LOTREL - amlodipine besylate and benazepril hydrochloride capsule
Physicians Total Care, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Lotrel safely and effectively. See full prescribing information for Lotrel.
Lotrel (amlodipine besylate and benazepril hydrochloride) Capsules
Initial U.S. Approval: 1995

WARNING: FETAL TOXICITY

See full prescribing information for complete boxed warning

When pregnancy is detected, discontinue Lotrel as soon as possible (5.4). Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus (5.4).

RECENT MAJOR CHANGES

Boxed Warning: Fetal Toxicity 01/2012
Warnings and Precautions: Fetal Toxicity (5.4) 01/2012

INDICATIONS AND USAGE

Lotrel is a combination tablet of amlodipine, a dihydropyridine calcium channel blocker (DHP CCB) and benazepril, an angiotensin converting enzyme (ACE) inhibitor. Lotrel is indicated for the treatment of hypertension in patients not adequately controlled on monotherapy with either agent (1)

DOSAGE AND ADMINISTRATION

- Dose once-daily
- May be used as add-on therapy for patients not adequately controlled with either a dihydropyridine calcium channel blocker or an ACE inhibitor (2.2)
- Patients who experience edema with amlodipine may be switched to Lotrel containing a lower dose of amlodipine (2.2)
- Start Lotrel at 2.5/10 mg in patients ≥ 75 years old or in patients with hepatic impairment (2)

DOSAGE FORMS AND STRENGTHS

Capsules (amlodipine/benazepril mg): 2.5/10, 5/10, 5/20, 5/40, 10/20, 10/40 (3)

CONTRAINDICATIONS

Lotrel is contraindicated in patients with a history of angioedema, with or without previous ACE inhibitor treatment, or patients who are hypersensitive to benazepril, to any other ACE inhibitor, or to amlodipine. (4)

WARNINGS AND PRECAUTIONS

- Watch for anaphylactoid reactions, including angioedema (head, neck or intestinal).
- Warn patients with severe obstructive coronary artery disease about the risk of myocardial infarction or increased angina (5.2)
- Assess for hypotension and hyperkalemia (5.3 and 5.7)
- Titrate slowly in patients with impaired hepatic (5.5) or severely impaired renal (5.6) function.

ADVERSE REACTIONS

Discontinuation because of adverse reactions occurred in 4% of Lotrel-treated patients and 3% of placebo-treated patients. The most common reasons for discontinuation of therapy with Lotrel were cough and edema. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Potassium supplements / Potassium-sparing diuretics: risk of hyperkalemia
- Lithium: Increased serum Lithium levels; toxicity symptoms
- Injectable gold: facial flushing, nausea, vomiting, or hypotension may occur
- NSAID: Risk of renal dysfunction, loss of antihypertensive effect (7.1)
- If simvastatin is co-administered with amlodipine, do not exceed doses greater than 20 mg daily of simvastatin (7.1)

USE IN SPECIFIC POPULATIONS

Nursing Mothers: It is not known whether amlodipine is excreted in human milk. Nursing or drug should be discontinued. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: FETAL TOXICITY

When pregnancy is detected, discontinue Lotrel as soon as possible (5.4). Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus (5.4)

1 INDICATIONS AND USAGE

1.1 Hypertension

Lotrel is indicated for the treatment of hypertension in patients not adequately controlled on monotherapy with either agent.

2 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.

The antihypertensive effect of Lotrel is largely attained within 2 weeks.

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.

Renal Impairment: 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). Lotrel is not recommended in patients with more severe renal impairment.

Hepatic Impairment and Elderly Patients: The recommended initial dose of amlodipine, as monotherapy or as a component of combination therapy, is 2.5 mg.

2.2 Add-on Therapy

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.

In patients whose blood pressure is adequately controlled with amlodipine but who experience unacceptable edema, combination therapy may achieve similar (or better) blood pressure control with less edema.

2.3 Replacement Therapy

Lotrel may be substituted for the titrated components.

3 DOSAGE FORMS AND STRENGTHS

Lotrel (amlodipine/benazepril) capsules are available as follows:

2.5/10 mg, 5/10 mg, 5/20 mg, 5/40 mg, 10/20 mg, and 10/40 mg.

