodipine alone or in combination with a beta-blocking agent has been shown, in clinical and electrophysiologic studies, to have no significant effect on cardiac conduction (P-R, P-Q and H-V intervals).

In clinical trials in hypertensive patients without clinical evidence of left ventricular dysfunction, no symptoms suggestive of a negative inotropic effect were noted; however none would be expected in this population (see PRECAUTIONS).

Renal/Endocrine Effects

Renal vascular resistance is decreased by felodipine while glomerular filtration rate remains unchanged. Mild diuresis, natriuresis and kaliuresis have been observed during the first week of therapy. No significant effects on serum electrolytes were observed during short- and long-term therapy.

In clinical trials in patients with hypertension increases in plasma noradrenaline levels have been observed.

Clinical Studies

Felodipine produces dose-related decreases in systolic and diastolic blood pressure as demonstrated in six placebo-controlled, dose response studies using either immediate-release or extended-release dosage forms. These studies enrolled over 800 patients on active treatment, at total daily doses ranging from 2.5 to 20 mg. In those studies felodipine was administered either as monotherapy or was added to beta

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blockers. The results of the two studies with PLENDIL given once daily as monotherapy are shown in the table below:

MEAN REDUCTIONS IN BLOOD PRESSURE (mmHg)* Systolic/Diastolic

Dose	N	Mean Peak Response	Mean Trough Response	Trough/Peak Ratios (%s)
		Study 1 (8 weeks)		
2.5 mg	68	9.4/4.7	2.7/2.5	29/53
5 mg	69	9.5/6.3	2.4/3.7	25/59
10 mg	67	18.0/10.8	10.0/6.0	56/56
		Study 2 (4 weeks)		
10 mg	50	5.3/7.2	1.5/3.2	33/40**
20 mg	50	11.3/10.2	4.5/3.2	43/34**

*Placebo response subtracted
**Different number of patients available for peak and trough measurements

INDICATIONS AND USAGE

PLENDIL is indicated for the treatment of hypertension. PLENDIL may be used alone or concomitantly with other antihypertensive agents.

CONTRAINDICATIONS

PLENDIL is contraindicated in patients who are hypersensitive to this product.

PRECAUTIONS

General

Hypotension: Felodipine, like other calcium antagonists, may occasionally precipitate significant hypotension and rarely syncope. It may lead to reflex tachycardia which in susceptible individuals may precipitate angina pectoris. (See ADVERSE REACTIONS.)

Heart Failure: Although acute hemodynamic studies in a small number of patients with NYHA Class II or III heart failure treated with felodipine have not demonstrated negative inotropic effects, safety in patients with heart failure has not been established. Caution therefore should be exercised when using PLENDIL in patients with heart failure or compromised ventricular function, particularly in combination with a beta blocker.

Elderly Patients or Patients with Impaired Liver Function: Patients over 65 years of age or patients with impaired liver function may have elevated plasma concentrations of felodipine and may respond to lower doses of PLENDIL, therefore a starting dose of 2.5 mg once a day is recommended. These patients should have their blood pressure monitored closely during dosage adjustment of PLENDIL. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

Peripheral Edema: Peripheral edema, generally mild and not associated with generalized fluid retention, was the most common adverse event in the clinical trials. The incidence of peripheral edema was both dose- and age-dependent. Frequency of peripheral edema ranged from about 10 percent in patients under 50 years of age taking 5 mg daily to about 30 percent in those over 60 years of age taking 20 mg daily. This adverse effect generally occurs within 2-3 weeks of the initiation of treatment.

Information for Patients

Patients should be instructed to take PLENDIL whole and not to crush or chew the tablets. They should be told that mild gingival hyperplasia (gum swelling) has been reported. Good dental hygiene decreases its incidence and severity.

NOTE: As with many other drugs, certain advice to patients being treated with PLENDIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Beta-Blocking Agents: A pharmacokinetic study of felodipine in conjunction with metoprolol demonstrated no significant effects on the pharmacokinetics of felodipine. The AUC and C_{max} of metoprolol, however, were increased approximately 31 and 38 percent, respectively. In controlled clinical trials, however, beta blockers including metoprolol were concurrently administered with felodipine and were well tolerated.

