

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**19-834/S022**

***Trade Name:*** Plendil

***Generic Name:*** Felodipine

***Sponsor:*** AstraZeneca LP

***Approval Date:*** June 7, 2004

***Indications:*** The treatment of hypertension.

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***APPLICATION NUMBER:***

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*APPLICATION NUMBER:*

**19-834/S022**

**APPROVAL LETTER**



NDA 19-834/S-022

AstraZeneca LP  
Attention: Ms. Judy W. Firor  
1800 Concord Pike  
P.O. Box 8355  
Wilmington, DE 19803-8355

Dear Ms. Firor:

Please refer to your supplemental new drug application dated December 11, 2003, submitted electronically under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PLENDIL (felodipine) 2.5, 5, and 10 mg Extended-Release Tablets.

This "Changes Being Effected" supplemental new drug application provides for revisions to the **PRECAUTIONS** section of the labeling. Information has been added to include information regarding a tacrolimus drug interaction. It also includes updates to the **HOW SUPPLIED** section of the labeling, NDC, and revision date.

The proposed changes to the labeling are as follows:

1. Under **PRECAUTIONS/Drug Interactions**, the following was added after the *Anticonvulsants* paragraph:

*Tacrolimus*- Felodipine may increase the blood concentration of tacrolimus. When given concomitantly with felodipine, the tacrolimus blood concentration should be followed and the tacrolimus dose may need to be adjusted.

2. Under **HOW SUPPLIED**, the 30 count bottle was deleted for the 2.5, 5, and 10 mg tablets.
3. Updates to the package insert are as follows:
  - a. The trademark date, 2003, was added after ©AstraZeneca 2000.
  - b. The Package Insert revision date was changed from \_\_\_\_\_ to 11/03.
  - c. The NDC number was changed from \_\_\_\_\_ to 9179716 and \_\_\_\_\_ was changed to 630002-16.

We have completed our review of this supplemental application and it is approved, effective on the date of this letter, for use as recommended in the submitted electronic final printed labeling (package insert included in your submission dated December 11, 2003).

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We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Ms. Denise M. Hinton  
Regulatory Health Project Manager  
(301) 594-5333

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Acting Director  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure

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this page is the manifestation of the electronic signature.**  
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/s/

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Norman Stockbridge  
6/7/04 03:14:17 PM

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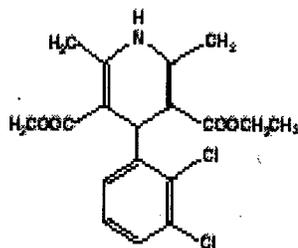
**LABELING**

9179716

630002-16

**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  $\pm$  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.

*Geriatric Use*— 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).

### **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 (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.

*Patients with Impaired Liver Function*—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 (eg, 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 (eg, 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.

*Tacrolimus*— Felodipine may increase the blood concentration of tacrolimus. When given concomitantly with felodipine, the tacrolimus blood concentration should be followed and the tacrolimus dose may need to be adjusted.

*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 61 times\*\* the maximum recommended human dose on a mg/m<sup>2</sup> 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 (61 times\*\* the maximum recommended human dose on a mg/m<sup>2</sup> 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 (61 times\*\* the maximum recommended human dose on a mg/m<sup>2</sup> basis) for periods of up to 80 weeks in males and 99 weeks in females.

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\*\* Based on patient weight of 50 kg

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 (1100 times\*\* the maximum recommended human dose on a mg/m<sup>2</sup> 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 (up to 24 times\*\* the maximum recommended human dose on a mg/m<sup>2</sup> basis) 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 0.8 to 8 times\*\* the maximum recommended human dose on a mg/m<sup>2</sup> 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 (8 times\*\* the maximum human dose on a mg/m<sup>2</sup> 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

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\*\* Based on patient weight of 50 kg

(2.1 times the maximum human dose on a mg/m<sup>2</sup> 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.

**Geriatric Use:**

Clinical studies of felodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Pharmacokinetics, however, indicate that the availability of felodipine is increased in older patients (see CLINICAL PHARMACOLOGY, Geriatric Use). In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

**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).

**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
<b><i>Body as a Whole</i></b>				
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)
<b><i>Cardiovascular</i></b>				
Palpitation	2.4 (0.0)	0.4 (0.0)	1.4 (0.3)	2.5 (0.5)
<b><i>Digestive</i></b>				
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)
<b><i>Nervous</i></b>				
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)
<b><i>Respiratory</i></b>				
Upper Respiratory				
Infection	1.8 (0.0)	3.9 (0.0)	1.9 (0.0)	0.7 (0.0)
Cough	0.3 (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)
<b>Skin</b>				
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:** *Angioedema, contusion, erythema, urticaria, leukocytoclastic vasculitis;* **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.