4 CONTRAINDICATIONS

Lotrel is contraindicated in patients with a history of angioedema, with or without previous ACE inhibitor treatment, or patients who are hypersensitive to benazepril, to any other ACE inhibitor, or to amlodipine.

5 WARNINGS AND PRECAUTIONS

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

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, discontinue treatment with Lotrel and treat immediately. *When involvement of the tongue, glottis, or larynx appears likely to cause airway obstruction, appropriate therapy, e.g., administer subcutaneous epinephrine injection 1:1000 (0.3-0.5 mL), promptly* [see *Adverse Reactions (6)*].

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.

5.2 Increased Angina and/or Myocardial Infarction

Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration 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.

5.3 Hypotension

Lotrel can cause symptomatic hypotension. Symptomatic hypotension is most likely to occur in patients who have been volume or salt depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting.

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, start Lotrel therapy under close medical supervision; follow 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.

Symptomatic hypotension is also possible in patients with severe aortic stenosis.

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

5.4 Fetal Toxicity

Pregnancy Category D

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Lotrel as soon as possible [*see Use in Specific Populations (8.1)*].

5.5 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.

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, titrate Lotrel slowly in patients with severe hepatic impairment.

5.6 Impaired Renal Function

Lotrel should not be used in patients with severe renal disease (Clearance creatinine < 30 ml/min) [see *Dosage and Administration (2)*].

In patients with severe heart failure, whose renal function may depend on the activity of the renin-angiotensin aldosterone system, treatment with benazepril may be associated with oliguria 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, monitor renal function 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.

Renal function should be monitored periodically in patients receiving benazepril.

5.7 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. Serum potassium should be monitored periodically in patients receiving benazepril.

5.8 Cough

Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, generally resolving after discontinuation of therapy. Consider ACE inhibitor-induced cough in the differential diagnosis of cough.

5.9 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.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

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 (including angioedema).

The peripheral edema associated with amlodipine use is dose-dependent. When benazepril is added to a regimen of amlodipine, the incidence of edema is substantially reduced.

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.

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. Cough was the only adverse event with at least possible relationship to treatment that was more common on Lotrel (3.3%) than on placebo (0.2%).

PERCENT INCIDENCE IN U.S. PLACEBO-CONTROLLED TRIALS

	Benazepril/Amlodipine	Benazepril	Amlodipine	Placebo
	N=760	N=554	N=475	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 greater in patients treated with amlodipine monotherapy (5.1%) than in patients treated with Lotrel (2.1%) or placebo (2.2%).

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:

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.

Hematologic: Neutropenia

Metabolic and Nutritional: Hypokalemia.

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

Respiratory: Pharyngitis.

Urogenital: Sexual problems such as impotence, and polyuria.

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.

6.2 Post-marketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In postmarketing experience with benazepril, there have been rare reports of Stevens-Johnson syndrome, pancreatitis, hemolytic anemia, pemphigus, and thrombocytopenia. Gingival hyperplasia, tachycardia, 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 (CCBs). Other infrequently reported events included chest pain, ventricular extrasystole, gout, neuritis, tinnitus, alopecia, upper respiratory tract infection, palpitations and somnolence.

7 DRUG INTERACTIONS

7.1 Drug/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, 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. When coadministering Lotrel and lithium, frequent monitoring of serum lithium levels is recommended.

Gold: Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have

been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy.

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ACE inhibitors, including benazepril, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving benazepril and NSAID therapy.

The antihypertensive effect of ACE inhibitors, including benazepril, may be attenuated by NSAIDs.

Simvastatin: Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

Other: Benazepril has been used concomitantly with oral anticoagulants, beta-adrenergic-blocking agents, calcium-blocking agents, cimetidine, diuretics, digoxin, and hydralazine 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.

7.2 Clinical Laboratory Test Findings

Serum Electrolytes: [see *Warnings and Precautions* (5)].

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 *Warnings and Precautions* (5)].

