NOVARTIS

Lotrel®

(amlodipine besylate and benazepril hydrochloride)
Combination Capsules

2.5 mg/10 mg
5 mg/10 mg
5 mg/20 mg
5 mg/40 mg
10 mg/20 mg
10 mg/40 mg

Rx only

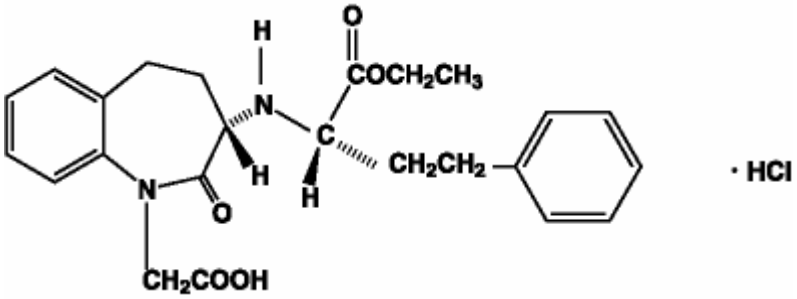
Prescribing Information

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, Lotrel should be discontinued as soon as possible. See **WARNINGS, Fetal/Neonatal Morbidity and Mortality.**

DESCRIPTION

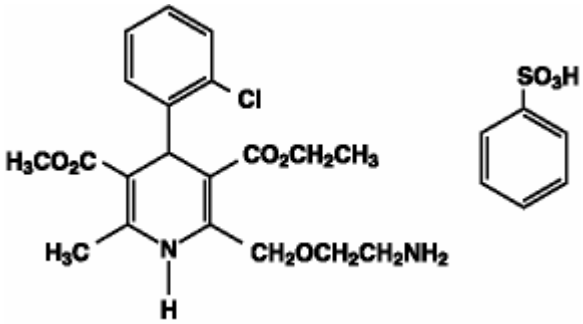
Benazepril hydrochloride is a white to off-white crystalline powder, soluble (>100 mg/mL) in water, in ethanol, and in methanol. Benazepril hydrochloride's chemical name is 3-[[1-(ethoxycarbonyl)-3-phenyl-(1S)-propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3S)-benzazepine-1-acetic acid monohydrochloride; its structural formula is



Its empirical formula is $C_{24}H_{28}N_2O_5$•HCl, and its molecular weight is 460.96.

Benazeprilat, the active metabolite of benazepril, is a nonsulfhydryl angiotensin-converting enzyme (ACE) inhibitor. Benazepril is converted to benazeprilat by hepatic cleavage of the ester group.

Amlodipine besylate is a white to pale yellow crystalline powder, slightly soluble in water and sparingly soluble in ethanol. Its chemical name is (R,S)3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulfonate; its structural formula is



Its empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$, and its molecular weight is 567.1.

Amlodipine besylate is the besylate salt of amlodipine, a dihydropyridine calcium channel blocker.

Lotrel is a combination of amlodipine besylate and benazepril hydrochloride. The capsules are formulated in six different strengths for oral administration with a combination of amlodipine besylate equivalent to 2.5 mg, 5 mg or 10 mg of amlodipine, with 10 mg, 20 mg or 40 mg of benazepril hydrochloride providing for the following available combinations: 2.5/10 mg, 5/10 mg, 5/20 mg, 5/40 mg, 10/20 mg and 10/40 mg. The inactive ingredients of the capsules are calcium phosphate, cellulose compounds, colloidal silicon dioxide, crospovidone, gelatin, hydrogenated castor oil (not present in 5/40 mg or 10/40 mg strengths), iron oxides, lactose, magnesium stearate, polysorbate 80, silicon dioxide, sodium lauryl sulfate, sodium starch (potato) glycolate, starch (corn), talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Benazepril and benazeprilat inhibit angiotensin-converting enzyme (ACE) in human subjects and in animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex.

Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. Hypertensive patients treated with benazepril and amlodipine for up to 56 weeks had elevations of serum potassium up to 0.2 mEq/L (see PRECAUTIONS).

Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. In animal studies, benazepril had no inhibitory effect on the vasopressor response to angiotensin II and did not interfere with the hemodynamic effects of the autonomic neurotransmitters acetylcholine, epinephrine, and norepinephrine.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of Lotrel remains to be elucidated.

While the mechanism through which benazepril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, benazepril has an antihypertensive effect even in patients with low-renin hypertension.