*Geriatric Use*—Patients over 65 years of age are likely to develop higher plasma concentrations of felodipine (see CLINICAL PHARMACOLOGY). In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range (2.5 mg daily). Elderly patients should have their blood pressure closely monitored during any dosage adjustment.

*Patients with Impaired Liver Function*—Patients with impaired liver function may have elevated plasma concentrations of felodipine and may respond to lower doses of PLENDIL; therefore, patients should have their blood pressure monitored closely during dosage adjustment of PLENDIL (see CLINICAL PHARMACOLOGY).

## 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

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

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

**Storage:**

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

PLENDIL is a trademark of the AstraZeneca group of companies

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Rev 11/03

Manufactured for: AstraZeneca LP

Wilmington, DE 19850

By: Merck & Co., Inc., Whitehouse Station, NJ, 08889 USA

9179716

630002-16

AstraZeneca 

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**19-834/S022**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## RHPM Review of Labeling

NDA: 19-834/S-022  
Drug: PLENDIL (felodipine) Extended-Release Tablets  
Sponsor: AstraZeneca LP  
Date of Document: December 11, 2003  
Date of review: May 4, 2004

### Background:

AstraZeneca LP electronically submitted this "Changes Being Effected" (CBE) for Plendil (felodipine) Extended Release Tablets to provide for revisions to the PRECAUTIONS/Drug Interactions section of the labeling to include information regarding a tacrolimus drug interaction. The Sponsor proposed to start implementing the changes in March 2004.

The date of the last approved labeling for PLENDIL was May 22, 2002. In that CBE, final printed labeling was submitted that provided for additions of leukocytoclastic vasculitis and angioedema to the **ADVERSE REACTIONS** section as part of postmarketing safety surveillance. It also included changes in the **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility and Pregnancy** subsections as requested in the Agency's August 28, 2000 letter.

### Review:

The proposed changes to the labeling are as follows:

1. Under **PRECAUTIONS/Drug Interactions**, the following was added after the 8<sup>th</sup> subsection:

*Tacrolimus*- Felodipine may increase the blood concentration of tacrolimus. When given concomitantly with felodipine, the tacrolimus blood concentration should be followed and the tacrolimus dose may need to be adjusted.

2. Under **HOW SUPPLIED**, the 30 count bottle was deleted for the 2.5, 5, and 10 mg tablets.
3. General updates were made to the labeling as follows:
  - a. The trademark date was changed from 2000 to 2003.
  - b. The Package Insert revision date was changed from \_\_\_\_\_ to 11/03.
  - c. The NDC was changed from \_\_\_\_\_ to 9179716-and \_\_\_\_\_ was changed to 630002-16.

**Recommendation:**

The labeling submitted electronically on December 11, 2003 was compared to their last approved labeling dated May 22, 2002. No additional changes were noted with the exception of those listed above. An approval letter will be drafted for Dr. Stockbridge's signature, as the changes were made in accordance with 21CFR 314.70 (c)(2).

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Denise M. Hinton  
Regulatory Health Project Manager, HFD-110

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/s/

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Denise Hinton  
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CSO

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**19-834/S022**

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

## CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

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**NDA:** 19,834 SLR 022  
**Submission Date:** December 11, 2003  
**Drug Name:** Plendil (felodipine)  
**Formulation:** Extended release tablets  
**Applicant:** AstraZeneca LP  
**Submission:** Special Supplemental NDA, (Changes Being Effected, CBE)  
**Reviewer:** Elena V. Mishina, Ph.D.

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AstraZeneca LP is seeking approval of labeling changes for Plendil (felodipine ER) based on submission of the information in the supplemental NDA 19,834. Plendil (felodipine ER) is an extended release tablet formulation of felodipine, a dihydropyridine calcium antagonist with a high degree of vascular selectivity.

NDA 19-834 SLR-022 includes an article published in the literature, labeling history, revised labeling text and final printed package insert (PI). The final printed PI provided changes in the label including the changes under PRECAUTIONS/Drug Interactions.

The proposed changes are as follows:

Under **PRECAUTIONS/Drug Interactions**, the following was added after the 8<sup>th</sup> subsection:

“Tacrolimus-Felodipine may increase the blood concentration of tacrolimus. When given concomitantly with felodipine, the tacrolimus blood concentration should be followed and the tacrolimus dose may need to be adjusted”.