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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Lotrel as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes

for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue Lotrel, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based 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. Closely observe infants with histories of in utero exposure to Lotrel for hypotension, oliguria, and hyperkalemia *[see Use in Specific Populations (8.4)]*.

8.2 Labor and Delivery

The effect of Lotrel on labor and delivery has not been studied.

8.3 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. Nursing or drug should be discontinued.

8.4 Pediatric Use

Neonates with a history of in utero exposure to Lotrel:

If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a 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.

8.5 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* (2)].

10 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.

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. 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.

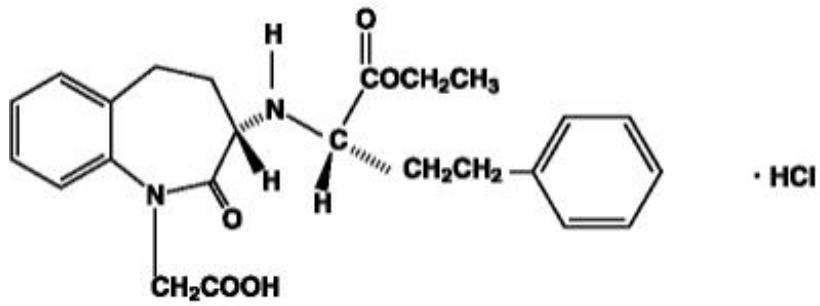
No data are available to suggest physiologic maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of amlodipine, benazepril, or their metabolites. Benazeprilat is only slightly dialyzable; attempted clearance of amlodipine by hemodialysis or hemo-perfusion has not 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.

11 DESCRIPTION

Lotrel is a combination of amlodipine besylate and benazepril hydrochloride.

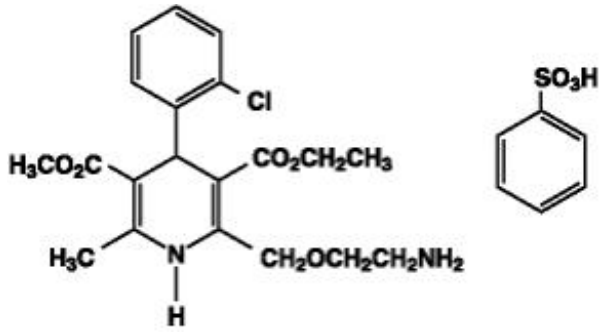
Benazepril hydrochloride is a white to off-white crystalline powder, soluble (>100 mg/mL) in water, in ethanol, and in methanol. Benazepril hydrochloride's chemical name is 3-[[1-(ethoxycarbonyl)-3-phenyl-(1S)-propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3S)-benzazepine-1-acetic acid monohydrochloride;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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Benazepril

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 *Warnings and Precautions* (5)].

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

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.

12.2 Pharmacodynamics

Benazepril

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 and Precautions* (5)].

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.

Amlodipine

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.

12.3 Pharmacokinetics

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 (2)*]. 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 (2)*]. 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity and mutagenicity studies have not been conducted with this combination. However, these studies have been conducted with amlodipine and benazepril alone (see below). No adverse effects on fertility occurred when the benazepril:amlodipine combination was given orally to rats of either sex at doses up to 15:7.5 mg (benazepril:amlodipine)/kg/day, prior to mating and throughout gestation.

Benazepril

No evidence of carcinogenicity was found when benazepril was administered to rats and mice for up to two years at doses of up to 150 mg/kg/day. When compared on the basis of body surface area, this dose is 18 and 9 times (rats and mice, respectively) the maximum recommended human dose (calculations assume a patient weight of 60 kg). 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 (6-60 times the maximum recommended human dose on a body surface area basis), benazepril had no adverse effect on the reproductive performance of male and female rats.

Amlodipine

Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg amlodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a body surface area basis, similar to the maximum recommended human dose [MRHD] of 10 mg amlodipine/day. For the

rat, the highest dose was, on a body surface area basis, about two and a half times the MRHD. (Calculations based on a 60 kg patient.) Mutagenicity studies conducted with amlodipine maleate revealed no drug-related effects at either the gene or chromosome level. There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses of up to 10 mg amlodipine/kg/day (about 10 times the MRHD of 10 mg/day on a body surface area basis).