Cimetidine: In healthy subjects pharmacokinetic studies showed an approximately 50 percent 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. Therefore, it is recommended that low doses of PLENDIL be used when given concomitantly with cimetidine.

Digoxin: When given concomitantly with PLENDIL the pharmacokinetics of digoxin in patients with heart failure were not significantly altered.

Anticonvulsants: In a pharmacokinetic study, maximum plasma concentrations of felodipine were considerably lower in epileptic patients on long-term anticonvulsant therapy (e.g., phenytoin, carbamazepine, or phenobarbital) than in healthy volunteers. In such patients, the mean area under the felodipine plasma concentration-time curve was also reduced to approximately six percent of that observed in healthy volunteers. Since a clinically significant interaction may be anticipated, alternative antihypertensive therapy should be considered in these patients.

TABLETS
PLENDIL®
(FELODIPINE)
EXTENDED-RELEASE TABLETS
Circular Number 7909008

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TABLETS PLENDIL® (FELODIPINE) EXTENDED-RELEASE TABLETS 7909008

7909008 TABLETS PLENDIL® (FELODIPINE) EXTENDED-RELEASE TABLETS

Other Concomitant Therapy: In healthy subjects there were no clinically significant interactions when felodipine was given concomitantly with indomethacin or spironolactone.

Interaction with Food: See CLINICAL PHARMACOLOGY, *Pharmacokinetics and Metabolism.*

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two-year carcinogenicity study in rats fed felodipine at doses of 7.7, 23.1 or 69.3 mg/kg/day (up to 28 times* the maximum recommended human dose on a mg/m² basis), a dose-related increase in the incidence of benign interstitial cell tumors of the testes (Leydig cell tumors) was observed in treated male rats. These tumors were not observed in a similar study in mice at doses up to 138.6 mg/kg/day (28 times* the maximum recommended human dose on a mg/m² basis). Felodipine, at the doses employed in the two-year rat study, has been shown to lower testicular testosterone and to produce a corresponding increase in serum luteinizing hormone in rats. The Leydig cell tumor development is possibly secondary to these hormonal effects which have not been observed in man.

In this same rat study a dose-related increase in the incidence of focal squamous cell hyperplasia compared to control was observed in the esophageal groove of male and female rats in all dose groups. No other drug-related esophageal or gastric pathology was observed in the rats or with chronic administration in mice and dogs. The latter species, like man, has no anatomical structure comparable to the esophageal groove.

Felodipine was not carcinogenic when fed to mice at doses of up to 138.6 mg/kg/day (28 times* the maximum recommended human dose on a mg/m² basis) for periods of up to 80 weeks in males and 99 weeks in females.

Felodipine did not display any mutagenic activity *in vitro* in the Ames microbial mutagenicity test or in the mouse lymphoma forward mutation assay. No clastogenic potential was seen *in vivo* in the mouse micronucleus test at oral doses up to 2500 mg/kg (506 times* the maximum recommended human dose on a mg/m² basis) or *in vitro* in a human lymphocyte chromosome aberration assay.

A fertility study in which male and female rats were administered doses of 3.8, 9.6 or 26.9 mg/kg/day showed no significant effect of felodipine on reproductive performance.

Pregnancy

Pregnancy Category C

Teratogenic Effects: Studies in pregnant rabbits administered doses of 0.46, 1.2, 2.3 and 4.6 mg/kg/day (from 0.4 to 4 times* the maximum recommended human dose on a mg/m² basis) showed digital anomalies consisting of reduction in size and degree of ossification of the terminal phalanges in the fetuses. The frequency and severity of the changes appeared dose-related and were noted even at the lowest dose. These changes have been shown to occur with other members of the dihydropyridine class and are possibly a result of compromised uterine blood flow. Similar fetal anomalies were not observed in rats given felodipine.

In a teratology study in cynomolgus monkeys no reduction in the size of the terminal phalanges was observed but an abnormal position of the distal phalanges was noted in about 40 percent of the fetuses.

Nonteratogenic Effects: A prolongation of parturition with difficult labor and an increased frequency of fetal and early postnatal deaths were observed in rats administered doses of 9.6 mg/kg/day (4 times* the maximum human dose on a mg/m² basis) and above.

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 (equal to the maximum human dose on a mg/m² basis). This effect occurred only in pregnant rabbits and regressed during lactation. Similar changes in the mammary glands were not observed in rats or monkeys.