The reviewer performed the literature search based on key words: “felodipine drug interaction” (104 references); “tacrolimus and felodipine” (10 references).

Ten references were reviewed:

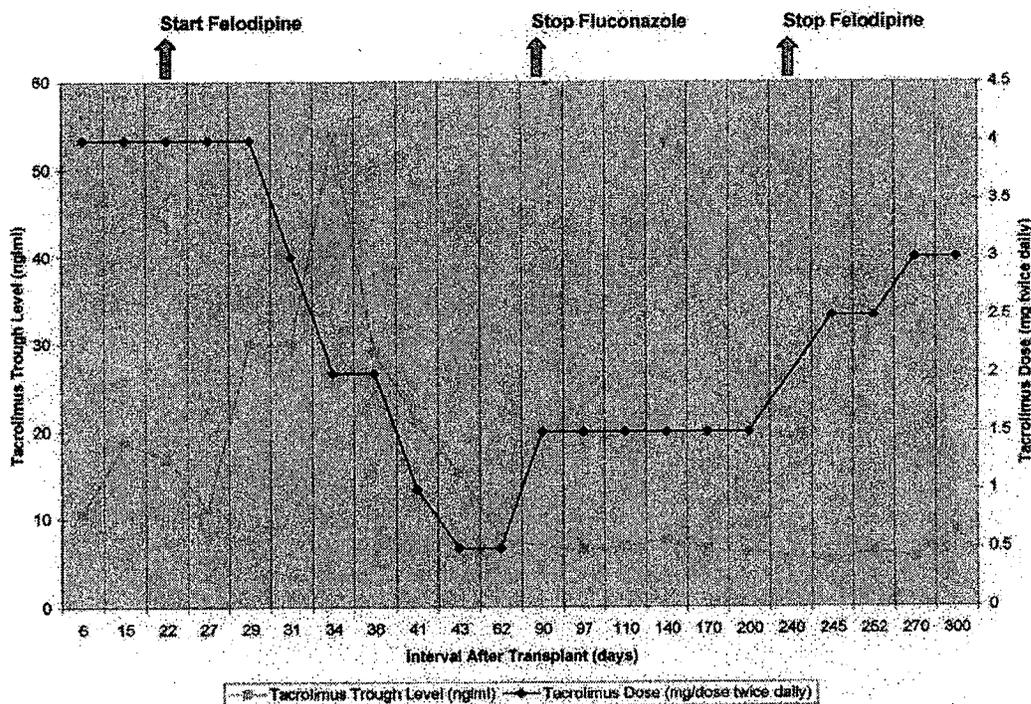
- 1: Wu CY, Benet LZ. Disposition of tacrolimus in isolated perfused rat liver: influence of troleandomycin, cyclosporine, and gg918. *Drug Metab Dispos.* 2003 Nov;31(11):1292-5.
- 2: Benet LZ, Cummins CL, Wu CY. Transporter-enzyme interactions: implications for predicting drug-drug interactions from in vitro data. *Curr Drug Metab.* 2003 Oct;4(5):393-8.
- 3: Butani L, Berg G, Makker SP. Effect of felodipine on tacrolimus pharmacokinetics in a renal transplant recipient. *Transplantation.* 2002 Jan 15;73(1):159-60.
- 4: Pea F, Furlanut M. Pharmacokinetic aspects of treating infections in the intensive care unit: focus on drug interactions. *Clin Pharmacokinet.* 2001;40(11):833-68.
- 5: Chiou WL, Chung SM, Wu TC, Ma C. A comprehensive account on the role of efflux transporters in the gastrointestinal absorption of 13 commonly used substrate drugs in humans. *Int J Clin Pharmacol Ther.* 2001 Mar;39(3):93-101.
- 6: Krisp A, Hoffmann R. [Letter concerning the article by E.C.Bornhovd, E.Schuller, T.Bieber, A.Wollenberg: "Immunosuppressive macrolides and their use in dermatology". *Der Hautarzt* (2000) 51:646-654] *Hautarzt.* 2001 Mar;52(3):255-6.
- 7: Venkatakrishnan K, von Moltke LL, Greenblatt DJ. Effects of the antifungal agents on oxidative drug metabolism: clinical relevance. *Clin Pharmacokinet.* 2000 Feb;38(2):111-80.

