CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-834/S014

Trade Name: Plendil

Generic Name: Felodipine

Sponsor: AstraZeneca LP

Approval Date: February 8, 2000

Indications: The treatment of hypertension.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-834/S014

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-834/S014

APPROVAL LETTER

amy

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

FEB - 8 2000

NDA 19-834/S-014

AstraZeneca LP
Attention: Steven J. Miller, Ph.D.
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

Dear Dr. Miller:

Please refer to your supplemental new drug application dated April 1, 1998, received April 2, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plendil (felodipine) Extended Release Tablets.

We acknowledge receipt of your submissions dated January 21, May 7 and December 9, 1999. Your submission of December 9, 1999 constituted a complete response to our January 12, 1999 action letter.

This supplemental new drug application provides for final printed labeling revised to replace the first paragraph of your proposed **PRECAUTIONS: Drug Interactions** section with the following text:

PRECAUTIONS

Drug Interactions
CYP3A4 Inhibitors: Felodipine is metabolized by CYP3A4. Co-administration of CYP 3A4 inhibitors (e.g., ketoconazole, itraconazole, erythromycin, grapefruit juice, cimetidine) with felodipine may lead to several-fold increases in the plasma levels of felodipine, either due to an increase in bioavailability or due to a decrease in metabolism. These increases in concentration may lead to increased effects (lower blood pressure and increased heart rate). These effects have been observed with co-administration of itraconazole (a potent CYP3A4 inhibitor). Caution should be used when CYP3A4 inhibitors are co-administered with felodipine. A conservative approach to dosing felodipine should be taken. The following specific interactions have been reported:

Itraconazole: Co-administration of another extended release of felodipine with itraconazole resulted in approximately 8-fold increase in the AUC, more than 6-fold increase in the Cmax, and 2-fold prolongation in the half-life of felodipine.

Erythromycin: Co-administration of felodipine (Plendil) with erythromycin resulted in approximately 2.5-fold increase in the AUC and Cmax, and about 2-fold prolongation in the half-life of felodipine.

Grapefruit juice: Co-administration of felodipine with grapefruit juice resulted in more than 2-fold increase in the AUC and Cmax, but no prolongation in the half-life of felodipine.

Cimetidine: Co-administration of felodipine with cimetidine (a non-specific CYP-450 inhibitor) resulted in an increase of approximately 50% in the AUC and the Cmax, of felodipine.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for usé as recommended in the submitted final printed labeling (package insert included in your December 9, 1999 submission). Accordingly, the supplemental application is approved effective on the date of this letter.

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, pleases call:

Mr. David Roeder
Regulatory Project Manager
(301) 594-5332

Sincerely,

RL 4/8/00

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

cc:
Archival NDA 19-834
HFD-110/Div. Files
HFD-110/D.Roeder
HFD-110/Reviewers and Team Leaders
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-101/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-21/ACS (with labeling)
HFD-095/DDMS-IMT (with labeling)
HFD-810/DNDC Division Director
DISTRICT OFFICE

Drafted by: dlr/January 10, 2000
Initialed by: R Mittal/1/10/00
N Morgenstern/1/11/00
Final: asb/2/4/00
Filename: 19-834s014(ap).doc

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-834/S014

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-834/S-014

JAN 12 1999

Astra Pharmaceuticals, L.P.
Attention: Eric Couture, Ph.D.
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

Dear Dr. Couture:

Please refer to your supplemental new drug application dated April 1, 1998, received April 2, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plendil (felodipine) Tablets.

