



NDA 020364/S-056; S-057

**SUPPLEMENT APPROVAL**

Novartis Pharmaceuticals Corporation  
Attention: Yifeng Jia, Ph.D.  
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Dear Dr. Jia:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received March 12, 2012 (S-056), and August 10, 2012 (S-057), submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lotrel (amlodipine besylate and benazepril hydrochloride) 2.5/10 mg, 5/10 mg, 5/20 mg, 10/20 mg, 5/40 mg, and 10/40 mg Tablets.

These “Prior Approval” supplemental new drug applications provide for labeling revised as follows (additions are marked as underlined text and deletions are marked as ~~struckthrough text~~):

1. In **HIGHLIGHTS/RECENT MAJOR CHANGES**, the following text was added:

Boxed Warning: Fetal Toxicity	01/2012
<u>Dosage and Administration (2)</u>	<u>10/2012</u>
<u>Contraindications (4)</u>	<u>10/2012</u>
Warnings and Precautions: Fetal Toxicity ( <u>5.5</u> )	01/2012

2. In **HIGHLIGHTS/CONTRAINDICATIONS**, the following text was added:

Do not co-administer aliskiren with ARBs or ACEIs, including Lotrel in patients with diabetes (4)

3. In **HIGHLIGHTS/DRUG INTERACTIONS**, the following bullet was added:

- Dual inhibition of the renin-angiotensin system: Increased risk of renal impairment, hypotension, and hyperkalemia (7.1)

4. Under **DOSAGE AND ADMINISTRATION**, the following text was added/deleted:

**2.1 General considerations**

The recommended initial dose of Lotrel is one capsule of amlodipine 2.5 mg/benazepril 10 mg orally once daily.

It is usually appropriate to begin therapy with Lotrel only after a patient has either (a) failed to achieve the desired antihypertensive effect with amlodipine or benazepril monotherapy, or (b) demonstrated inability to achieve adequate antihypertensive effect with amlodipine therapy without developing edema.

The antihypertensive effect of Lotrel is largely attained within 2 weeks. If blood pressure remains uncontrolled, the dose may be titrated up to amlodipine 10 mg/benazepril 40 mg once daily. The dosing should be individualized and adjusted according to the patient's clinical response.

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.

~~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.~~

## **2.2 Dosage adjustment in renal impairment**

Renal Impairment: Lotrel is not recommended in patients with creatinine clearance  $\leq 30$  mL/min. No dose adjustment of Lotrel is required in patients with 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<sup>2</sup> (serum creatinine roughly  $\leq 3$  mg/dL or 265  $\mu$ mol/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.

5. Under **CONTRAINDICATIONS**, the following text was added:

- Do not co-administer aliskiren with angiotensin receptor blockers, ACE inhibitors, including Lotrel in patients with diabetes.
- 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, or to any of the excipients of Lotrel.

6. Under **WARNINGS AND PRECAUTIONS**, the following text was added/deleted:

### **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.~~

Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of amlodipine, particularly in patients with severe obstructive coronary artery disease.

### **5.3 Patients with Aortic and Mitral Valve Stenosis, Obstructive Hypertrophic Cardiomyopathy**

As with all other vasodilators, special caution is required when using amlodipine in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

### **5.4 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.~~

### **5.5 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)*].

### **5.6 Hepatitis and 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.~~

There have been rare reports of predominantly cholestatic hepatitis and isolated cases of acute liver failure, some of them fatal, in patients on ACE inhibitors. The mechanism is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevation of hepatic enzymes should discontinue the ACE inhibitor and be kept under medical surveillance.

### **5.7 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. Monitor renal function periodically in patients treated with Lotrel. Changes in renal function, including acute renal failure, can be caused by drugs that affect the renin-angiotensin system. Patients whose renal function may depend in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, severe heart failure, post-myocardial infarction or volume depletion) or who are on NSAIDs or angiotensin receptor blockers may be at particular risk of developing acute renal failure on Lotrel. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on Lotrel.

### **5.8 Hyperkalemia**

Monitor serum potassium periodically in patients receiving Lotrel. Drugs that affect the renin-angiotensin system can cause hyperkalemia. 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- 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.

### **5.9 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.

### **5.10 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.

7. In **ADVERSE REACTIONS/Postmarketing-Experience**, the following text was added to the second and third paragraphs:

In postmarketing experience with benazepril, there have been rare reports of Stevens-Johnson syndrome, pancreatitis, hemolytic anemia, pemphigus, thrombocytopenia, paresthesia, dysgeusia, orthostatic symptoms and hypotension, angina pectoris and arrhythmia, pruritus, photosensitivity reaction, arthralgia,

arthritis, myalgia, BUN increase, serum creatinine increased, renal impairment, impaired vision, agranulocytosis, neutropenia.

Rare reports in association with use of amlodipine: 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, leucocytopenia, allergic reaction, hyperglycemia, dysgeusia, hypoesthesia, paresthesia, syncope, peripheral neuropathy, hypertonia, visual impairment, diplopia, hypotension, vasculitis, rhinitis, gastritis, hyperhidrosis, pruritis, skin discoloration, urticaria, erythema multiform, muscle spasms, arthralgia, micturition disorder, nocturia, erectile dysfunction, malaise, weight decrease or gain.

