CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-668/S-003

Final Printed Labeling
Lexel®
(enalapril maleate-felodipine ER) TABLETS

USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Lexel® should be discontinued as soon as possible. See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION
Lexel® (enalapril maleate-felodipine ER) is a combination product, consisting of an outer layer of enalapril maleate surrounding a core tablet of an extended-release felodipine formulation. Enalapril maleate is the maleate salt of enalapril, the ethyl ester of a long-acting angiotensin converting enzyme inhibitor, enalaprilat. Enalapril maleate is chemically described as (S)-1-[N-(ethylcarbethoxy)-2-(3-phenylpropyl)-L-alanyl]-L-proline, (2S,3S)-2-butenedioic acid. Its empirical formula is \( C_{28}H_{31}N_{2}O_{6} \), and its structural formula is:

Felodipine is a dihydropyridine calcium channel blocker that reduces the influx of Ca** by an effect on the voltage-dependent calcium channels in vascular smooth muscle and cultured rabbit aortic cells, and blocks potassium-induced contraction of the rat portal vein. Pharmacologic 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 consequences of vasodilation produced by felodipine include a modest, short-lived reflex increase in heart rate. A mild diuretic effect is seen in several animal species and man, but most of the effects of felodipine are accounted for by its effects on peripheral vascular resistance.

Pharmacokinetics and Metabolism
Concomitant administration of enalapril and felodipine as an extended-release formulation has little effect on the bioavailability of either compound. The rate and extent of absorption of enalapril from Lexel® is not significantly different from that of enalapril in IASOTES® (enalapril maleate). The rate and extent of absorption of felodipine from Lexel® has not been directly compared to the extended-release formulation of felodipine in PLENOL® ** (Felodipine). Following oral administration of Lexel®, peak concentrations of enalapril occur within about one hour. Enalapril is hydrolyzed to enalaprilat, which is a more potent angiotensin converting enzyme inhibitor than enalapril. Peak serum concentrations of enalaprilat occur about three hours after an oral dose of Lexel®. Based on urinary recovery, the extent of absorption of enalapril is approximately 60%. Peak concentrations of the isomers of felodipine are generally seen at 3-6 hours after administration of Lexel®. Following oral administration of felodipine, bioavailability is almost completely absorbed and undergoes extensive first-pass metabolism; the systemic bioavailability of felodipine ER is approximately 20%. When Lexel® is taken with food (a substantial meal of 650 kcal or greater), some of the pharmacokinetics of its components are changed. Although the AUC(0-t) of felodipine is not changed, the peak concentration of its isomers is almost doubled, and the trough concentration is approximately halved. The bioavailability of enalapril, as measured by total urinary recovery of enalaprilat, is slightly reduced. As with other dihydropyridine calcium channel blockers, the bioavailability of felodipine was increased when taken with grapefruit juice, compared to when taken with water or orange juice. The systemic plasma clearance of felodipine in young healthy subjects is about 0.8 L/min, and the apparent volume of distribution is 10 L/kg. Approximately 90% of felodipine is bound to plasma proteins. Following administration of \( ^{14} \)C-labeled intravenous or immediate-release oral 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 was recovered in the urine and feces (<0.2%). Six metabolites, which account for 23% of the oral dose, have been identified, none has significant vasodilating activity. Following oral administration of the immediate-release formulation, the plasma levels of felodipine declined exponentially with a mean terminal half-life of 11 to 16 hours. Excretion of enalaprilat and enalapril is primarily renal. Approximately 94% of the dose is recovered in the urine and 6% in the feces. The principal components of urine are enalaprilat, accounting for about 40% of the dose, and intact enalapril. There is no evidence of metabolites of enalaprilat, other than enalapril. The serum concentration profile of enalaprilat exhibits a prolonged terminal phase, apparently representing a small fraction of the administered dose that has bound to ACE. The amount bound does not increase with dose, indicating a saturable site of binding. The effective half-life for accumulation of enalaprilat following multiple doses of enalapril maleate is 11 hours.