This supplement provides for draft labeling revised under **PRECAUTIONS: Drug Interactions** to update information on the effects of concomitant administration of drugs that interfere with the cytochrome P450 enzyme system, specifically the CYP 3A4 subfamily, on plasma concentrations of felodipine.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling revised to replace the first paragraph of your proposed **PRECAUTIONS: Drug Interactions** subsection with the following text:

PRECAUTIONS

Drug Interactions
CYP3A4 Inhibitors: Felodipine is metabolized by CYP3A4. Co-administration
CYP 3A4 inhibitors (e.g., ketoconazole, itraconazole, erythromycin, grapefruit juice, cimetidine) may lead to several-fold increases in the plasma levels of felodipine, either due to an increase in bioavailability or due to a decrease in metabolism. These increases in concentration may lead to increased effects (lower blood pressure and increased heart rate). These effects have been observed with co-administration of itraconazole (a potent CYP3A4 inhibitor).
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Erythromycin: Co-administration of felodipine (Plendil) with erythromycin resulted in approximately 2.5-fold increase in the AUC and Cmax, and about 2-fold prolongation in the half-life of felodipine.

Grapefruit juice: Co-administration of felodipine with grapefruit juice resulted in more than 2-fold increase in the AUC and Cmax, but no prolongation in the half-life of felodipine.

Cimetidine: Co-administration of felodipine with cimetidine (a non-specific CYP-450 inhibitor) resulted in an increase of approximately 50% in the AUC and the Cmax, of felodipine.

In addition, all previous revisions as reflected in the most recently approved labeling 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.

Please submit 20 copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material.

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

Within 10 days after the date of this letter, you are required to amend the 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 any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, please contact:

Mr. David Roeder
Regulatory Health Project Manager
(301) 594-5313

Sincerely yours,

RK 1/12/95

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

cc:
Archival NDA 19-834
HFD-110/Div. Files
HFD-110/D.Roeder
HFD-95/DDMS
DISTRICT OFFICE

Drafted by: dlr/December 23, 1998
Initialed by: E Fadiran/1/5/99
A Karkowsky/1/5/99
N Morgenstern/1/5/99
final:sb/1/6/99
filename: 19834s014ae.doc

APPROVABLE (AE)

1-12-99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-834/S014

LABELING

TABLETS

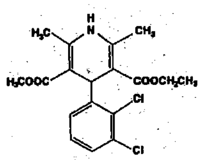
Plendil®

(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%. 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% 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%, respectively, in the order of increasing $t_{1/2}$.

Following oral administration of the immediate-release formulation, the plasma level of felodipine also declined polyexponentially with a mean terminal $t_{1/2}$ 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% of the dose of radioactivity was recovered in urine and 10% in the feces. A negligible amount of intact felodipine is recovered in the urine and feces (< 0.5%). Six metabolites, which account for 23% 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% higher than after a single dose. Blood pressure response is correlated with plasma concentrations of felodipine.

The bioavailability of PLENDIL is influenced by the presence of food. When administered either with a high fat or carbohydrate diet, C_{max} is increased by approximately 60%; AUC is unchanged. When PLENDIL was administered after a light meal (orange juice, toast, and cereal), however, there is no effect on felodipine's pharmacokinetics. The bioavailability of felodipine was increased approximately two-fold when taken with grapefruit juice. Orange juice does not appear to modify the kinetics of PLENDIL. A similar finding has been seen with 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% of that of young volunteers (mean age 26). At steady state mean AUC for young patients was 39% 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% 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 2 to 5 hours. During chronic administration, substantial blood pressure control lasts for 24 hours, with trough reductions in diastolic blood pressure approximately 40–50% 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).

*Registered trademark of Astra AB

Labeling: HFD-110
NDA No. 19-834 Rcv'd 12-1
Reviewed by: [signature]
APPROVED
FEB - 8 2000

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 blockers. The results of the 2 studies with PLENDIL given once daily as monotherapy are shown in the table below:

MEAN REDUCTIONS IN BLOOD PRESSURE (mmHg)*

Dose	N	Systolic/Diastolic Mean Peak Response	Mean Trough Response	Trough/Peak Ratios (%s)
		Study 1 (6 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.)