8. In **DRUG INTERACTIONS**, the following text was added/deleted:

### **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.~~

#### **Amlodipine**

~~**Simvastatin:** Co-administration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.~~

~~**CYP3A4 Inhibitors:** Co-administration with CYP3A inhibitors (moderate and strong) results in increased systemic exposure to amlodipine and may require dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A4 inhibitors to determine the need for dose adjustment.~~

~~**CYP3A4 Inducers:** No information is available on the quantitative effects of CYP3A4 inducers on amlodipine. Blood pressure should be monitored when amlodipine is co-administered with CYP3A4 inducers.~~

#### **Benazapril**

~~**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.

**Dual Blockade of the Renin-Angiotensin System (RAS):** Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function and electrolytes in patients on Lotrel and other agents that block the RAS.

**Do not co-administer aliskiren with Lotrel in patients with diabetes. Avoid use of aliskiren with Lotrel in patients with renal impairment (GFR <60 ml/min).**

**~~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.~~

9. Under **USE IN SPECIFIC POPULATIONS**, the following text was added:

### **8.5 Geriatric Use**

In geriatrics, exposure to amlodipine is increased, thus consider lower initial doses of Lotrel [see *Clinical Pharmacology (12.3)*].

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.

### **8.6 Hepatic Impairment**

Exposure to amlodipine is increased in patients with hepatic insufficiency, thus consider using lower doses of Lotrel [see *Clinical Pharmacology (12.3)*].

### **8.7 Renal Impairment**

In patients with severe renal impairment systemic exposure to benazepril is increased. The recommended dose of benazepril in this subgroup is 5 mg which is not an available strength with Lotrel. Lotrel is not recommended in patients with severe renal impairment. No dose adjustment of Lotrel is needed in patients with mild or moderate impairment of renal function [see Dosing and Administration (2.2), Warnings and Precaution (5.7) and Clinical Pharmacology (12.3)].

10. Under **OVERDOSAGE**, the following text was added:

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:** Patients should be admitted to hospital and, generally, should be managed in an intensive care setting, with continuous monitoring of cardiac function, blood gases, and blood biochemistry. Emergency supportive measures such as artificial ventilation or cardiac pacing should be instituted if appropriate.

In the event of a potentially life-threatening oral overdose, use induction of vomiting or gastric lavage and/or activated charcoal to remove the drug from the gastrointestinal tract (only if presented within 1 hour after ingestion of Lotrel).

Other clinical manifestations of overdose should be managed symptomatically based on modern methods of intensive care.

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. Under **CLINICAL PHARMACOLOGY/Pharmacodynamics**, the following section was added:

***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.

With chronic once daily administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105-114 mmHg) had about 50% greater response than patients with mild hypertension (diastolic pressure 90-104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressure (+1/-2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

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.

Amlodipine has demonstrated beneficial clinical effects in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

12. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics**, the following text was added/deleted:

~~The rate and extent of absorption of benazepril and amlodipine from Lotrel are the same as when administered as individual tablets, 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.~~

**Absorption:** 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. Absolute bioavailability has been calculated as between 64% and 90%. Following oral administration of Lotrel, the peak plasma concentrations of benazepril are reached in 0.5-2 hours. The 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%. Amlodipine and benazepril exhibit dose proportional pharmacokinetics between the therapeutic dose range of 2.5 and 10 mg and 10 and 20 mg, respectively. after administration of Lotrel; the extent of absorption is 64%-90%.

**Distribution:** The apparent volumes of distribution of amlodipine and benazeprilat are is about 21 L/kg and 0.7 L/kg, respectively. In vitro studies indicate that approximately 93% of circulating amlodipine is bound to plasma proteins in hypertensive patients. The apparent volume of distribution of benazeprilat is about 0.7 L/kg. 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.

**Metabolism:** ~~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. Amlodipine is extensively (approximately 90%) metabolized in the liver to inactive metabolites. Benazepril is extensively metabolised to form benazeprilat as the main metabolite, which occur by enzymatic hydrolysis, mainly in the liver. Two minor metabolites are the acyl glucuronide conjugates of benazepril and benazeprilat.~~

**Elimination:** ~~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. Amlodipine elimination from plasma is biphasic with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after once-daily dosing for 7–8 days. 10% of unchanged drug and 60% of amlodipine metabolites are excreted in urine. Effective elimination half-life of amlodipine is 2 days. Benazepril is eliminated mainly by metabolic clearance. Benazeprilat is eliminated via the kidneys and the bile; renal excretion is the main route in patients with normal renal function. In the urine, benazepril accounts for less than 1% and benazeprilat for about 20% of an oral dose. Elimination of benazeprilat is biphasic with an initial half-life of about 3 hours and a terminal half-life of about 22 hours. Benazeprilat's effective elimination half-life is 10–11 h, 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.~~

### **Special populations**

**Geriatric patients:** No specific clinical studies were performed to understand the impact of age on the pharmacokinetics of amlodipine and benazepril as fixed dose combination. As individual component 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 [see *Use in Specific Populations (8.5)*].