There are no adequate and well-controlled studies in pregnant women. If felodipine is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus, possible digital anomalies of the infant, and the potential effects of felodipine on labor and delivery, and on the mammary glands of pregnant females.

Nursing Mothers

It is not known whether this drug is secreted in human milk and because of the potential for serious adverse reactions from felodipine in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

In controlled studies in the United States and overseas approximately 3000 patients were treated with felodipine as either the extended-release or the immediate-release formulation.

The most common clinical adverse events reported with PLENDIL administered as monotherapy at the recommended dosage range of 2.5 mg to 10 mg once a day were peripheral edema and headache. Peripheral edema was generally mild, but it was age- and dose-related and resulted in discontinuation of therapy in about 3 percent of the enrolled patients. Discontinuation of therapy due to any clinical adverse event occurred in about 6 percent of the patients receiving PLENDIL, principally for peripheral edema, headache, or flushing.

Adverse events that occurred with an incidence of 1.5 percent or greater at any of the recommended doses of 2.5 mg to 10 mg once a day (PLENDIL, N=861; Placebo, N=334), without regard to causality, are compared to placebo and are listed by dose in the table below. These events are reported from controlled clinical trials with patients who were randomized to a fixed dose of PLENDIL or titrated from an initial dose of 2.5 mg or 5 mg once a day. A dose of 20 mg once a day has been evaluated in some clinical studies. Although the antihypertensive effect of PLENDIL is increased at 20 mg once a day, there is a disproportionate increase in adverse events, especially those associated with vasodilatory effects (see DOSAGE AND ADMINISTRATION).

Percent of Patients with Adverse Events in Controlled Trials* of PLENDIL (N=861) as Monotherapy without Regard to Causality (Incidence of discontinuations shown in parentheses)

Body System Adverse Events	Placebo N=334	2.5 mg N=255	5 mg N=581	10 mg N=408
Body as a Whole				
Peripheral Edema	3.3 (0.0)	2.0 (0.0)	8.8 (2.2)	17.4 (2.5)
Asthenia	3.3 (0.0)	3.9 (0.0)	3.3 (0.0)	2.2 (0.0)
Warm Sensation	0.0 (0.0)	0.0 (0.0)	0.9 (0.2)	1.5 (0.0)
Cardiovascular				
Palpitation	2.4 (0.0)	0.4 (0.0)	1.4 (0.3)	2.5 (0.5)
Digestive				
Nausea	1.5 (0.0)	1.2 (0.0)	1.7 (0.3)	1.0 (0.7)
Dyspepsia	1.2 (0.0)	0.8 (0.0)	0.7 (0.0)	0.5 (0.0)
Constipation	0.9 (0.0)	1.2 (0.0)	0.3 (0.0)	1.5 (0.2)
Nervous				
Headache	10.2 (0.9)	10.6 (0.4)	11.0 (1.7)	14.2 (2.0)
Dizziness	2.7 (0.3)	2.7 (0.0)	3.6 (0.5)	3.7 (0.5)
Paresthesia	1.5 (0.3)	1.6 (0.0)	1.2 (0.0)	1.2 (0.2)
Respiratory				
Upper Respiratory Infection	7.8 (0.0)	3.9 (0.0)	7.9 (0.0)	7.7 (0.0)
Cough	0.9 (0.0)	0.8 (0.0)	1.2 (0.0)	1.7 (0.0)
Rhinorrhea	0.0 (0.0)	1.6 (0.0)	0.2 (0.0)	0.2 (0.0)
Sneezing	0.0 (0.0)	1.6 (0.0)	0.0 (0.0)	0.0 (0.0)
Skin				
Rash	0.3 (0.0)	2.0 (0.0)	0.2 (0.0)	0.2 (0.0)
Flushing	0.9 (0.3)	3.5 (0.0)	5.3 (0.7)	6.9 (1.2)

*Patients in titration studies may have been exposed to more than one dose level of PLENDIL.