13.3 Reproductive Toxicity

When rats received benazepril:amlodipine at doses ranging from 5:2.5 to 50:25 mg/kg/day, dystocia was observed at an increasing dose-related incidence at all doses tested. On a body surface area 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 twice 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 doses of up to 50:25 mg (benazepril:amlodipine)/kg/day (24 times the maximum recommended human dose on a body surface area basis, assuming a 50-kg woman). Rabbits received doses of up to 1.5:0.75 mg/kg/day (equivalent to the maximum recommended dose of Lotrel given to a 50-kg woman).

Benazepril

No teratogenic effects of benazepril were seen in studies of pregnant rats, mice, and rabbits. On a body surface area basis, the maximum doses used in these studies were 60 times (in rats), 9 times (in mice), and about equivalent to (in rabbits) the maximum recommended human dose (assuming a 50-kg woman).

Amlodipine

No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses of up to 10 mg amlodipine/kg/day (respectively, about 10 and 20 times the maximum recommended human dose [MRHD] of 10 mg amlodipine on a body surface area basis) during their respective periods of major organogenesis. (Calculations based on a patient weight of 60 kg.) However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) for rats receiving amlodipine maleate at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose. There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

14 CLINICAL STUDIES

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

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.

16 HOW SUPPLIED/STORAGE AND HANDLING

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.

Capsules are imprinted with “Lotrel” and appropriate code.

Dose	Capsule Color/Code	Bottles of	NDC Code
2.5/10 mg	white with 2 gold bands/2255	10	54868-4066-1
		30	54868-4066-0
5/10 mg	light brown with 2 white bands/2260	10	54868-4073-1
		30	54868-4073-0
		60	54868-4073-2
		100	54868-4073-3
5/20 mg	pink with 2 white bands/2265	10	54868-4074-2
		30	54868-4074-0
		60	54868-4074-4
		90	54868-4074-1
		100	54868-4074-3
5/40 mg	light blue with 2 white bankds/0384	10	54868-5783-0
		30	54868-5783-1
10/20 mg	purple (amethyst) with 2 white bands/0364	10	54868-4870-1
			54868

		30	54868-4870-0
		90	54868-4870-2
10/40 mg	dark blue with 2 white bands/0379	10	54868-5690-0
		30	54868-5690-1
		90	54868-5690-3
		100	54868-5690-2

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).

17 PATIENT COUNSELING INFORMATION

Information for Patients

Female patients of childbearing age should be told about the consequences of exposure to Lotrel during pregnancy. Discuss treatment options with women planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

FDA-Approved Patient Labeling

LOTREL®, (low-TREL)

amlodipine besylate/benazepril hydrochloride capsules

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 cause harm or death to an unborn baby.
- Talk to your doctor about other ways to lower your blood pressure if you plan to become pregnant.
- If you get pregnant while taking LOTREL, tell your doctor right away.

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 the 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.

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

T2012-43/T2012-44
January 2012/January 2012

Relabeling and Repackaging by:
Physicians Total Care, Inc.
Tulsa, Oklahoma 74146

PRINCIPAL DISPLAY PANEL

Package Label – 2.5 / 10 mg

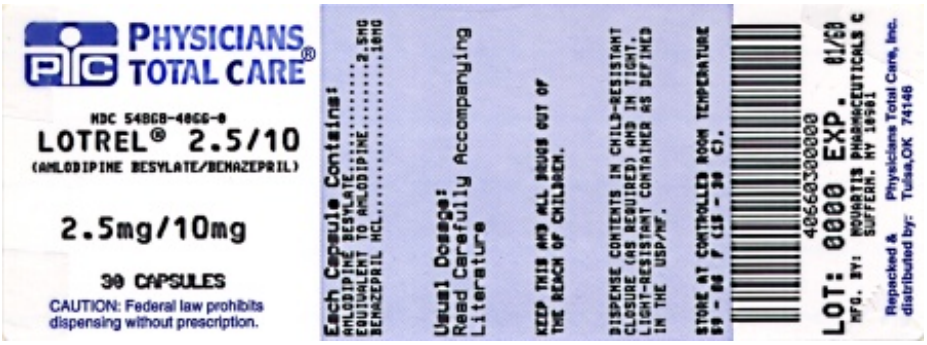
Rx Only

Lotrel®

amlodipine besylate

(equivalient to amlodipine 2.5 mg)