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with

a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

Pharmacokinetics and Metabolism

The rate and extent of absorption of benazepril and amlodipine from Lotrel are not significantly different, respectively, from the rate and extent of absorption of benazepril and amlodipine from individual tablet formulations. Absorption from the individual tablets is not influenced by the presence of food in the gastrointestinal tract; food effects on absorption from Lotrel have not been studied.

Following oral administration of Lotrel, peak plasma concentrations of benazepril are reached in 0.5-2 hours. Cleavage of the ester group (primarily in the liver) converts benazepril to its active metabolite, benazeprilat, which reaches peak plasma concentrations in 1.5-4 hours. The extent of absorption of benazepril is at least 37%.

Peak plasma concentrations of amlodipine are reached 6-12 hours after administration of Lotrel; the extent of absorption is 64%-90%.

The apparent volumes of **distribution** of amlodipine and benazeprilat are about 21 L/kg and 0.7 L/kg, respectively. Approximately 93% of circulating amlodipine is bound to plasma proteins, and the bound fraction of benazeprilat is slightly higher. On the basis of in vitro studies, benazeprilat's degree of protein binding should be unaffected by age, by hepatic dysfunction, or—over the therapeutic concentration range—by concentration.

Benazeprilat has much greater ACE-inhibitory activity than benazepril, and the **metabolism** of benazepril to benazeprilat is almost complete. Only trace amounts of an administered dose of benazepril can be recovered unchanged in the urine; about 20% of the dose is excreted as benazeprilat, 8% as benazeprilat glucuronide, and 4% as benazepril glucuronide.

Amlodipine is extensively metabolized in the liver, with 10% of the parent compound and 60% of the metabolites excreted in the urine. In patients with hepatic dysfunction, decreased clearance of amlodipine may increase the area-under-the-plasma-concentration curve by 40%-60%, and dosage reduction may be required (see DOSAGE AND ADMINISTRATION). In patients with renal impairment, the pharmacokinetics of amlodipine are essentially unaffected.

Benazeprilat's effective **elimination** half-life is 10-11 hours, while that of amlodipine is about 2 days, so steady-state levels of the two components are achieved after about a week of once-daily dosing. The clearance of benazeprilat from the plasma is primarily renal, but biliary excretion accounts for 11%-12% of benazepril elimination in normal subjects. In patients with severe renal insufficiency (creatinine clearance less than 30 mL/min), peak benazeprilat levels and the time to steady state may be increased (see DOSAGE AND ADMINISTRATION). In patients with hepatic impairment, on the other hand, the pharmacokinetics of benazeprilat are essentially unaffected.

Although the pharmacokinetics of benazepril and benazeprilat are unaffected by **age**, clearance of amlodipine is decreased in the elderly, with resulting increases of 35%-70% in peak plasma levels, elimination half-life, and area-under-the-plasma-concentration curve. Dose adjustment may be required.

Pharmacodynamics

Single and multiple doses of 10 mg or more of **benazepril** cause inhibition of plasma ACE activity by at least 80%-90% for at least 24 hours after dosing. For up to 4 hours after a 10-mg dose, pressor responses to exogenous angiotensin I were inhibited by 60%-90%.

Administration of benazepril to patients with mild-to-moderate hypertension results in a reduction of both supine and standing blood pressure to about the same extent, with no compensatory tachycardia. Symptomatic postural hypotension is infrequent, although it can occur in patients who are salt and/or volume depleted (see WARNINGS, Hypotension).

The antihypertensive effects of benazepril were not appreciably different in patients receiving high- or low-sodium diets.

In normal human volunteers, single doses of benazepril caused an increase in renal blood flow but had no effect on glomerular filtration rate.

Following administration of therapeutic doses to patients with hypertension, **amlodipine** produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Plasma concentrations correlate with effect in both young and elderly patients.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when coadministered with beta blockers to humans.

Amlodipine does not change sinoatrial (SA) nodal function or atrioventricular (AV) conduction in intact animals or humans. In clinical studies in which amlodipine was administered in combination with beta blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed.

Over 950 patients received Lotrel once daily in six double-blind, placebo-controlled studies. Lotrel lowered blood pressure within 1 hour, with peak reductions achieved 2-8 hours after dosing. The antihypertensive effect of a single dose persisted for 24 hours.

Once-daily doses of benazepril/amlodipine using benazepril doses of 10-20 mg and amlodipine doses of 2.5-10 mg decreased seated pressure (systolic/diastolic) 24 hours after dosing by about 10-25/6-13 mmHg.