Adverse events that occurred in 0.5 up to 1.5 percent of patients who received PLENDIL in all controlled clinical trials at the recommended dosage range of 2.5 mg to 10 mg once a day and serious adverse events that occurred at a lower rate or events reported during marketing experience (those lower rate events are in italics) are listed below. These events are listed in order of decreasing severity within each category and the relationship of these events to administration of PLENDIL is uncertain: ***Body as a Whole:*** Chest pain, facial edema, flu-like illness; ***Cardiovascular:*** *Myocardial infarction, hypotension, syncope, angina pectoris, arrhythmia;* tachycardia, premature beats; ***Digestive:*** Abdominal pain, diarrhea, vomiting, dry mouth, flatulence, acid regurgitation; ***Hematologic:*** *Anemia;* ***Metabolic:*** ALT (SGPT) increased; ***Musculoskeletal:*** Arthralgia, back pain, leg pain, foot pain, muscle cramps, myalgia, arm pain, knee pain, hip pain; ***Nervous/Psychiatric:*** Insomnia, depression, anxiety disorders, irritability, nervousness, somnolence, decreased libido; ***Respiratory:*** Dyspnea, pharyngitis, bronchitis, influenza, sinusitis, epistaxis, respiratory infection; ***Skin:*** Contusion, erythema, urticaria; ***Special Senses:*** Visual disturbances; ***Urogenital:*** Impotence, urinary frequency, urinary urgency, dysuria, polyuria.

Gingival Hyperplasia: Gingival hyperplasia, usually mild, occurred in <0.5 percent of patients in controlled studies. This condition may be avoided or may regress with improved dental hygiene. (See PRECAUTIONS, *Information for Patients.*)

Clinical Laboratory Test Findings

Serum Electrolytes: No significant effects on serum electrolytes were observed during short- and long-term therapy (see CLINICAL PHARMACOLOGY, *Renal/Endocrine Effects*).

Serum Glucose: No significant effects on fasting serum glucose were observed in patients treated with PLENDIL in the U.S. controlled study.

Liver Enzymes: One of two episodes of elevated serum transaminases decreased once drug was discontinued in clinical studies; no follow-up was available for the other patient.

OVERDOSAGE

Oral doses of 240 mg/kg and 264 mg/kg in male and female mice, respectively and 2390 mg/kg and 2250 mg/kg in male and female rats, respectively, caused significant lethality.

In a suicide attempt, one patient took 150 mg felodipine together with 15 tablets each of atenolol and spironolactone and 20 tablets of nitrazepam. The patient's blood pressure and heart rate were normal on admission to hospital; he subsequently recovered without significant sequelae.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly bradycardia.

If severe hypotension occurs, symptomatic treatment should be instituted. The patient should be placed supine with the legs elevated. The administration of intravenous fluids

*Based on patient weight of 50 kg

PLENDIL® (Felodipine) Extended-Release Tablets

may be useful to treat hypotension due to overdosage with calcium antagonists. In case of accompanying bradycardia, atropine (0.5-1 mg) should be administered intravenously. Sympathomimetic drugs may also be given if the physician feels they are warranted.

It has not been established whether felodipine can be removed from the circulation by hemodialysis.

DOSAGE AND ADMINISTRATION

The recommended starting dose is 5 mg once a day. Depending on the patient's response the dosage can be decreased to 2.5 mg or increased to 10 mg once a day. These adjustments should occur generally at intervals of not less than two weeks. The recommended dosage range is 2.5-10 mg once daily. In clinical trials, doses above 10 mg daily showed an increased blood pressure response but a large increase in the rate of peripheral edema and other vasodilatory adverse events (see ADVERSE REACTIONS). Modification of the recommended dosage is usually not required in patients with renal impairment.

PLENDIL should be swallowed whole and not crushed or chewed.

Use in the Elderly or Patients with Impaired Liver Function: Patients over 65 years of age or patients with impaired liver function, may develop higher plasma concentrations of felodipine, therefore a starting dose of 2.5 mg once a day is recommended. Dosage may be adjusted as described above. (See PRECAUTIONS.)