benazepril HCL 10 mg



PRINCIPAL DISPLAY PANEL

Package Label – 5/ 10 mg

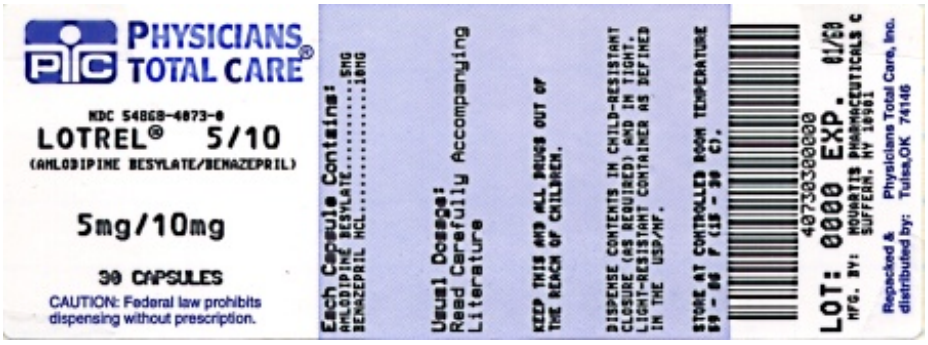
Rx Only

Lotrel®

amlodipine besylate

(equivalient to amlodipine 5 mg)

benazepril HCL 10 mg



PRINCIPAL DISPLAY PANEL

Package Label – 5/ 20 mg

Rx Only

Lotrel®

amlodipine besylate

(equivalient to amlodipine 5 mg)

benazepril HCL 20 mg

PRINCIPAL DISPLAY PANEL

Package Label – 5/ 40 mg

Rx Only

Lotrel®

amlodipine besylate

(equivalient to amlodipine 5 mg)

benazepril HCL 40 mg

PRINCIPAL DISPLAY PANEL

Package Label – 10 / 20 mg

Rx Only

Lotrel®

amlodipine besylate

(equivalient to amlodipine10 mg)

benazepril HCL 20 mg

PRINCIPAL DISPLAY PANEL

Package Label – 10 / 40 mg

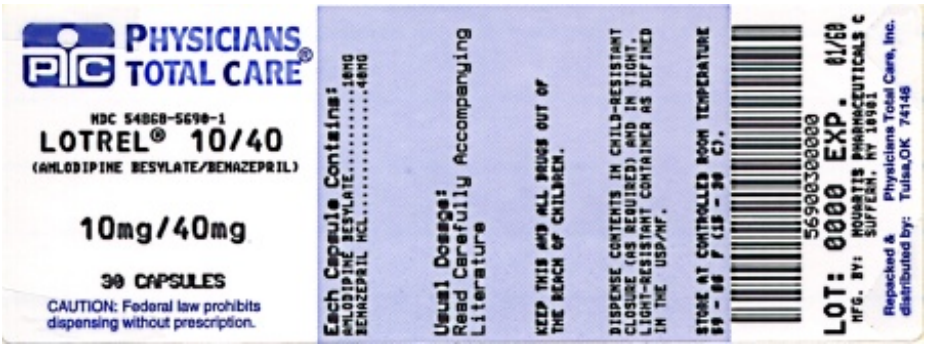
Rx Only

Lotrel®

amlodipine besylate

(equivalient to amlodipine10 mg)

benazepril HCL 40 mg



LOTREL

amlodipine besylate and benazepril hydrochloride capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:54868-4066(NDC:0078-0404)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
AMLODIPINE BESYLATE (UNII: 864V2Q084H) (AMLODIPINE - UNII:1J444QC288)	AMLODIPINE	2.5 mg
BENAZEPRIL HYDROCHLORIDE (UNII: N1SN99T69T) (BENAZEPRILAT - UNII:JRM708L703)	BENAZEPRIL HYDROCHLORIDE	10 mg