In two studies in patients not adequately controlled on either benazepril 40 mg alone (n=329) or amlodipine 10 mg alone (n=812) once daily doses of Lotrel 10/40 mg further decreased seated blood pressure compared to the respective monotherapy alone.

Combination therapy was effective in blacks and nonblacks. Both components contributed to the antihypertensive efficacy in nonblacks, but virtually all of the antihypertensive effect in blacks could be attributed to the amlodipine component. Among nonblack patients in placebo-controlled trials comparing Lotrel to the individual components, the blood pressure lowering effects of the combination were shown to be additive and in some cases synergistic.

During chronic therapy with Lotrel, the maximum reduction in blood pressure with any given dose is generally achieved after 1-2 weeks. The antihypertensive effects of Lotrel have continued during therapy for at least 1 year. Abrupt withdrawal of Lotrel has not been associated with a rapid increase in blood pressure.

INDICATIONS AND USAGE

Lotrel 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 Lotrel, consideration should be given to the fact that an ACE inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that benazepril does not have a similar risk (see WARNINGS, Neutropenia/Agranulocytosis).

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to nonblacks.

CONTRAINDICATIONS

Lotrel is contraindicated in patients who are hypersensitive to benazepril, to any other ACE inhibitor, or to amlodipine.

WARNINGS

Anaphylactoid and Possibly Related Reactions

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including Lotrel) may be subject to a variety of adverse reactions, some of them serious. These reactions usually occur after one of the first few doses of the ACE inhibitor, but they sometimes do not appear until after months of therapy.

Head and Neck Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors. In U.S. clinical trials, symptoms consistent with angioedema were seen in none of the subjects who received placebo and in about 0.5% of the subjects who received benazepril. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with Lotrel should be discontinued and appropriate therapy instituted immediately. *When involvement of the tongue, glottis, or larynx appears likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine injection 1:1000 (0.3-0.5 mL), should be promptly administered (see ADVERSE REACTIONS).*

Intestinal Angioedema: Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Anaphylactoid Reactions During Desensitization: Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid Reactions During Membrane Exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration, and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Hypotension

Lotrel can cause symptomatic hypotension. Like other ACE inhibitors, benazepril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume and/or salt depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with Lotrel.

Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration of amlodipine. Nonetheless, caution should be exercised when administering Lotrel as with any other peripheral vasodilator, particularly in patients with severe aortic stenosis.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria, azotemia, and (rarely) with acute renal failure and death. In such patients, Lotrel therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of the benazepril component is increased or a diuretic is added or its dose increased.

If hypotension occurs, the patient should be placed in a supine position, and if necessary, treated with intravenous infusion of physiologic saline. Lotrel treatment usually can be continued following restoration of blood pressure and volume.

Neutropenia/Agranulocytosis

Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients (incidence probably less than once per 10,000 exposures) but more frequently (incidence possibly as great as once per 1000 exposures) in patients with renal impairment, especially those who also have collagen-vascular diseases such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of benazepril are insufficient to show that benazepril does not cause agranulocytosis at similar rates. Monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

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, Lotrel 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 death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine 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 benazepril as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to 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 intra-amniotic environment.

If oligohydramnios is observed, benazepril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon 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 should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or peritoneal dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Benazepril, which crosses the placenta, can theoretically be removed from the neonatal circulation by these means; there are occasional reports of benefit from these maneuvers, but experience is limited.

Lotrel has not been adequately studied in pregnant women. When rats received benazepril:amlodipine at doses ranging from 5:2.5 to 50:25 mg/kg/day, dystocia was observed with increasing dose-related incidence at all doses tested. On a mg/m^2 basis, the 2.5 mg/kg/day dose of amlodipine is 3.6 times the amlodipine dose delivered when the maximum recommended dose of Lotrel is given to a 50-kg woman. Similarly, the 5 mg/kg/day dose of benazepril is approximately 2 times the benazepril dose delivered when the maximum recommended dose of Lotrel is given to a 50-kg woman.

No teratogenic effects were seen when benazepril and amlodipine were administered in combination to pregnant rats or rabbits. Rats received dose ratios up to 50:25 mg/kg/day (benazepril:amlodipine) (24 times the maximum recommended human dose on a mg/m^2 basis, assuming a 50-kg woman). Rabbits received doses of up to 1.5:0.75 (benazepril:amlodipine) mg/kg/day; on a mg/m^2 basis, this is 0.97 times the size of a maximum recommended dose of Lotrel given to a 50-kg woman.