HOW SUPPLIED

No. 3584 — Tablets PLENDIL, 2.5 mg, are sage green, round convex tablets, with code 450 on one side and PLENDIL on the other. They are supplied as follows:

NDC 61113-450-28 unit dose packages of 100
NDC 61113-450-58 unit of use bottles of 100
NDC 61113-450-31 unit of use bottles of 30

No. 3585 — Tablets PLENDIL, 5 mg, are light red-brown, round convex tablets, with code 451 on one side and PLENDIL on the other. They are supplied as follows:

NDC 61113-451-28 unit dose packages of 100
(6505-01-350-0354, 5 mg individually sealed 100's)
NDC 61113-451-58 unit of use bottles of 100
(6505-01-350-0356, 5 mg 100's)
NDC 61113-451-31 unit of use bottles of 30
(6505-01-350-0352, 5 mg 30's).

No. 3586 — Tablets PLENDIL, 10 mg, are red-brown, round convex tablets, with code 452 on one side and PLENDIL on the other. They are supplied as follows:

NDC 61113-452-28 unit dose packages of 100
(6505-01-350-0353, 10 mg individually sealed 100's).
NDC 61113-452-58 unit of use bottles of 100
(6505-01-350-0355, 10 mg 100's)
NDC 61113-452-31 unit of use bottles of 30
(6505-01-350-0357, 10 mg 30's).

Storage

Store below 30°C (86°F). Keep container tightly closed. Protect from light.

Distributed by:
ASTRA MERCK
Wayne, PA 19087, USA

Manufactured by: MERCK & CO., INC., West Point, PA 19486, USA

Issued July 1995 Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

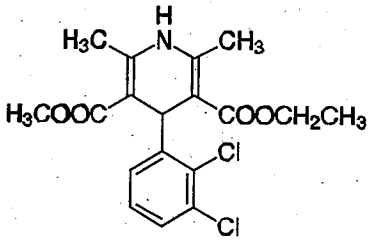
APPLICATION NUMBER:

19-834/S004

CHEMISTRY REVIEW(S)

JUN 12 1995

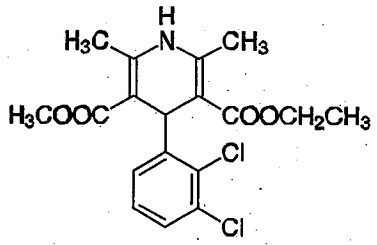
NDA 19-834 PLENDIL ASTRA-MERCK

CHEMIST'S REVIEW	1. ORGANIZATION HFD - 110	2. NDA Number 19-834
3. Name and Address of Applicant (City & State) Astra Merck 725 Chesterbrook Blvd. Wayne, Pa 19087-5677		4. Supplement(s) Number/Date SLR(AF)-004 06-01-95
5. Drug Name PLENDIL	6. Nonproprietary Name Felodipine	8. Amendments & Other (reports, etc) - Dates
7. Supplnt amendment provide for: Final Printed Labeling as per Agency's letter of May 30, 1995.		
9. Pharmacological Category Hypertension	10. How Dispensed /x/ RX / / OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Tablets	13. Potency(ies) 2.5 mg, 5 mg and 10 mg	
14. Chemical Name and Structure (±) Ethylmethyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine-dicarboxylate. 		15. Records/Reports Current /x/ Yes / / No Reviewed /x/ Yes / / No
16. Comments: Description and How Supplied sections of the printed labeling is identical in content to that submitted in draft on March 20, 1995.		
17. Conclusions and Recommendations: From the standpoint of CMC related sections (How Supplied and Description), the FPL is satisfactory and supplement can be approved.		
18. REVIEWER		
Name Ramsharan D. Mittal	Signature	Date Completed 06-12-95
19. Distribution: / / Original Jacket / / Reviewer / / Division File / / CSO		

6/12/95

NDA 19-834 PLENDIL ASTRA-MERCK

MAY 2 - 1995

CHEMIST'S REVIEW	1. ORGANIZATION HFD - 110	2. NDA Number 19-834
3. Name and Address of Applicant (City & State) Astra Merck 725 Chesterbrook Blvd. Wayne, Pa 19087-5677		4. Supplement(s) Number/Date SLR-004 03-20-95
5. Drug Name PLENDIL	6. Nonproprietary Name Felodipine	8. Amendments & Other (reports, etc) - Dates
7. Supplnt amendment provide for: Revised labeling as per Agency's letter of February 9, 1995.		
9. Pharmacological Category Hypertension	10. How Dispensed /x/ RX / / OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Tablets	13. Potency(ies) 2.5 mg, 5 mg and 10 mg	
14. Chemical Name and Structure (±) Ethylmethyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridine-dicarboxylate. 		15. Records/Reports Current /x/ Yes / / No Reviewed /x/ Yes / / No
16. Comments: The labeling revisions did not effect "DESCRIPTION" AND " HOW SUPPLIED" sections.		
17. Conclusions and Recommendations: The "DESCRIPTION" AND " HOW SUPPLIED" sections remain satisfactry.		
18. REVIEWER		
Name Ramsharan D. Mittal	Signature	Date Completed 04-28-95
19. Distribution: / / Original Jacket / / Reviewer / / Division File / / CSO		