CLINICAL PHARMACOLOGY
Mechanism of Action
The two components of Lexel® have complementary antihypertensive actions. Enalapril is a prodrug; following oral administration, it is bioactivated by hydrolysis of the ethyl ester to enalaprilat, which is the active angiotensin converting enzyme (ACE) inhibitor. Enalaprilat inhibits angiotensin-1 converting enzyme in humans and animals. ACE is a peptide dipeptidase that catalyzes the conversion of angiotensin I to the vasconstrictive substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. The beneficial effects of enalaprilat in hypertension appear to result primarily from suppression of the renin-angiotensin-aldosterone system.
Lexxel® (enalapril maleate-felodipine ER) Tablets

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 for young volunteers (mean age 26). At steady state, the 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.

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

Blood Brain Barrier and Blood Placental Barrier—A number of studies have shown that felodipine crosses the blood brain barrier. The plasma to brain concentration ratio of felodipine is about 20:1. Felodipine cross the placenta. Fetal plasma levels of felodipine are similar to maternal plasma levels. Studies in dogs indicate that enalapril crosses the blood brain barrier poorly, if at all; enalaprilat does not enter the brain. Multiple does of enalapril maleate in rats do not result in accumulation in any tissues. Milk of lactating rats contains radioactivity following administration of 14C enalapril maleate. Radioactivity was found to cross the placenta following administration of labeled drug to pregnant hamsters.

Pharmacodynamics
Administration of enalapril maleate in patients with hypertension of severity ranging from mild to severe results in a reduction of both supine and standing blood pressure, usually with no orthostatic component. Symptomatic postural hypotension is infrequent with enalapril alone, although it might be anticipated in volume-depleted patients. In most patients studied, after oral administration of a single dose of enalapril, onset of antihypertensive activity was seen at one hour, with peak reduction of blood pressure achieved by 4 to 6 hours. At recommended doses, antihypertensive effects have been maintained for at least 24 hours. In some patients the effects may diminish toward the end of the dosing interval.

In most patients, achievement of optimal blood pressure reduction may require several weeks of therapy. The antihypertensive effects of enalapril have continued during long-term therapy. Abrupt withdrawal of enalapril has not been associated with a rapid increase in blood pressure. In hemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with an increase in cardiac output and little or no change in heart rate. Following administration of enalapril maleate, there is an increase in renal blood flow, glomerular filtration rate is usually unchanged. The effects appear to be similar in patients with renovascular hypertension.

In a clinical pharmacology study, indomethacin or sulindac was administered to hypertensive patients receiving enalapril. In this study there was no evidence of a blunting of the antihypertensive action of enalapril.

The effect of felodipine on blood pressure is principally a consequence of a dose-related decrease in peripheral vascular resistance. Blood pressure response following administration of felodipine ER to hypertensive patients is correlated with dose and plasma concentrations of felodipine. A reduction in blood pressure generally occurs within 2 to 5 hours. During chronic administration, substantial blood pressure central lasts for 24 hours, with trough reductions in diastolic blood pressure approximated 40-50% of peak reductions. 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.

Felodipine has no significant effect on cardiac conduction (PR, QT, and HV 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.

In an 8-week, fixed-dose, parallel-group, double-blind study, 707 hypertensive patients were randomized among all possible combinations of enalapril (0, 5, or 20 mg), and extended-release felodipine (0.2, 5, or 10 mg), both taken once daily. Each of the non-placebo combinations was significantly more effective than placebo in reducing seated systolic and diastolic blood pressure at peak (3 to 5 hours after dosing) and trough (24 hours after dosing). Enalapril and felodipine contributed additively to the effect, so that the active combination was significantly more effective than either of its component monotherapies. Most of the drug effect seen at peak was still present at trough. The efficacy of combination therapy relative to monotherapy was not significantly affected by race, sex or age.