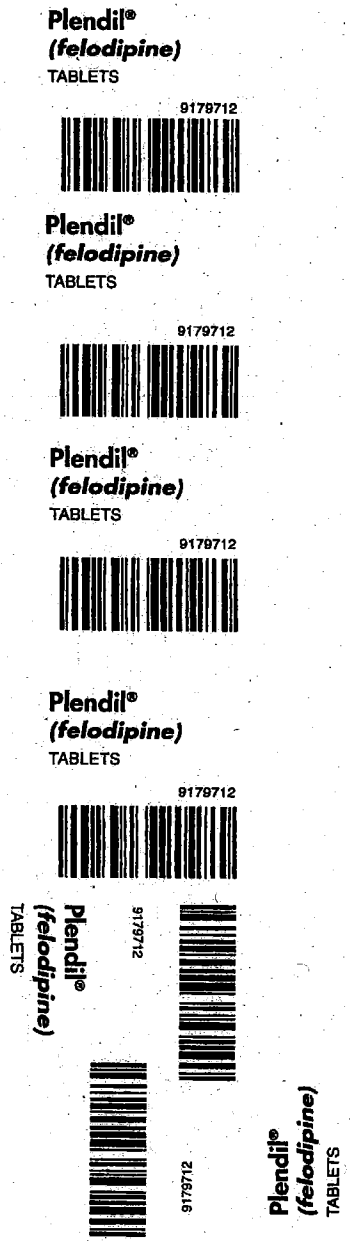
Heart Failure— Although acute hemodynamic studies in a small number of patients with NYHA Class II or III heart failure treated with felodipine have not demonstrated negative inotropic effects, safety in patients with heart failure has not been established. Caution, therefore, should be exercised when 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% in patients under 50 years of age taking 5 mg daily to about 30% 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

CYP3A4 Inhibitors— Felodipine is metabolized by CYP3A4. Co-administration of CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, erythromycin, grapefruit juice, cimetidine) with felodipine may lead to several-fold increases in the plasma levels of felodipine, either due to an increase in bioavailability or due to a decrease in metabolism. These increases in concentration may lead to increased effects, (lower blood pressure and increased heart rate). These effects have been observed with co-administration of itraconazole (a potent CYP3A4 inhibitor). Caution should be used when CYP3A4 inhibitors are co-administered with felodipine. A conservative approach to dosing felodipine should be taken. The following specific interactions have been reported:

Itraconazole— Co-administration of another extended release formulation of felodipine with itraconazole resulted in approximately 8-fold increase in the AUC, more than 6-fold increase in the C_{max}, and 2-fold prolongation in the half-life of felodipine.

Erythromycin— Co-administration of felodipine (PLENDIL) with erythromycin resulted in approximately 2.5-fold increase in the AUC and C_{max}, and about 2-fold prolongation in the half-life of felodipine.

Grapefruit juice— Co-administration of felodipine with grapefruit juice resulted in more than 2-fold increase in the AUC and C_{max}, but no prolongation in the half-life of felodipine.

Cimetidine— Co-administration of felodipine with cimetidine (a non-specific CYP-450 inhibitor) resulted in an increase of approximately 50% in the AUC and the C_{max} of felodipine.

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%, respectively. In controlled clinical trials, however, beta blockers including metoprolol were concurrently administered with felodipine and were well tolerated.

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 6% of that observed in healthy volunteers. Since a clinically significant interaction may be anticipated, alternative antihypertensive therapy should be considered in these patients.

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 2-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 2-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 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.

Plendil® (felodipine) Extended-Release Tablets

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% 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 pediatric patients 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% of the enrolled patients. Discontinuation of therapy due to any clinical adverse event occurred in about 6% of the patients receiving PLENDIL, principally for peripheral edema, headache, or flushing.

Adverse events that occurred with an incidence of 1.5% 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).

** Based on patient weight of 50 kg

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 (0.9)	1.2 (0.0)	1.7 (0.3)	1.0 (0.7)
Dyspepsia	1.2 (0.0)	3.9 (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)	14.7 (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	1.8 (0.0)	3.9 (0.0)	1.9 (0.0)	0.7 (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	0.9 (0.0)	2.0 (0.0)	0.2 (0.0)	0.2 (0.0)
Flushing	0.9 (0.3)	3.9 (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% 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; ***Endocrine:*** Gynecomastia; ***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% 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— 1 of 2 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 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.