- 8: Albengres E, Le Louet H, Tillement JP. Systemic antifungal agents. Drug interactions of clinical significance. *Drug Saf.* 1998 Feb;18(2):83-97.
- 9: Grobecker HF, Riebel K, Wellenhofer T. Cyclosporine A-induced hypertension in SHR and WKY: role of the sympatho-adrenal system. *Clin Exp Pharmacol Physiol Suppl.* 1995 Dec;22(1):S94-5.
- 10: Bergstrand H, Lundquist B. Human basophil histamine release is differently affected by inhibitors of calmodulin, diacylglycerol kinase and peptidyl prolyl cis-trans isomerase in a secretagogue specific manner. *Allergy.* 1992 Aug;47(4 Pt 2):353-61.

From the listed publications only #3 was related to the interaction in vivo (a single case described in clinic) between felodipine and tacrolimus.

A renal transplant recipient developed a previously unreported interaction while receiving tacrolimus and felodipine. A 13-year-old boy with renal dysplasia, received a living-related renal transplant from his mother. Due to the development of hypertension, the patient was started on felodipine (2.5 mg/day) on day 15 post-operation. His other medications at this time were prednisolone 50 mg/day, tacrolimus 4 mg BID (0.2 mg/kg/day), mycophenolate mofetil 500 mg BID, oral ganciclovir 1 g TID, trimethoprim-cotrimoxazole 80 mg QD, and fluconazole 100 mg QD. Laboratory studies showed stable 12-hr tacrolimus trough levels ranging from 10.6 to 20.0 ng/ml.

Figure 1 below illustrates the changes in tacrolimus plasma concentrations and dose in regard to the administration of felodipine and fluconazole.



Two weeks after starting felodipine, his tacrolimus trough level became very high (>30 ng/ml); therefore, the tacrolimus dose was reduced (3 mg BID). The trough tacrolimus plasma concentrations 3 days later (53.9 ng/mL) continued to increase. A further dose reduction was

made (2 mg BID and then to a final dose of 0.5 mg BID) to attain stable target trough levels (8.9-9.4 ng/ml). At discontinuation of fluconazole 3 months after transplantation, this patient's tacrolimus dose needed to be increased to 1.5 mg twice daily to maintain target trough levels. An abbreviated tacrolimus pharmacokinetic profile at this dose demonstrated the 12-hr area under the concentration time curve (AUC) to be 126.31 ng.hr/ml. Eight months after transplantation (4.5 months after the AUC determination), due to normalization of the patient's blood pressure, his felodipine was stopped. One week later, the tacrolimus trough level dropped (5.1 ng/ml), necessitating a dose increase to 2.5 mg twice daily. The dose was further increased to 3 mg twice daily 1 month later when the tacrolimus trough drifted down again (5.5 ng/ml). Once the patient was maintained on this stable dose for a month, a repeat abbreviated pharmacokinetic profile was obtained. The 12-hr AUC (124.01 ng.hr/ml) was similar to the first value, which had been obtained on half the present tacrolimus dose.

This report demonstrates the significant interaction between felodipine and tacrolimus, resulting in a three-fold elevation in the plasma tacrolimus trough concentrations and a two-fold elevation in his dose-adjusted AUC after starting felodipine.

There was no formal study to investigate the interactions between felodipine and tacrolimus. However, CYP3A4 is involved in the metabolism of both of them and therefore, this interaction is not unpredictable. In the PI for tacrolimus, the following information is in the **PRECAUTIONS/Drug Interaction** Section:

“Since tacrolimus is metabolized mainly by the CYP3A enzyme systems, substances known to inhibit these enzymes may decrease the metabolism or increase bioavailability of tacrolimus as indicated by increased whole blood or plasma concentrations. Drugs known to induce these enzyme systems may result in an increased metabolism of tacrolimus or decreased bioavailability as indicated by decreased whole blood or plasma concentrations. Monitoring of blood concentrations and appropriate dosage adjustments are essential when such drugs are used concomitantly.”

The caution should be exercised when felodipine and tacrolimus are coadministered due to the severe adverse effects which can be observed in case of tacrolimus overdose.

**Comment:**

The sponsor's proposed labeling changes seem reasonable and should be included in the PI.

**Recommendation:**

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed a supplemental NDA 19-834 SLR 022. The proposed labeling changes are acceptable.

Clinical Pharmacology Review, NDA 19-834, Plendil  
Elena Mishina

5/17/04

Date \_\_\_\_\_

\_\_\_\_\_  
Elena Mishina, Ph. D.  
Clinical Pharmacology Reviewer

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Bach Nhi Beasley, Pharm. D.  
Acting Cardio-Renal Team Leader

cc list: NDA 19-834, MehulM, PMarroum, MishinaE, HFD 110 BIOPHARM

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Nhi Beasley  
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