During chronic dosing with LEXXEL, the maximum reduction in blood pressure is generally achieved after one to two weeks. The antihypertensive effects of LEXXEL have continued during chronic therapy for at least one year.

INDICATIONS AND USAGE
LEXXEL is indicated for the treatment of hypertension. This fixed combination drug is not indicated for the initial therapy of hypertension. (See DOSAGE AND ADMINISTRATION.)

In using LEXXEL, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that enalapril (a component of LEXXEL) does not have a similar risk. (See WARNINGS, Neutropenia/Agranulocytosis.)

In considering use of LEXXEL, it should be noted that black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks. (See WARNINGS, Angioedema.)

CONTRAINDICATIONS
LEXXEL is contraindicated in patients who are hypersensitive to any component of this product. Because of the enalapril component, LEXXEL is contraindicated in patients with a history of angioedema related to previous
WARNINGS

Anaphylactic and Possibly Related Reactions—Presumably because angioedema-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including LEXXEL) may be subject to a variety of adverse reactions, among them angioedema.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with angioedema-converting enzyme inhibitors, including enalapril. This may occur at any time during treatment. In such cases LEXXEL should be promptly discontinued, and appropriate therapy and monitoring should be provided until full recovery. Anaphylaxis, involving the airways, skin, and/or gastrointestinal tract, has also been reported in patients receiving angioedema-converting enzyme inhibitors. Where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although anaphylaxis has been observed in patients receiving angioedema-converting enzyme inhibitors. Therefore, it is important to assess the risk of angioedema before beginning treatment with angioedema-converting enzyme inhibitors.

Hypotension—LEXXEL may occasionally cause symptomatic hypotension. Excessive hypotension is rare in uncomplicated hypertensive patients treated with enalapril. However, patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia, and rarely with acute renal failure, may have an increase in diuretic dose, an increase in diuretic dose and renal dialysis, or severe volume and/or salt depletion. If this occurs, patients should be treated with high-flux membranes and treated concomitantly with an ACE inhibitor. Several cases of progressive renal failure, including renal insufficiency and acute renal failure, have been reported in patients receiving enalapril who concurrently received other drugs that may cause hypotension.

Neutropenia/Agranulocytosis—Anaphylaxis-related hypotension may result in a myocardial infarction or cerebrovascular accident. If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of enalapril maleate, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, volume expansion or discontinuation of enalapril or diuretic may be necessary. If a patient suffers a myocardial infarction or cerebrovascular accident, it may be necessary to discontinue angiotensin-converting enzyme inhibitors. (See ADVERSE REACTIONS.)

Hepatic Failure—Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestasis and progresses to fulminant hepatic necrosis and/or death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should be considered for liver transplantation or appropriate medical follow-up.

Fetal/Neonatal Morbidity and Mortality—ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, LEXXEL should be discontinued as soon as possible. The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and rarely, neonatal death. Cerebrovascular hemorrhage has been reported in infants born to patients treated with angiotensin-converting enzyme inhibitors. In those cases, discontinuation of therapy was not associated with fetal or neonatal injury. Cerebrovascular hemorrhage may occur in infants born to patients treated with angiotensin-converting enzyme inhibitors. In those cases, discontinuation of therapy was not associated with fetal or neonatal injury. Cerebrovascular hemorrhage may occur in infants born to patients treated with angiotensin-converting enzyme inhibitors. In those cases, discontinuation of therapy was not associated with fetal or neonatal injury. Cerebrovascular hemorrhage may occur in infants born to patients treated with angiotensin-converting enzyme inhibitors. In those cases, discontinuation of therapy was not associated with fetal or neonatal injury.

Cough—Presumably due to the inhibition of the degradation of endothelial bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, although the incidence may vary. Cough should be considered a potential adverse reaction to enalapril. In patients undergoing major surgery or during anesthesia with agents that produce hypertension, enalapril may block angiotensin II formation secondary to compensatory renin release.