Inactive Ingredients	
Ingredient Name	**Strength**

CALCIUM PHOSPHATE (UNII: 97Z1WI3NDX)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (UNII: 68401960MK)	
GELATIN (UNII: 2G86QN327L)	
HYDROGENATED CASTOR OIL (UNII: ZF94AP8MEY)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
LACTOSE (UNII: J2B2A4N98G)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
STARCH, CORN (UNII: O8232NY3SJ)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	WHITE (white with 2 gold bands)	**Score**	no score
Shape	CAPSULE	**Size**	19mm
Flavor		**Imprint Code**	Lotrel;2255
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54868-4066-0	30 in 1 BOTTLE, PLASTIC		
2	NDC:54868-4066-1	10 in 1 BOTTLE, PLASTIC		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020364	02/02/2005	

LOTREL

amlodipine besylate and benazepril hydrochloride capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:54868-4073(NDC:0078-0405)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength

AMLODIPINE BESYLATE (UNII: 864V2Q084H) (AMLODIPINE - UNII:1J444QC288)	AMLODIPINE	5 mg
BENAZEPRIL HYDROCHLORIDE (UNII: N1SN99T69T) (BENAZEPRILAT - UNII:JRM708L703)	BENAZEPRIL HYDROCHLORIDE	10 mg

Inactive Ingredients

Ingredient Name	Strength
CALCIUM PHOSPHATE (UNII: 97Z1WI3NDX)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (UNII: 68401960MK)	
GELATIN (UNII: 2G86QN327L)	
HYDROGENATED CASTOR OIL (UNII: ZF94AP8MEY)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
LACTOSE (UNII: J2B2A4N98G)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
STARCH, CORN (UNII: O8232NY3SJ)	

Product Characteristics

Color	BROWN (light brown with 2 white bands)	**Score**	no score
Shape	CAPSULE	**Size**	19mm
Flavor		**Imprint Code**	Lotrel;2260
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54868-4073-0	30 in 1 BOTTLE, PLASTIC		
2	NDC:54868-4073-1	10 in 1 BOTTLE, PLASTIC		
3	NDC:54868-4073-2	60 in 1 BOTTLE, PLASTIC		
4	NDC:54868-4073-3	100 in 1 BOTTLE, PLASTIC		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020364	07/01/1999	

LOTREL

amlodipine besylate and benazepril hydrochloride capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:54868-4074(NDC:0078-0406)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AMLODIPINE BESYLATE (UNII: 864V2Q084H) (AMLODIPINE - UNII:1J444QC288)	AMLODIPINE	5 mg
BENAZEPRIL HYDROCHLORIDE (UNII: N1SN99T69T) (BENAZEPRILAT - UNII:JRM708L703)	BENAZEPRIL HYDROCHLORIDE	20 mg

Inactive Ingredients

Ingredient Name	Strength
CALCIUM PHOSPHATE (UNII: 97Z1WI3NDX)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (UNII: 68401960MK)	
GELATIN (UNII: 2G86QN327L)	
HYDROGENATED CASTOR OIL (UNII: ZF94AP8MEY)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
LACTOSE (UNII: J2B2A4N98G)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
STARCH, CORN (UNII: O8232NY3SJ)	

Product Characteristics

Color	PINK (pink with 2 white bands)	**Score**	no score
Shape	CAPSULE	**Size**	19mm
Flavor		**Imprint Code**	Lotrel;2265
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54868-4074-0	30 in 1 BOTTLE, PLASTIC		
2	NDC:54868-4074-1	90 in 1 BOTTLE, PLASTIC		
3	NDC:54868-4074-2	10 in 1 BOTTLE, PLASTIC		
4	NDC:54868-4074-3	100 in 1 BOTTLE, PLASTIC		
5	NDC:54868-4074-4	60 in 1 BOTTLE, PLASTIC		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020364	11/28/2000	