**Hepatic impairment:** Patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40–60%. Pharmacokinetics of benazepril is not significantly influenced by hepatic impairment [see *Use in Specific Populations (8.6)*].

**Renal impairment:** The disposition of benazepril and benazeprilat in patients with mild-to-moderate renal insufficiency (creatinine clearance > 30 mL/min) is similar to that in patients with normal renal function. In patients with creatinine clearance < 30 mL/min, peak benazeprilat levels and the effective half-life increase, resulting in higher systemic exposures. Pharmacokinetics of amlodipine is not significantly influenced by renal impairment [see *Dosage and Administration (2.2)*, *Use in Specific Populations (8.7)* and *Warnings and Precautions (5.7)*].

### **Drug interactions**

#### **Amlodipine**

*In vitro* data in human plasma indicate that amlodipine has no effect on the protein binding of digoxin, phenytoin, warfarin, and indomethacin.

*Cimetidine:* Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

*Grapefruit juice:* Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

*Maalox<sup>®</sup> (antacid):* Co-administration of the antacid Maalox with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

*Sildenafil:* A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Atorvastatin: Co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady-state pharmacokinetic parameters of atorvastatin.

Digoxin: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

Ethanol (alcohol): Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

Warfarin: Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

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.

CYP3A inhibitors: Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent.

### **Benazepril**

The pharmacokinetic properties of benazepril are not affected by hydrochlorothiazide, furosemide, chlorthalidone, digoxin, propranolol, atenolol, nifedipine, amlodipine, naproxen, acetylsalicylic acid, or cimetidine. Likewise the administration of benazepril does not substantially affect the pharmacokinetics of these medications.

13. The Table of Contents was updated to reflect the changes to **FULL PRESCRIBING INFORMATION**.

14. In **FDA-Approved Patient Labeling/What should I tell my Doctor before taking LOTREL?**, the following text was added/deleted:

- **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.~~
- you are about to have an operation (including dental surgery) or emergency treatment
- you are suffering from several episodes of vomiting or diarrhea
- ~~you are about to receive Hymenoptera venom treatment (a venom used to test or treat allergy to insect stings).~~
- you are treated for hyperkalemia (too much potassium in the blood)
- you are taking already a diuretic (a medicine to increase the amount of urine you produce)
- ~~you are about to receive Hymenoptera venom treatment (a venom used to test or treat allergy to insect stings).~~

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:

- Simvastatin, (a medicine used to control elevated cholesterol)
- medicines for high blood pressure or heart failure
- water pills, extra potassium or a salt substitute
- Lithium (Eskalith<sup>®</sup>, Lithobid<sup>®</sup>)
- potassium-containing medicines, potassium supplements or salt substitutes containing potassium;
- cyclosporine, an immunosuppressant medicine used in transplanted patients to reduce the risk of organ rejection;
- ~~heparin, a medicine that prevents the formation of blood clots in your blood.~~
- indomethacin and other non-steroidal anti-inflammatory agents, medicines used to relieve pain and inflammation;
- insulin or oral antidiabetics, medicines that help a person with diabetes to control their level of glucose (sugar) in the blood;
- ~~erythropoietin, a medicine used to regulate the production of red blood cells;~~
- gold for the treatment of rheumatoid arthritis;
- probenecid, a medicine used to treat gout and hyperuricemia;
- medicines used to prevent and treat fungal skin infections (e.g. ketoconazole, itraconazole)
- medicines used to treat AIDS or HIV infections (e.g. ritonavir, indinavir)
- medicines used to treat bacterial infections (e.g. clarithromycin)
- ~~Simvastatin, (a medicine used to control elevated cholesterol)~~

Avoid alcohol until you have discussed the matter with your doctor. Alcohol may make blood pressure fall more and/or increase the possibility of dizziness or fainting.

15. In **FDA-Approved Patient Labeling/What are the possible side effects of LOTREL?**, the following text was ~~deleted~~:

- ~~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.

The more common side effects of LOTREL are:

- dizziness, fainting on standing up
- cough (dry, non-productive, mainly at night, continuing)
- swelling of the feet, ankles, and hands
- ~~pharyngitis, sore throat and throat irritation (possible signs of upper respiratory tract infections)~~
- ~~stomach upset~~
- ~~fast heartbeat~~
- ~~flushing~~
- ~~headache~~
- ~~tiredness~~
- ~~increased frequency of urination~~
- ~~itching~~
- ~~increased sensitivity of the skin to sun~~

16. The revision date and version number were updated.

There are no other changes from the last approved package insert.

We have completed our review of these supplemental applications, and they are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories. Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

## **REPORTING REQUIREMENTS**

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

If you have any questions, please call:

Lori Anne Wachter, RN, BSN  
Regulatory Project Manager for Safety  
(301) 796-3975

Sincerely,

*{See appended electronic signature page}*

Mary Ross Southworth, PharmD.  
Deputy Director for Safety  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation 1  
Center for Drug Evaluation and Research

ENCLOSURE:  
Content of Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARY R SOUTHWORTH  
10/05/2012