LEXXEL (enalapril maleate-lisinopril ER) Tablets

These adverse effects do not appear to have resulted from intravenous ACE inhibitor exposure that has been limited to the first trimester. Mothers, whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of LEXXEL as soon as possible.

Rarity (probably less often than once in every thousand pregnancies), no other adverse effects of ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intracranial environment.

If oligohydramnios is observed, LEXXEL should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or fetal biophysical profile (FBP) may be appropriate, depending on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to ACE inhibitors may show signs of hypotension, oliguria, and hyponatremia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hyponatremia and/or substituting for disordered renal function. Enalapril, which crosses the placenta, has been removed from the female circulation by peritoneal dialysis in monkeys with clinical benefit, and theoretically may be removed by exchange dialysis, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats and rabbits. On a body surface area basis, the doses used were 57 times and 12 times, respectively, the maximum recommended human daily dose (MHD).

In rats administered the combination of enalapril and feldene (enalapril [E]; 1-9 mg/kg/d, feldene [F]; 2.5 mg/kg/d), an increased incidence of fetuses and dams of reduced fetal weight was observed. However, there was no evidence of this effect in the offspring piscine. In mice, at a dose of 225 mg/kg/d, there was an increased incidence of both early and late in utero deaths. Other than a transient and slight decrease in body weight gain in the first generation offspring, there were no apparent effects in offspring with regard to sexual maturation, behavioral development, fertility or fecundity.

Enalapril maleate given to pregnant mice (enalapril (E); 20, 80, and 400 mg/kg/d) and rats (enalapril (E); 27 mg/kg/d) produced plasma levels (C) and AUC values of enalapril/enalaprilat that were 76 to 410-fold greater and plasma levels of feldene that were 301 to 47-fold greater than those expected in humans (non-pregnant) at the dose to be used in humans.

PRECAUTIONS

General

Impaired Renal Function—As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals treated with enalapril. In patients with severe renal failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical trials in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood creatinine and serum creatinine were observed in 20% of patients treated with enalapril. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some enalapril-treated patients with hypertension or heart failure, with no apparent pre-existing renal vascular disease, have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalapril or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hyperkalemia—Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials treated with enalapril alone. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia has been stated as a contraindication to discontinuation of therapy in 0.2% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril. (See Drug Interactions.)

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 feldene. (See DOSAGE AND ADMINISTRATION.)

Cough—Presumably due to the inhibition of the degradation of endothelial bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, although the incidence may vary. Cough should be considered a potential adverse reaction to enalapril. In patients undergoing major surgery or during anesthesia with agents that produce hypertension, enalapril may block angiotensin II formation secondary to compensatory renin release.

Patient Information

LEXXEL Tablets (enalapril maleate and feldene ER) Tablets (enalapril maleate-lisinopril ER) Tablets
If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion. 

Perinatal Fetal—Perinatal edema, generally mild and not associated with general fluid retention, was the most common adverse event in the feldipine clinical trials. The incidence of perinatal edema was both dose and age dependent. This adverse event generally occurs within 2-3 weeks of the initiation of treatment.

Information for Patients

Patients should be instructed to take LEXELL whole and not to divide, crush or chew the tablet.

All patients should be advised to consult their physician if they experience any of the following conditions:

Arthrograms—Arthrograms, including long axial edema, may occur at any time during treatment with angiotensin converting enzyme inhibitors, including enalapril. Patients should be so advised and told to report immediately any symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypertension—Patients should be cautioned to report light-headedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue LEXELL until they have consulted with the prescribing physician. All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduced fluid volume. Other causes of volume depletion, such as vomiting or diarrhea, may also lead to a fall in blood pressure, patients should be advised to consult with the physician.

Hyperkalemia—Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neuropathy—Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neuropathy.

Pregnancy—Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should be also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Gingival Hyperplasia—Patients should be told that mired 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 LEXELL is warranted on long-term use and the effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Hypertension—Patients on Diuretic Therapy: Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release—The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Agents Increasing Serum Potassium—Enalapril attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or other agents increasing serum potassium may lead to significant increases in serum potassium. Therefore, it is recommended that these agents be used with caution and with frequent monitoring and with caution.