Similar results were seen in animal studies involving benazepril alone and amlodipine alone.

Hepatic Failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

PRECAUTIONS

General

Impaired Renal Function: Lotrel should be used with caution in patients with severe renal disease.

When the renin-angiotensin-aldosterone system is inhibited by benazepril, changes in renal function may be anticipated in susceptible individuals. In patients with **severe congestive heart failure**, whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors (including benazepril) may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death.

In a small study of hypertensive patients with **unilateral or bilateral renal artery stenosis**, treatment with benazepril was associated with increases in blood urea nitrogen and serum creatinine; these increases were reversible upon discontinuation of benazepril therapy, concomitant diuretic therapy, or both. When such patients are treated with Lotrel, renal function should be monitored during the first few weeks of therapy.

Some benazepril-treated hypertensive patients with **no apparent preexisting renal vascular disease** have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when benazepril has been given concomitantly with a diuretic. Dosage reduction of Lotrel may be required. **Evaluation of the hypertensive patient should always include assessment of renal function** (see DOSAGE AND ADMINISTRATION).

Hyperkalemia: In U.S. placebo-controlled trials of Lotrel, hyperkalemia (serum potassium at least 0.5 mEq/L greater than the upper limit of normal) not present at baseline occurred in approximately 1.5% of hypertensive patients receiving Lotrel. Increases in serum potassium were generally reversible. 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.

Patients With Congestive Heart Failure: Although hemodynamic studies and a controlled trial in patients with NYHA Class II-III heart failure have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction, and clinical symptomatology, studies have not been performed in patients with NYHA Class IV heart failure. In general, all calcium channel blockers should be used with caution in patients with heart failure.

Patients With Hepatic Failure: In patients with hepatic dysfunction due to cirrhosis, levels of benazeprilat are essentially unaltered. However, since amlodipine is extensively metabolized by the liver and the plasma elimination half-life ($t_{1/2}$) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering Lotrel to patients with severe hepatic impairment (see also WARNINGS).

Cough: Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing surgery or during anesthesia with agents that produce hypotension, benazepril will block the angiotensin II formation that could otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

Drug Interactions

Diuretics: Patients on diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with Lotrel. The possibility of hypotensive effects with Lotrel can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with Lotrel.

Potassium Supplements and Potassium-Sparing Diuretics: Benazepril can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. If concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. Lotrel and lithium should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended.

Other: Benazepril has been used concomitantly with oral anticoagulants, beta-adrenergic-blocking agents, calcium-blocking agents, cimetidine, diuretics, digoxin, hydralazine, and naproxen without evidence of clinically important adverse interactions.

In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, nonsteroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

In vitro data in human plasma indicate that amlodipine has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin). Special studies have indicated that the coadministration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers; that coadministration with cimetidine did not alter the pharmacokinetics of amlodipine; and that coadministration with warfarin did not change the warfarin-induced prothrombin response time.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenicity was found when **benazepril** was given, via dietary administration, to rats and mice for 104 weeks at doses up to 150 mg/kg/day. On a body-weight basis, this dose is over 100 times the maximum recommended human dose; on a body-surface-area basis, this dose is 18 times (rats) and 9 times (mice) the maximum recommended human dose. No mutagenic activity was detected in the Ames test in bacteria, in an in vitro test for forward mutations in cultured mammalian cells, or in a nucleus anomaly test. At doses of 50-500 mg/kg/day (38-375 times the maximum recommended human dose on a body-weight basis; 6-61 times the maximum recommended dose on a body-surface-area basis), benazepril had no adverse effect on the reproductive performance of male and female rats.

Rats and mice treated with amlodipine in the diet for 2 years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day, showed no evidence of carcinogenicity. For mice, but not for rats, the highest dose was close to the maximum tolerated dose. On a mg/m^2 basis, this dose given to mice was approximately equal to the maximum recommended clinical dose. On the same basis, the same dose given to rats was approximately twice the maximum recommended clinical dose.

Mutagenicity studies with amlodipine revealed no drug-related effects at either the gene or chromosome levels.

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg/kg/day (8 times the maximum recommended human dose of 10 mg on a mg/m^2 basis, assuming a 50-kg person).

No adverse effects on fertility occurred when the benazepril:amlodipine combination was given orally to rats of either sex at dose ratios up to 15:7.5 mg/kg/day (benazepril:amlodipine), prior to mating and throughout gestation.