To obtain up-to-date information about the treatment of overdose, consult your Regional Poison-Control Center. Telephone numbers of certified poison-control centers are listed in the *Physicians' Desk Reference (PDR).* In managing overdose, consider the possibilities of multiple-drug overdoses, drug-drug interactions, and unusual drug kinetics in your patient.

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 2 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 regularly be taken either without food or with a light meal (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism). 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 0186-0450-28 unit dose packages of 100

NDC 0186-0450-58 unit of use bottles of 100

NDC 0186-0450-31 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 0186-0451-28 unit dose packages of 100

NDC 0186-0451-58 unit of use bottles of 100

NDC 0186-0451-31 unit of use bottles of 30

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 0186-0452-28 unit dose packages of 100

NDC 0186-0452-58 unit of use bottles of 100

NDC 0186-0452-31 unit of use bottles of 30

Storage

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

Revised October 1999

Manufactured by:
Merck & Co., Inc., West Point, PA 19486
Distributed by:
9179712
63000212
ASTRA Astra Pharmaceuticals, L.P., Wayne, PA 19087

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-834/S014

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

MAY 2 1 1999

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA 19-834 {SLR-014 (AL)} **SUBMISSION DATES:** May 7, 1998
Plendil® (Felodipine ER) Tablets (2.5, 5, and 10 mg)

ASTRA PHARMACEUTICALS **REVIEWER:** Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: LABELING UPDATE – DRAFT 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 sponsor submitted with their 1997 annual report a published article that shows a significant interaction between felodipine tablet (Hydac 5 mg depot tablets) and itraconazole (Jalava K, Olkkola, KT, and Neuvonen PJ. Clin Pharmacol Ther 1997;61:410-5). A labeling update was suggested in OCPB review dated January 27, 1998. The sponsor has now submitted a draft labeling for review by the Agency.

SUMMARY
The sponsor has accepted the Agency's recommendations on specific drug interactions but has modified the recommendation for CYP3A4 inhibitors. The sponsor stated that the modification based on medical rational that "Therapy with felodipine is chronic, while therapy with CYP3A4 inhibitors, with the exception of grapefruit juice, are usually given sporadically to treat acute conditions (e.g. requiring antibiotics, cimetidine). Therefore, when CYP3A4 inhibitors are considered to be added to felodipine therapy, caution should be exercised because of their potential interaction with felodipine". However, the labeling is for felodipine, so the emphasis should be on felodipine. Additionally, there could be patients on chronic administration of antifungals who may be put on felodipine if they are not responding to other antihypertensives. It is therefore recommended that the suggested labeling update for CYP3A4 inhibitors in the Agency's approvable letter of February 12, 1999 should be used (see below).

SUGGESTED LABELING UPDATE TO BE SENT TO THE SPONSOR:

PRECAUTIONS

Drug Interactions
CYP3A4 Inhibitors: Felodipine is metabolized by CYP3A4. Co-administration of CYP3A4 inhibitors (e.g. Ketoconazole, itraconazole, erythromycin, grapefruit juice, cimetidine) may lead to several fold increases in the plasma levels of felodipine. These increases in concentration may lead to increased effects (lower blood pressure and increased heart rate). These effects have been observed with co-administration of itraconazole (a potent CYP3A4 inhibitor). The following specific interactions have been

reported:

RECOMMENDATION:
The Division of Pharmaceutical Evaluation I has reviewed the sponsor's draft labeling and recommends that the felodipine labeling should be updated as proposed above. Please forward the labeling comment above to the sponsor.