Lithium—Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which decrease elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant anilpril and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

Beta-Blocking Agents—Enalapril has been used concomitantly with beta adrenergic-blocking agents without evidence of clinically significant adverse interactions.

A pharmacokinetic study of feldipine in conjunction with metoprolol demonstrated no significant effects on the pharmacokinetics of feldipine. The AUC and Cmax of metoprolol, however, were increased approximately 31% and 38%, respectively. In controlled clinical trials, however, beta blockers including metoprolol were concurrently administered with feldipine and were well tolerated.

Clofibrate—In healthy subjects, pharmacokinetic studies showed an approximately 50% increase in the area under the plasma concentration-time curve (AUC) as well as the Cmax of feldipine when given concomitantly with clofibrate. It is anticipated that a clinically significant interaction may occur in some hypertensive patients.

Diogest—Enalapril has been used concomitantly with digoxin without evidence of clinically significant adverse interactions.

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

Anticonvulsants—In a pharmacokinetic study, maximum plasma concentrations of feldipine were considerably lower in patients on long-term anticonvulsant therapy (e.g., phenytoin, carbamazepine, or phenobarbital) than in healthy volunteers. In such patients, the mean area under the feldipine plasma concentration-time curve was reduced to approximately 85% 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 feldipine was given concomitantly with indomethacin or spironolactone.

Enalapril has been used concomitantly with methyldopa, nitrites, hydralazine, and prazosin without evidence of clinically significant adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term carcinogenicity tests have been performed with the combination. Enalapril-feldipine was not mutagenic with or without metabolic activation in vivo or in vitro assays. Enalapril was not clastogenic in the Chinese hamster ovary (CHO) mammalian cell cytogenetics assay. An in vivo mouse bone marrow cytogenetics assay was not negative.

In rats given enalapril-feldipine, there was no effect on fertility in males at doses up to 9.9 mg/kg/day or in females at doses up to 17.3/22.5 mg/kg/day.

There was no evidence of a tumorigenic effect when enalapril was administered for 105 weeks to male and female rats at doses up to 90 mg/kg/day or for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively. These doses are 25 times (in rats and female mice) and 13 times (in male mice) the maximum recommended human daily dose (MRHDD) when compared on a body surface area basis.

Neither enalapril maleate nor the active isomer of feldipine in the Ames bacterial mutagenicity test or in vitro mammalian cell mutation assay with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: bacterial reverse mutation assay with S. typhimurium and E. coli; sister chromatid exchange with cultured mammalian cells; and the micronucleus test with mice, as well as in an in vivo cytogenetic study using mouse bone marrow.

There were no adverse effects on reproductive performance of male and female rats treated with up to 90 mg/kg/day of enalapril (20 times the MRHDD when compared on a body surface area basis).

In a 2-year carcinogenicity study in rats fed feldipine at doses of 7.7, 23.1 or 69.3 mg/kg/day (up to 20 times the maximum recommended human dose on a mg/m² basis), a dose-related increase in the incidence of benign adenocarcinoma of the liver in male rats (Leydig cell tumors) was observed in treated male rats. These tumors were not observed in a similar study in mice at doses up to 136.8 mg/kg/day (38 times the maximum recommended human dose on a mg/m² basis). Feldipine at the doses employed in the 2-year rat study has been shown to lower total liver 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 the 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 any of the studies or with chronic administration in mice and dogs. The latter species, like man, has no anatomical structure comparable to the esophageal groove.

Feldipine 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. Feldipine did not display any mutagenic activity in vitro in the Ames bacterial mutagenic test or in the mouse lymphoma forward mutation assay. No clastogenic potential was seen in vitro in the mouse micronucleus test or at oral doses up to 2500 mg/kg (506 times the maximum recommended human dose on a mg/m² basis) or in vivo in a human lymphocyte chromosomal 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 feldipine on reproductive performance.