Pregnancy

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

Nursing Mothers

Minimal amounts of unchanged benazepril and of benazeprilat are excreted into the breast milk of lactating women treated with benazepril, so that a newborn child ingesting nothing but breast milk would receive less than 0.1% of the maternal doses of benazepril and benazeprilat.

It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while Lotrel is administered.

Geriatric Use

Of the total number of patients who received Lotrel in U.S. clinical studies of Lotrel, over 19% were 65 or older while about 2% were 75 or older. Overall differences in effectiveness or safety were not observed between these patients and younger patients. Clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Benazepril and benazeprilat are substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Amlodipine is extensively metabolized in the liver. In the elderly, clearance of amlodipine is decreased with resulting increases in peak plasma levels, elimination half-life and area-under-the-plasma-concentration curve. Thus a lower starting dose may be required in older patients (see DOSAGE AND ADMINISTRATION).

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Lotrel has been evaluated for safety in over 2,991 patients with hypertension; over 500 of these patients were treated for at least 6 months, and over 400 were treated for more than 1 year.

In a pooled analysis of 5 placebo-controlled trials involving Lotrel doses up to 5/20, the reported side effects were generally mild and transient, and there was no relationship between side effects and age, sex, race, or duration of therapy. Discontinuation of therapy due to side effects was required in approximately 4% of patients treated with Lotrel and in 3% of patients treated with placebo.

The most common reasons for discontinuation of therapy with Lotrel in these studies were cough and edema.*

The side effects considered possibly or probably related to study drug that occurred in these trials in more than 1% of patients treated with Lotrel are shown in the table below.

PERCENT INCIDENCE IN U.S. PLACEBO-CONTROLLED TRIALS

	Benazepril/ Amlodipine N=760	Benazepril N=554	Amlodipine N=475	Placebo N=408
Cough	3.3	1.8	0.4	0.2
Headache	2.2	3.8	2.9	5.6
Dizziness	1.3	1.6	2.3	1.5
Edema*	2.1	0.9	5.1	2.2

*Edema refers to all edema, such as dependent edema, angioedema, facial edema.

The incidence of edema was statistically greater in patients treated with amlodipine monotherapy than in patients treated with the combination. Edema and certain other side effects are associated with amlodipine monotherapy in a dose-dependent manner, and appear to affect women more than men. The addition of benazepril resulted in lower incidences as shown in the following table; the protective effect of benazepril was independent of race and (within the range of doses tested) of dose.

PERCENT INCIDENCE BY SEX OF CERTAIN ADVERSE EVENTS

	Benazepril/ Amlodipine		Benazepril		Amlodipine		Placebo	
	Male N=329	Female N=431	Male N=269	Female N=285	Male N=277	Female N=198	Male N=217	Female N=191
Edema	0.6	3.2	0.0	1.8	2.2	9.1	1.4	3.1
Flushing	0.3	0.0	0.0	0.7	0.4	2.0	0.5	0.0
Palpitations	0.3	0.5	0.4	1.4	0.4	2.0	0.5	0.5
Somnolence	0.3	0.0	0.4	0.4	0.4	0.5	0.0	0.0

In a trial (n=386) comparing placebo, Lotrel 5/20, and Lotrel 10/20, edema and dizziness were most commonly reported in the Lotrel 10/20 group.

There were no appreciable differences in the safety profile of the 5/40 mg or 10/40 mg doses of Lotrel when studied in two trials (n=329 and n=812) conducted to establish the effectiveness of these doses vs. benazepril monotherapy and amlodipine monotherapy, respectively.

Other side effects considered possibly or probably related to study drug that occurred in U.S. placebo-controlled trials of patients treated with Lotrel or in postmarketing experience were the following:

Angioedema: Includes edema of the lips or face without other manifestations of angioedema (see WARNINGS, Angioedema).

Body as a Whole: Asthenia and fatigue.

CNS: Insomnia, nervousness, anxiety, tremor, and decreased libido.

Dermatologic: Flushing, hot flashes, rash, skin nodule, and dermatitis.

Digestive: Dry mouth, nausea, abdominal pain, constipation, diarrhea, dyspepsia, and esophagitis.

Metabolic and Nutritional: Hypokalemia.

Musculoskeletal: Back pain, musculoskeletal pain, cramps, and muscle cramps.

Respiratory: Pharyngitis.

Urogenital: Sexual problems such as impotence, and polyuria.

