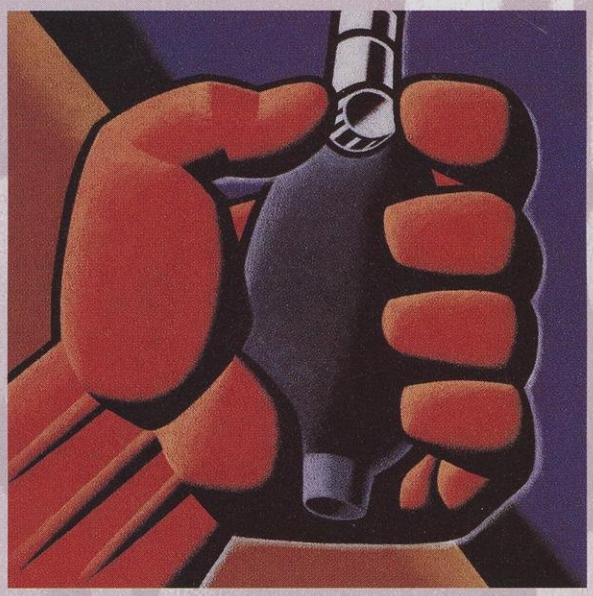
Plendil advertisement.

[s.l.]: [s.n.], 1998

The more you know, the better it looks.



In hypertension

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The most common unwanted effects are peripheral edema and headache.
PLENDIL is contraindicated in patients who are hypersensitive to this product.

24-hour control

Plendil®

(felodipine) *Tablets, 2.5 mg, 5 mg, 10 mg*

* This study did not evaluate the 2.5 mg dose for either product.

† 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. 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.

‡ The clinical significance has not been established.

§ Average Wholesale Price (AWP) at the recommended starting dosages for each product.

Source: Medi-Span, Inc. July 1998

Please see brief summary of Prescribing Information on the next page.

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24-hour control

Plendil®

(felodipine) *Tablets, 2.5 mg, 5 mg, 10 mg*

The more you know, the better it looks.

Starting dose: 5 mg once a day.
2.5 mg once a day for patients over 65 or those with liver impairment.

Most commonly dispensed dose[3]:
5 mg once a day.

Recommended dosage range:
2.5 mg to 10 mg once a day.

PLENDIL should be swallowed whole and not crushed or chewed.

References:

1. Koenig W. Efficacy and tolerability of felodipine and amlodipine in the treatment of mild to moderate hypertension. *Drug Invest.* 1993;5:200-205.
2. Landahl S, Edgar B, Gabrielsson M, et al. Pharmacokinetics and blood pressure effects of felodipine in elderly hypertensive patients: a comparison with young healthy subjects. *Clin Pharmacokinet.* 1988;14:374-383.
3. Data on file, DA-PLNI9.

BRIEF SUMMARY

PLENDIL® (FELODIPINE) EXTENDED-RELEASE TABLETS

Before prescribing, please consult full Prescribing Information.

CONTRAINDICATIONS: Hypersensitivity to this product.

PRECAUTIONS: ***General: Hypotension:*** May occasionally precipitate significant hypotension and, rarely, syncope. 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 sections of full Prescribing Information.)

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

Take PLENDIL tablets whole; do not crush or chew. Patients should be told that mild gingival hyperplasia (gum swelling) has been reported. Good dental hygiene decreases its incidence and severity.

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.

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* section of full Prescribing Information.

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 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

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. (See full Prescribing Information.)

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® (Felodipine) 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 (0.9)	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	0.3 (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)
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® (Felodipine).

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; ***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 percent of patients in controlled studies. This condition may be avoided or may regress with improved dental hygiene. (See PRECAUTIONS, *Information for Patients* section.)

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* section of full Prescribing Information.)

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.

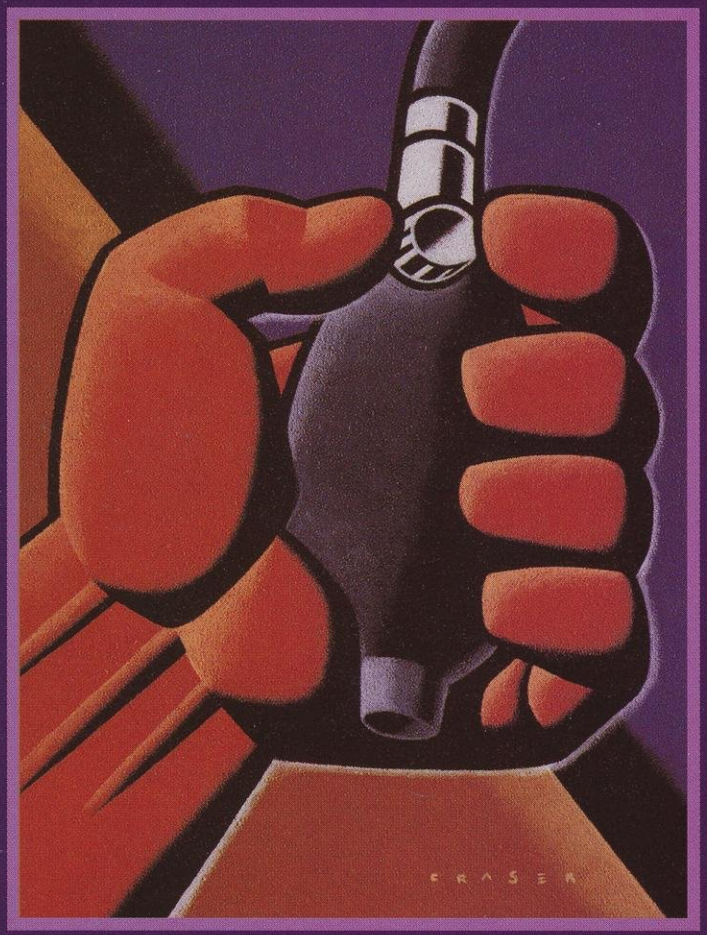
Distributed by:

ASTRA®
Astra Pharmaceuticals

Wayne, PA 19087, USA
Manufactured by: Merck & Co., Inc., West Point, PA 19486, USA

*Registered trademark of Astra AB.
†Based on patient weight of 50 kg

The more you know, the better it looks.



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Source: Medi-Span, Inc. March 1998

Plendil is a registered trademark of Astra AB. Norvasc is a registered trademark of Pfizer, Inc.

Please see brief summary of Prescribing Information on the next page.

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