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters). See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Teratogenic Effects—Studies in pregnant rabbits administered doses of feldipine 0.48, 1.2, 2.3, and 4.6 mg/kg/day (from 0.4 to 4 times1 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 feldipine. In a teratogenic study in cynomolgus monkeys, no reductions 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 feldipine doses of 9.6 mg/kg/day (4 times1 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).

1Based on patient weight of 50 kg
**Lexel® (enalapril maleate-felodipine ER) Tablets**

**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.

These are no adequate and well-controlled studies with felodipine 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**

Enalapril and enalaprilat are detected in human breast milk. It is not known whether felodipine administered as monotherapy is secreted in human milk. Studies of the combination of enalapril and felodipine in rats indicate that felodipine concentrates in milk to a level almost ten-fold that found in plasma. Because of the potential for serious adverse reactions from enalapril and felodipine in the infant, a decision should be made either to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Therefore, caution should be exercised when LEEXEL is given to a nursing mother.

**Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

**ADVERSE REACTIONS**

In a factorial study, combinations of enalapril at doses of 0, 5, and 10 mg and felodipine ER at doses of 0, 2.5, 5, and 10 mg were evaluated for safety in more than 700 patients with hypertension. In addition more than 500 patients received various combinations of enalapril (5 or 10 mg) and felodipine ER (2.5, 5, or 10 mg) with or without hydrochlorothiazide (12.5 mg) in an open-label study up to 52 weeks (mean 33 weeks). Adverse events were similar to those described with the individual components.

In general, treatment with enalapril maleate-felodipine ER was well tolerated and adverse events were mild and transient in nature. In the placebo-controlled, double-blind trial, discontinuation of therapy due to adverse events considered related (possibly, probably or definitely) occurred in 2.8% vs 1.3% of patients treated with the combination or placebo, respectively. The most frequently observed clinical adverse events considered related to treatment with the combination were headache, edema or swelling, and dizziness.

Clinical adverse events considered related (possibly, probably, or definitely) to treatment with enalapril-felodipine ER that occurred with an incidence of 1% or greater with the combination during the placebo-controlled, double-blind trial are compared to individual components and placebo in the table below:

### Percent of Patients with Adverse Events in the Double-Blind Trial

(Percent discontinuation shown in parentheses)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Enalapril</th>
<th>Enalapril ER</th>
<th>Felodipine ER</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=319</td>
<td>N=133</td>
<td>N=176</td>
<td>N=79</td>
<td></td>
</tr>
</tbody>
</table>

**Body as a Whole**

<table>
<thead>
<tr>
<th>Event</th>
<th>Enalapril</th>
<th>Enalapril ER</th>
<th>Felodipine ER</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema/Swelling</td>
<td>4 (0.3)</td>
<td>2 (0.8)</td>
<td>10 (1.7)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Asthenia/Fatigue</td>
<td>1.9 (0.0)</td>
<td>2 (0.8)</td>
<td>9 (0.5)</td>
<td>3 (0.8)</td>
</tr>
</tbody>
</table>

**Nervous/Psychiatric**

<table>
<thead>
<tr>
<th>Event</th>
<th>Enalapril</th>
<th>Enalapril ER</th>
<th>Felodipine ER</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>10 (3.6)</td>
<td>3 (0.0)</td>
<td>10 (2.1)</td>
<td>7 (1.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (1.3)</td>
<td>1 (0.0)</td>
<td>3 (0.6)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

**Respiratory**

<table>
<thead>
<tr>
<th>Event</th>
<th>Enalapril</th>
<th>Enalapril ER</th>
<th>Felodipine ER</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>2 (0.6)</td>
<td>2 (0.0)</td>
<td>2 (0.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Skin</td>
<td>1 (0.3)</td>
<td>0 (0.0)</td>
<td>2 (0.1)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

**Combination of dose of 5 and 20 mg daily**

**Combination of dose 2.5 and 10 mg daily**

Other clinical adverse events, considered related (possibly, probably, or definitely) to treatment with enalapril-felodipine ER that occurred with an incidence of less than 1% in the placebo-controlled, double-blind trial are listed below. These events are listed in order of decreasing frequency within each category.