Other infrequently reported events were seen in clinical trials (causal relationship unlikely) or in postmarketing experience. These included chest pain, ventricular extrasystole, gout, neuritis, tinnitus, alopecia and upper respiratory tract infection.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Monotherapies of benazepril and amlodipine have been evaluated for safety in clinical trials in over 6,000 and 11,000 patients, respectively. The observed adverse reactions to the monotherapies in these trials were similar to those seen in trials of Lotrel. In postmarketing experience with benazepril, there have been rare reports of Stevens-Johnson syndrome, pancreatitis, hemolytic anemia, pemphigus, and thrombocytopenia. Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis) severe enough to require hospitalization have been reported in association with use of amlodipine. Other potentially important adverse experiences attributed to other ACE inhibitors and calcium channel blockers include: eosinophilic pneumonitis (ACE inhibitors) and gynecomastia (CCB's).

Clinical Laboratory Test Findings

Serum Electrolytes: See PRECAUTIONS.

Creatinine: Minor reversible increases in serum creatinine were observed in patients with essential hypertension treated with Lotrel. Increases in creatinine are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis (see PRECAUTIONS, General).

Other (causal relationships unknown): Clinically important changes in standard laboratory tests were rarely associated with Lotrel administration. Elevations of serum bilirubin and uric acid have been reported as have scattered incidents of elevations of liver enzymes.

OVERDOSAGE

Only a few cases of human overdose with amlodipine have been reported. One patient was asymptomatic after a 250-mg ingestion; another, who combined 70 mg of amlodipine with an unknown large quantity of a benzodiazepine, developed refractory shock and died.

Human overdoses with any combination of amlodipine and benazepril have not been reported. In scattered reports of human overdoses with benazepril and other ACE inhibitors, there are no reports of death.

When mice were given single oral doses of benazepril/amlodipine, mortality was 20% at 50:25 mg/kg, 10% at 100:50 mg/kg, and 100% at 500:250 mg/kg. In rats, mortality was 25% (pooling two studies) at 500:250 mg/kg and 100% at 900:450 mg/kg.

Treatment: To obtain up-to-date information about the treatment of overdose, a good resource is your certified 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.

The most likely effect of overdose with Lotrel is vasodilation, with consequent hypotension and tachycardia. Simple repletion of central fluid volume (Trendelenburg positioning, infusion of crystalloids) may be sufficient therapy, but pressor agents (norepinephrine or high-dose dopamine) may be required. Overdoses of other dihydropyridine calcium channel blockers are reported to have been treated with calcium chloride and glucagon, but evidence of a dose-response relation has not been seen, and these interventions must be regarded as unproven. With abrupt return of peripheral vascular tone, overdoses of other dihydropyridine calcium channel blockers have sometimes progressed to pulmonary edema, and patients must be monitored for this complication.

Analyses of bodily fluids for concentrations of amlodipine, benazepril, or their metabolites are not widely available. Such analyses are, in any event, not known to be of value in therapy or prognosis.

No data are available to suggest physiologic maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of amlodipine, benazepril, or their metabolites. Benazeprilat is only slightly dialyzable; attempted clearance of amlodipine by hemodialysis or hemo-perfusion has not been reported, but amlodipine's high protein binding makes it unlikely that these interventions will be of value.

Angiotensin II could presumably serve as a specific antagonist-antidote to benazepril, but angiotensin II is essentially unavailable outside of scattered research laboratories.

DOSAGE AND ADMINISTRATION

Amlodipine is an effective treatment of hypertension in once-daily doses of 2.5-10 mg while benazepril is effective in doses of 10-80 mg. In clinical trials of amlodipine/benazepril combination therapy using amlodipine doses of 2.5-10 mg and benazepril doses of 10-40 mg, the antihypertensive effects increased with increasing dose of amlodipine in all patient groups, and the effects increased with increasing dose of benazepril in nonblack groups. All patient groups benefited from the reduction in amlodipine-induced edema (see below).

The hazards (see WARNINGS) of benazepril are generally independent of dose; those of amlodipine are a mixture of dose-dependent phenomena (primarily peripheral edema) and dose-independent phenomena, the former much more common than the latter. When benazepril is added to a regimen of amlodipine, the incidence of edema is substantially reduced. Therapy with any combination of amlodipine and benazepril will thus be associated with both sets of dose-independent hazards, but the incidence of edema will generally be less than that seen with similar (or higher) doses of amlodipine monotherapy.