LOTREL

amlodipine besylate and benazepril hydrochloride capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:54868-5783(NDC:0078-0384)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AMLODIPINE BESYLATE (UNII: 864V2Q084H) (AMLODIPINE - UNII:1J444QC288)	AMLODIPINE	5 mg
BENAZEPRIL HYDROCHLORIDE (UNII: N1SN99T69T) (BENAZEPRILAT - UNII:JRM708L703)	BENAZEPRIL HYDROCHLORIDE	40 mg

Inactive Ingredients

Ingredient Name	Strength
CALCIUM PHOSPHATE (UNII: 97Z1WI3NDX)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (UNII: 68401960MK)	
GELATIN (UNII: 2G86QN327L)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
LACTOSE (UNII: J2B2A4N98G)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
STARCH, CORN (UNII: O8232NY3SJ)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	BLUE (light blue with 2 white bands)	**Score**	no score
Shape	CAPSULE	**Size**	19mm
Flavor		**Imprint Code**	Lotrel;0384
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54868-5783-0	10 in 1 BOTTLE, PLASTIC		
2	NDC:54868-5783-1	30 in 1 BOTTLE, PLASTIC		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020364	06/20/2007	

LOTREL

amlodipine besylate and benazepril hydrochloride capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:54868-4870(NDC:0078-0364)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
AMLODIPINE BESYLATE (UNII: 864V2Q084H) (AMLODIPINE - UNII:1J444QC288)	AMLODIPINE	10 mg
BENAZEPRIL HYDROCHLORIDE (UNII: N1SN99T69T) (BENAZEPRILAT - UNII:JRM708L703)	BENAZEPRIL HYDROCHLORIDE	20 mg

Inactive Ingredients	
Ingredient Name	Strength
CALCIUM PHOSPHATE (UNII: 97Z1WI3NDX)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (UNII: 68401960MK)	
GELATIN (UNII: 2G86QN327L)	
HYDROGENATED CASTOR OIL (UNII: ZF94AP8MEY)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
LACTOSE (UNII: J2B2A4N98G)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
STARCH, CORN (UNII: O8232NY3SJ)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics			
Color	PURPLE (purple (amethyst) with 2 white bands)	**Score**	no score
Shape	CAPSULE	**Size**	19mm
Flavor		**Imprint Code**	Lotrel;0364
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:54868-4870-0	30 in 1 BOTTLE, PLASTIC		
2	NDC:54868-4870-1	10 in 1 BOTTLE, PLASTIC		
3	NDC:54868-4870-2	90 in 1 BOTTLE, PLASTIC		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020364	07/30/2003	

LOTREL

amlodipine besylate and benazepril hydrochloride capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:54868-5690(NDC:0078-0379)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
AMLODIPINE BESYLATE (UNII: 864V2Q084H) (AMLODIPINE - UNII:1J444QC288)	AMLODIPINE	10 mg
BENAZEPRIL HYDROCHLORIDE (UNII: N1SN99T69T) (BENAZEPRILAT - UNII:JRM708L703)	BENAZEPRIL HYDROCHLORIDE	40 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CALCIUM PHOSPHATE (UNII: 97Z1WI3NDX)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (UNII: 68401960MK)	
GELATIN (UNII: 2G86QN327L)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
LACTOSE (UNII: J2B2A4N98G)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
STARCH, CORN (UNII: O8232NY3SJ)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	BLUE (dark blue with 2 white bands)	**Score**	no score
Shape	CAPSULE	**Size**	19mm
Flavor		**Imprint Code**	Lotrel;0379
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54868-5690-0	10 in 1 BOTTLE, PLASTIC		
2	NDC:54868-5690-1	30 in 1 BOTTLE, PLASTIC		
3	NDC:54868-5690-2	100 in 1 BOTTLE, PLASTIC		
4	NDC:54868-5690-3	90 in 1 BOTTLE, PLASTIC		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020364	10/10/2006	

Labeler - Physicians Total Care, Inc. (194123980)

Establishment

Name	Address	ID/FEI	Business Operations
Physicians Total Care, Inc.		194123980	relabel, repack

Revised: 3/2012 Physicians Total Care, Inc.