5/21/99

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

FT Initialed by P. Marroum, Ph.D. --- 5/21/1999

cc: NDA 19-834, HFD-110, HFD-860 (Fadiran, Mehta), BIOPHARM - CDR.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-834/S014

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

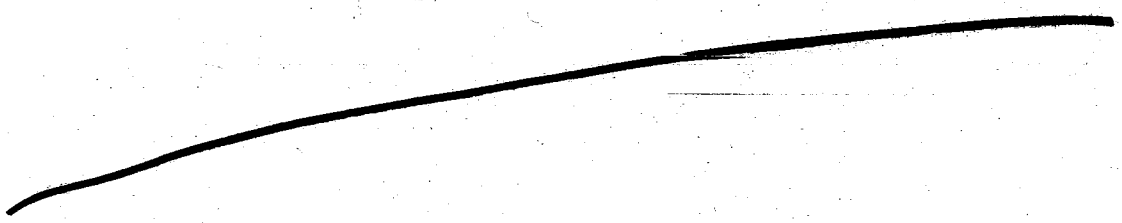
FEB - 8 2000

RHPM Review of Final Printed Labeling

Application:	NDA 19-834/S-014 Plendil (felodipine) Tablets
Sponsor:	Astra Pharmaceuticals, L.P.
Date of Supplement:	April 1, 1998
Receipt Date:	April 2, 1998

Review

NDA 19-834/S-014 originaly provided for labeling revised under **PRECAUTIONS Drug Interactions.** The following paragraph was added to the beginning of the subsection:



In addition, the paragraph concerning the interaction with cimetidine was deleted.

An approvable letter was issued on January 12, 1999 in which the biopharmaceutics reviewer's recommendations were conveyed to the sponsor. The above paragraph should be replaced with the following:

PRECAUTIONS

Drug Interactions
CYP3A4 Inhibitors: Felodipine is metabolized by CYP3A4. Co-administration [redacted] CYP 3A4 inhibitors (e.g., ketoconazole, itraconazole, erythromycin, grapefruit juice, cimetidine) may lead to several-fold increases in the plasma levels of felodipine, either due to an increase in bioavailability or due to a decrease in metabolism. These increases in concentration may lead to increased effects (lower blood pressure and increased heart rate). These effects have been observed with co-administration of itraconazole (a potent CYP3A4 inhibitor). [redacted] a conservative approach to dosing felodipine should be taken. The following specific interactions have been reported:

Itraconazole: Co-administration another extended release formulation of felodipine with itraconazole resulted in approximately 8-fold increase in the AUC, more than 6-fold increase in the Cmax, and 2-fold prolongation in the half-life of felodipine.

Erythromycin: Co-administration of felodipine (Plendil) with erythromycin resulted in approximately 2.5-fold increase in the AUC and Cmax, and about 2-fold prolongation in the half-life of felodipine.

Grapefruit juice: Co-administration of felodipine with grapefruit juice resulted in more than 2-fold increase in the AUC and Cmax, but no prolongation in the half-life of felodipine.

Cimetidine: Co-administration of felodipine with cimetidine (a non-specific CYP-450 inhibitor) resulted in an increase of approximately 50% in the AUC and the Cmax, of felodipine.

The sponsor proposed the following changes to our labeling recommendations in a submission dated May 7, 1999:

PRECAUTIONS

Drug Interactions
CYP3A4 Inhibitors: Felodipine is metabolized by CYP3A4. Co-administration of ——— CYP 3A4 inhibitors (e.g. ketoconazole, itraconazole, erythromycin, grapefruit juice, cimitidine) with felodipine may lead to several-fold increases in the plasma levels of felodipine, either due to an increase in bioavailability or due to a decrease in metabolism. These increases in concentration may lead to increased effects (lower blood pressure and increased heart rate). These effects have been observed with co-administration of itraconazole (a potent CYP3A4 inhibitor). ——— Caution should be used when CYP3A4 inhibitors are co-administered with felodipine. A conservative approach to dosing felodipine should be taken. The following specific interactions have been reported:

Itraconazole: Co-administration another extended release formulation of felodipine with itraconazole resulted in approximately 8-fold increase in the AUC, more than 6-fold increase in the Cmax, and 2-fold prolongation in the half-life of felodipine.