Rarely, the dose-independent hazards of benazepril are serious. To minimize dose-independent hazards, it is usually appropriate to begin therapy with Lotrel only after a patient has either (a) failed to achieve the desired antihypertensive effect with one or the other monotherapy, or (b) demonstrated inability to achieve adequate antihypertensive effect with amlodipine therapy without developing edema.

Dose Titration Guided by Clinical Effect: A patient whose blood pressure is not adequately controlled with amlodipine (or another dihydropyridine) alone or with benazepril (or another ACE inhibitor) alone may be switched to combination therapy with Lotrel. The addition of benazepril to a regimen of amlodipine should not be expected to provide additional antihypertensive effect in African-Americans. However, all patient groups benefit from the reduction in amlodipine-induced edema. Dosage must be guided by clinical response; steady-state levels of benazepril and amlodipine will be reached after approximately 2 and 7 days of dosing, respectively.

In patients whose blood pressures are adequately controlled with amlodipine but who experience unacceptable edema, combination therapy may achieve similar (or better) blood pressure control without edema. Especially in nonblacks, it may be prudent to minimize the risk of excessive response by reducing the dose of amlodipine as benazepril is added to the regimen.

Replacement Therapy: For convenience, patients receiving amlodipine and benazepril from separate tablets may instead wish to receive capsules of Lotrel containing the same component doses.

Use in Patients With Metabolic Impairments: Regimens of therapy with Lotrel need not take account of renal function as long as the patient's creatinine clearance is >30 mL/min/1.73m^2 (serum creatinine roughly ≤3 mg/dL or 265 μmol/L). In patients with more severe renal impairment, the recommended initial dose of benazepril is 5 mg. Lotrel is not recommended in these patients.

In small, elderly, frail, or hepatically impaired patients, the recommended initial dose of amlodipine, as monotherapy or as a component of combination therapy, is 2.5 mg.

HOW SUPPLIED

Lotrel is available as capsules containing amlodipine besylate equivalent to 2.5 mg, 5 mg or 10 mg of amlodipine, with 10 mg, 20 mg or 40 mg of benazepril hydrochloride providing for the following available combinations: 2.5/10 mg, 5/10 mg, 5/20 mg, 5/40 mg, 10/20 mg and 10/40 mg. All six strengths are packaged in bottles of 100 capsules. The 5/40 mg and 10/40 mg strengths are packaged with a desiccant.

Capsules are imprinted with "Lotrel" and appropriate code.

Dose	Capsule Color/Code	NDC Code Bottle of 100
2.5/10 mg	white with 2 gold bands/2255	NDC 0078-0404-05
5/10 mg	light brown with 2 white bands/2260	NDC 0078-0405-05
5/20 mg	pink with 2 white bands/2265	NDC 0078-0406-05
5/40 mg	light blue with 2 white bands/0384	NDC 0078-0384-05
10/20 mg	purple (amethyst) with 2 white bands/0364	NDC 0078-0364-05
10/40 mg	dark blue with 2 white bands/0379	NDC 0078-0379-05

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

[See USP controlled room temperature.]

Protect from moisture. Dispense in tight container (USP).

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REV: October 2005 Printed in U.S.A.

NOVARTIS

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

Manufactured by:
Novartis Pharmaceuticals Corporation
Suffern, New York 10901

Patient Summary of Information

LOTREL®, (low-TREL)
amlodipine besylate/benazepril hydrochloride capsules
2.5 mg/10 mg, 5 mg/10 mg, 5 mg/20 mg, 5mg/40 mg, 10 mg/20 mg, 10mg/40 mg
Rx only

Read this Patient Information leaflet before you start taking LOTREL and each time you get a refill. There may be new information. This leaflet does not replace talking with your doctor. If you have any questions, ask your doctor or pharmacist.

What is the most important information I should know about LOTREL?

LOTREL can harm an unborn baby and even cause death. If you get pregnant, stop taking LOTREL. Call your doctor right away. Talk to your doctor about other ways to lower your blood pressure if you plan to become pregnant.

What is LOTREL?

LOTREL contains two prescription medicines that work together to lower blood pressure: amlodipine besylate (the active ingredient found in Norvasc®), a calcium channel blocker, and benazepril hydrochloride (Lotensin®), an ACE inhibitor. Your doctor will prescribe LOTREL only after other medicines haven't worked.

High Blood Pressure (hypertension). Blood pressure is the force of blood in your blood vessels. You have high blood pressure when the force is too much. LOTREL can help your blood vessels relax so your blood pressure is lower.

LOTREL has not been studied in children.

Who should not take LOTREL?

Don't take LOTREL if you are allergic to any of the ingredients. There is a complete list at the end of this leaflet.