5-1-95

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-834/S004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 19-834/S-004

FEB -9 1996

Astra Merck
Attention: Daniel J. Cushing, Ph.D.
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

Dear Dr. Cushing:

We acknowledge the receipt of your August 23, 1995 submission containing final printed labeling in response to our July 14, 1995 letter approving your supplemental new drug application for Plendil (felodipine) Tablets 2.5, 5 and 10 mg.

We have reviewed the labeling that you have submitted in accordance with our July 14, 1995 letter, and we find it acceptable.

Sincerely yours,

R/f 2/9/96

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

cc:
Original NDA
HF-2/MedWatch (with labeling)
HFD-80 (with labeling)
HFD-100 (with labeling)
HFD-110
HFD-110/Project Manager
HFD-240 (with labeling)
HFD-613 (with labeling)
HFD-735/DBarash (with labeling)
HFD-110/DRoeder
sb/12/12/95;1/26/96
R/D: RMittal/1/11/96
RWolters /11/96
ADeFelice/1/11/96
AKarkowsky/1/11/96
NMorgenstern/1/17/96

NR 2-9-96

ACKNOWLEDGE AND RETAIN (AR)

RHPM Review of Final Printed Labeling

FEB - 9 1996

Application: NDA 19-834/S-004
Plendil (felodipine) Tablets

Sponsor: Astra Merck

Letter Date: August 23, 1995

Receipt Date: August 25, 1995

An approval letter was issued to Astra Merck for NDA 19-834/S-004 on July 14, 1995, based on draft labeling. The firm submitted final printed labeling in a submission dated August 23, 1995. This labeling is identical in content to the approved draft package insert.

An "acknowledge and retain" letter will be drafted.

David Roeder
Regulatory Health Project Manager

dr/12-8-95

cc: NDA 19-834
HFD-110
HFD-111/DRoeder
HFD-111/SBenton

DEPARTMENT OF HEALTH & HUMAN SERVICES 2011 Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-834/S-004

AUG 9 1995

Astrå Merck
Attention: Elliott T. Berger, Ph.D.
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

Dear Dr. Berger:

Please refer to your March 20, 1995 supplemental new drug application submitted on March 23, 1995 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plendil (felodipine) Tablets.

We wish to correct an error in the July 14, 1995 approval letter for this supplement. The July 14, 1995 letter stated:

> The **DOSAGE AND ADMINISTRATION** section was revised to recommend a starting dose of 2.5 mg daily in elderly.

It should have read:

> The **DOSAGE AND ADMINISTRATION** section was revised to recommend a starting dose of 2.5 mg daily in the elderly or patients with impaired hepatic function.

Please note that the draft labeling included with the approval letter is correct.

The supplemental application provided for draft labeling revised as follows:

> The phrase, "in patients with hypertension" was inserted into the second paragraph of the **Renal/Endocrine Effects** subsection after the words "In clinical trials."
>
> The **PRECAUTIONS: General: Elderly Patients or Patients with Impaired Liver Function** was revised to recommend a starting dose of 2.5 mg in those patients.
>
> The **PRECAUTIONS: Drug Interactions: Digoxin** subsection was revised to read as follows:
>
> > When given concomitantly with Plendil, the pharmacokinetics of digoxin in patients with heart failure were not significantly altered.

The **ADVERSE REACTIONS** section was revised to remove [redacted] A statement was added to say that, although the antihypertensive effect is increased with 20 mg, there is a disproportionate increase in adverse events.

The **DOSAGE AND ADMINISTRATION** section was revised to recommend a starting dose of 2.5 mg daily in the elderly or patients with impaired hepatic function.