Erythromycin: Co-administration of felodipine (Plendil) with erythromycin resulted in approximately 2,5-fold increase in the AUC and Cmax, and about 2-fold prolongation in the half-life of felodipine.

Grapefruit juice: Co-administration of felodipine with grapefruit juice resulted in more than 2-fold increase in the AUC and Cmax, but no prolongation in the half-life of felodipine.

Cimetidine: Co-administration of felodipine with cimetidine (a non-specific CYP-450 inhibitor) resulted in an increase of approximately 50% in the AUC and the Cmax, of felodipine.

Dr. Lipicky agreed with the sponsor's proposal, and the firm was asked to submit final printed labeling.

I have reviewed the final printed labeling and it is identical to the draft package insert in their May 7, 1999 submission.

Recommendation

I recommend that the application be approved.

David Roeder

dr/1-4-99

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

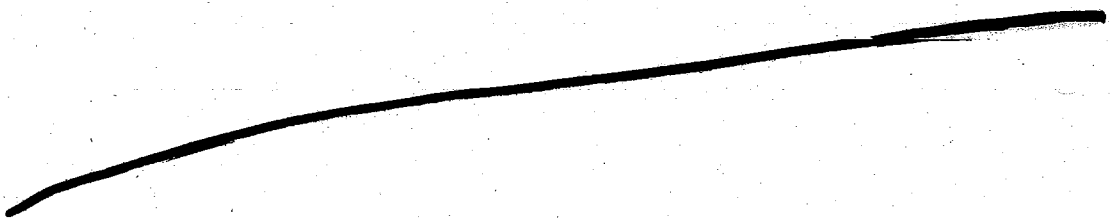
RHPM Review of Draft Labeling

JAN 12 1999

Application:	NDA 19-834/S-014 Plendil (felodipine) Tablets
Sponsor:	Astra Pharmaceuticals, L.P.
Date of Supplement:	April 1, 1998
Receipt Date:	April 2, 1998

Review

NDA 19-834/S-014 provides for draft labeling under **PRECAUTIONS Drug Interactions.** The following paragraph was added to the beginning of the subsection:



In addition, the paragraph concerning the interaction with cimetidine was deleted.

The biopharmaceutics reviewer recommended that the above paragraph be replaced with the following:

PRECAUTIONS

Drug Interactions
CYP3A4 Inhibitors: Felodipine is metabolized by CYP3A4. Co-administration ———— CYP 3A4 inhibitors (e.g. ketoconazole, itraconazole, erythromycin, grapefruit juice, cimitidine) may lead to several-fold increases in the plasma levels of felodipine, either due to an increase in bioavailability or due to a decrease in metabolism. These increases in concentration may lead to increased effects (lower blood pressure and increased heart rate). These effects have been observed with co-administration of itraconazole (a potent CYP3A4 inhibitor). ———— a conservative approach to dosing felodipine should be taken. The following specific interactions have been reported:

Itraconazole: Co-administration ————with itraconazole resulted in approximately 8-fold increase in the AUC, more than 6-fold increase in the Cmax, and 2-fold prolongation in the half-life of felodipine.

Erythromycin: Co-administration of felodipine (Plendil) with erythromycin resulted in approximately 2.5-fold increase in the AUC and Cmax, and about 2-fold prolongation in the half-life of felodipine.

Grapefruit juice: Co-administration of felodipine with grapefruit juice resulted in more than 2-fold increase in the AUC and Cmax, but no prolongation in the half-life of felodipine.

Cimetidine: Co-administration of felodipine with cimetidine (a non-specific CYP-450 inhibitor) resulted in an increase of approximately 50% in the AUC and the Cmax, of felodipine.

Recommendation

An approvable letter will be drafted with the above recommendation

David Roeder

dr/1-4-99

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