**Body as a Whole:** Gynecomastia, edema, dermatological effects, chest pain, hypotension, edema, tachycardia, premature ventricular contraction, increased blood pressure, **Dyspepsia:** dry mouth, constipation, dysphagia, tachycardia, hallucination, vomiting, diarrhea, nausea, anorectal pain.

**Cardiovascular:** Palpitations, hypertension, bradycardia, premature ventricular contraction, increased blood pressure.

**Dizziness:** Dizziness, syncope, unsafe, orthostatic effects, chest pain, hypotension, bradycardia, premature ventricular contraction, increased blood pressure.

**Metabolic:** Gout, **Musculoskeletal:** Neck pain, joint swelling, **Nervous/Psychiatric:** insomnia, nervousness, dizziness, ataxia, agitation, paresthesia, tremor.

**Respiratory:** Dyspnea, respiratory congestion, pharyngeal discomfort, dry throat.

**Skin:** Itch, angioedema, pruritus, alopecia, dry skin.

**Special Senses:** Increased intraocular pressure, **Urogenital:** Impotence, hallucinations.

Other frequently reported adverse events were seen in clinical trials with enalapril-felodipine ER (causal relationship unknown). These included:

**Body as a Whole:** Abdominal pain, fever, **Dental:** Dental pain, **Metabolic:** increased ALP and AST, hyperglycemia.

**Musculoskeletal:** Back pain, myalgia, foot pain, knee pain, shoulder pain, tendinitis.

**Respiratory:** Upper respiratory infection, sinusitis, pharyngitis, bronchitis, nasal congestion, influenza, sinus disorder.

**Special Senses:** Conjunctivitis, **Urogenital:** Proctitis, pyuria, urinary tract infection.
LEXXEL (enalapril maleate-felodipine ER) Tablets

Container Closure Labels

Roll Label for 30 Count

Unit of Use Bottle – Immediate Container Label
Roll Label for 100 Count Unit Dose Package – Outer Carton (Panel) Label

Lexxel®
(enalapril maleate-felodipine ER)
Each tablet contains 5 mg enalapril maleate and 2.5 mg felodipine extended-release formulation.

100 Tablets

Manufactured by:
MERCK & CO., Inc., West Point, PA 19486
Distributed by:
ASTRA
Astra Pharmaceuticals, L.P., Wayne, PA 19087
LEXCEL is a registered trademark of Astra Pharmaceuticals, L.P.
LEXXEL® 5-2.5
(enalapril maleate-felodipine ER)
Each tablet contains 5 mg enalapril maleate and 2.5 mg felodipine extended-release formulation.

100 Tablets

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

Distributed by:
ASTRA
Astra Pharmaceuticals, L.P., Wayne, PA 19087
LEXXEL is a registered trademark of Astra Pharmaceuticals, L.P.

NDC 0186-0002-28

LEXXEL® 5-2.5
(enalapril maleate-felodipine ER)
Each tablet contains 5 mg enalapril maleate and 2.5 mg felodipine extended-release formulation.

100 Tablets  Rx only

USUAL ADULT DOSAGE: See package insert.
Store at 25°C (77°F), excursions 15-30°C (59-86°F).
Protect from moisture and light.
Tablets should be swallowed whole, not divided, crushed or chewed.
This is a bulk package and not intended for dispensing.

NDA 20-668/S-003
LEXXEL (enalapril maleate-felodipine ER) Tablets

Container Closure Labels

Roll Label for 100 Count Unit Dose Package – Outer Carton (Overlap) Label
LEXXEL (enalapril maleate-felodipine ER) Tablets

Container Closure Labels

Blister Cell for 100 Count Unit Dose Package