If you have any questions, please contact:

Mr. David Roeder
Regulatory Health Project Manager
(301) 594-5300

Sincerely yours,

RJL 8/9/95

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

cc:
Original NDA
HF-2/MedWatch (with labeling)
HFD-80 (with labeling)
HFD-110
HFD-110/CSO
HFD-240 (with labeling)
HFD-613 (with labeling)
HFD-735/DBarash (with labeling)
HFD-110/KBongiovanni
sb/7/28/95;7/31/95
R/D: NMorgenstern/7/28/95

8-2-95

GENERAL CORRESPONDENCE

CSO Review of Labeling

JUL 14 1995

Application: NDA 19-834/S-004
Plendil (felodipine) Tablets

Sponsor: Astra Merck

Letter Date: June 1, 1995

Receipt Date: June 2, 1995

An approvable letter was issued to Astra Merck for NDA 19-834/S-004 on May 30, 1995. This supplemental application provides for the following labeling revisions:

The second paragraph of the **CLINICAL PHARMACOLOGY: Cardiovascular Effects** subsection was revised to read as follows:

> A reflex increase in heart rate ———————————

The phrase, "in patients with hypertension" was inserted into the second paragraph of the **Renal/Endocrine Effects** subsection after the words "In clinical trials."

The **PRECAUTIONS: General: Elderly Patients or Patients with Impaired Liver Function** was revised to recommend a starting dose of 2.5 mg in those patients.

The **PRECAUTIONS: Drug Interactions: Digoxin** subsection was revised to read as follows:

> When given concomitantly with Plendil, the pharmacokinetics of digoxin in patients with heart failure were not significantly altered.

The **ADVERSE REACTIONS** section was revised to remove ——————————— A statement was added to say that, although the antihypertensive effect is increased with 20 mg, there is a disproportionate increase in adverse events.

The **DOSAGE AND ADMINISTRATION** section was revised to recommend a starting dose of 2.5 mg daily in elderly ———————————

The firm submitted final printed labeling that was identical in content to the submitted draft. Upon closer examination of the labeling, however, Dr. Lipicky had some questions about the statement concerning the effects of felodipine on heart rate. Dr. Karkowsky looked over the data and concluded that the statement in the labeling was not supported by the available data. Dr. Lipicky decided that he could not approve the labeling with that statement, so we will

approve the supplement with draft labeling.

David Roeder
Regulatory Health Project Manager

dr/6-21-95/7-7-95

cc: NDA 19-834
HFD-110
HFD-111/DRoeder
HFD-111/SBenton

CSO Review of Draft Labeling

MAY 30 1995

Application: NDA 19-834/S-004
Plendil (felodipine) Tablets

Sponsor: Astra Merck

Supplement Date: March 20, 1995

Receipt Date: March 23, 1995

Background

[redacted] Most of the changes that the sponsor proposed [redacted] This approach would simplify the administrative handling of those changes.

The firm submitted a new supplemental application, NDA 19-834/S-004, that provides for those changes that were noted to be acceptable in the [redacted] They are as follows:

The second paragraph of the **CLINICAL PHARMACOLOGY: Cardiovascular Effects** subsection was revised to read as follows:

> A reflex increase in heart rate : [redacted]

The phrase, "in patients with hypertension" was inserted into the second paragraph of the **Renal/Endocrine Effects** subsection after the words "In clinical trials."

The **PRECAUTIONS: General: Elderly Patients or Patients with Impaired Liver Function** was revised to recommend a starting dose of 2.5 mg in those patients.

The **PRECAUTIONS: Drug Interactions: Digoxin** subsection was revised to read as follows:

> When given concomitantly with Plendil, the pharmacokinetics of digoxin in patients with heart failure were not significantly altered.

The **ADVERSE REACTIONS** section was revised to remove [redacted] A statement was added to say that, although the antihypertensive effect is increased with 20 mg, there is a disproportionate increase in adverse events.

The **DOSAGE AND ADMINISTRATION** section was revised to recommend a starting dose of 2.5 mg daily in elderly ——————.

——————————————————— and have been made in accordance with our recommendations ——————————————————. I recommend that the application be approved.

David Roeder

David Roeder
Regulatory Health Project Manager

dr/5-16-95

cc: Orig NDA
HFD-110
HFD-111/DRoeder
HFD-111/SBenton