What should I tell my Doctor before taking LOTREL?

Tell your doctor about all your medical conditions, including if:

- **you are pregnant or plan to become pregnant.** See "What is the most important information I should know about LOTREL?"
- **you are breastfeeding.** LOTREL may pass into your milk. Don't breastfeed while you are taking LOTREL.
- you have a heart condition
- you have liver problems
- you have kidney problems
- you have diabetes (high blood sugar)
- you have systemic lupus erythematosus (SLE), scleroderma or a collagen vascular disease. Ask your doctor if you are not sure.

Keep a list of your medicines with you, including vitamins and natural or herbal remedies, to show your doctor or pharmacist. Some of your other medicines and LOTREL could affect each other, causing serious side effects. Tell your doctor about all your medicines, especially:

- medicines for high blood pressure or heart failure
- water pills, extra potassium or a salt substitute
- Lithium (Eskalith®, Lithobid®)

How do I take LOTREL?

- Take LOTREL exactly as your doctor tells you.
- Take LOTREL at the same time each day, with or without food.
- If you miss a dose, take it as soon as you remember. If it is more than 12 hours, just take your next dose at the regular time.

- Your doctor may test for kidney problems or check your blood potassium level.
- If you take too much LOTREL, call your doctor or Poison Control Center, or go to the emergency room.
- Tell all your doctors or dentist you are taking LOTREL if you:
  - are going to have surgery
  - are getting allergy shots for bee stings
  - go for kidney dialysis

What are the possible side effects of LOTREL?

LOTREL can cause serious side effects including:

- **serious allergic reactions that can be life threatening.**
  Stop LOTREL and get emergency help right away if you get:
  - swelling of your face, eyelids, lips, tongue or throat
  - have trouble swallowing
  - asthma (wheezing) or other breathing problems

These allergic reactions are rare but happen more times in people who are African-American.

- **low blood pressure** (hypotension). Low blood pressure is most likely to happen if you also take water pills, are on a low salt diet, get dialysis treatments, have heart problems or get sick with vomiting or diarrhea. Lie down if you feel faint or dizzy.
- **liver problems.** Call your doctor if:
- you have nausea
- you feel more tired or weaker than usual
- you have itching
- your skin or eyes look yellow
- you have pain in your upper right stomach
- you have flu-like symptoms
- **low white blood cells.** Low white blood cells happen more in people who have kidney problems and collagen vascular diseases. Low white blood cells can give you a higher chance for getting infections. Call your doctor if you get a fever, sore throat, or other signs of infection that do not go away.
- **kidney problems.** Kidney problems may get worse in people that already have kidney disease. Some people will have changes on blood tests for kidney function and need a lower dose of LOTREL. Call your doctor if you get swelling in your feet, ankles, or hands or unexplained weight gain.
- **more chest pain and heart attacks** in people that already have severe heart problems. Get emergency help if you get worse chest pain or chest pain that does not go away.

The more common side effects of LOTREL are:

- Cough
- Dizziness
- Headache
- Swelling of the feet, ankles, and hands

These are not all side effects of LOTREL. For a complete list, ask your doctor or pharmacist.

How do I store LOTREL?

- Store LOTREL at room temperature (59-86°F).
- Keep LOTREL in a closed container in a dry place.
- Keep LOTREL and all medicines out of the reach of children.

General Information about LOTREL

Doctors can also use medicine for a condition that is not in the patient information leaflet. Take LOTREL the way your doctor tells you. Do not share it with other people. It may harm them.

For more information, ask your doctor or pharmacist, visit www.LOTREL.com on the Internet, or call 1-888-669-6682.

What are the ingredients in LOTREL?

Active ingredients: amlodipine besylate (the active ingredient found in Norvasc®), benazepril hydrochloride (Lotensin®)

Inactive ingredients: calcium phosphate, cellulose compounds, colloidal silicon dioxide, crospovidone, gelatin, hydrogenated castor oil (not present in 5/40 mg and 10/40 mg strengths), iron oxides, lactose, magnesium stearate, polysorbate 80, silicon dioxide, sodium lauryl sulfate, sodium starch (potato) glycolate, starch (corn), talc, and titanium dioxide.

OCTOBER 2005 Printed in U.S.A.

NOVARTIS

Manufactured by:
Novartis Pharmaceuticals Corp.
Suffern, New York 10901

Distributed by:
Novartis Pharmaceuticals Corp.
East Hanover, New Jersey 07936