AMLODIPINE BESYLATE AND BENAZEPRIL HYDROCHLORIDE- amlodipine besylate and benazepril hydrochloride capsule
Lupin Pharmaceuticals, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Amlodipine Besylate and Benazepril Hydrochloride Capsules safely and effectively. See full prescribing information for Amlodipine Besylate and Benazepril Hydrochloride Capsules.

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 amlodipine besylate and benazepril hydrochloride capsules 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
Dosage and Administration (2) 10/2012
Contraindications (4) 10/2012
Warnings and Precautions: Fetal Toxicity (5.5) 01/2012

INDICATIONS AND USAGE

Amlodipine besylate and benazepril hydrochloride capsule is a combination tablet of amlodipine, a dihydropyridine calcium channel blocker (DHP CCB) and benazepril, an angiotensin converting enzyme (ACE) inhibitor. Amlodipine besylate and benazepril hydrochloride 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 amlodipine besylate and benazepril hydrochloride containing a lower dose of amlodipine (2.2)
- Start amlodipine besylate and benazepril hydrochloride at 2.5 mg/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

- Do not co-administer aliskiren with ARBs or ACEIs, including amlodipine besylate and benazepril hydrochloride in patients with diabetes (4)
- Amlodipine besylate and benazepril hydrochloride 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) (5.1)
- 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)
- Avoid fetal or neonatal exposure (5.4)
- 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 amlodipine besylate and benazepril hydrochloride-treated

patients and 3% of placebo-treated patients. The most common reasons for discontinuation of therapy with amlodipine besylate and benazepril hydrochloride were cough and edema. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Lupin Pharmaceuticals, Inc. at 1-800-399-2561 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Potassium supplements / Potassium-sparing diuretics: risk of Hyperkalemia (7.1)
- Lithium: Increased serum lithium levels; toxicity symptoms (7.1)
- Injectable gold: facial flushing, nausea, vomiting, or hypotension may occur (7.1)
- NSAIDS: 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 simvstatin (7.1)
- Dual inhibition of the renin-angiotensin system: Increased risk of renal impairment, hypotension, and Hyperkalemia (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: 9/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: FETAL TOXICITY

See full prescribing information for complete boxed warning

When pregnancy is detected, discontinue amlodipine besylate and benazepril hydrochloride capsules 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

Amlodipine besylate and benazepril hydrochloride capsules are indicated for the treatment of hypertension in patients not adequately controlled on monotherapy with either agent.

2. DOSAGE AND ADMINISTRATION

2.1 General Considerations

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

It is usually appropriate to begin therapy with amlodipine besylate and benazepril hydrochloride 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 amlodipine besylate and benazepril hydrochloride 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 to 10 mg while benazepril is effective in doses of 10 to 80 mg. In clinical trials of amlodipine/benazepril combination therapy using amlodipine doses of 2.5 to 10 mg and benazepril doses of 10 to 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.

2.2 Dosage Adjustment In Renal Impairment

Renal Impairment

Amlodipine besylate and benazepril hydrochloride is not recommended in patients with creatinine clearance ≤ 30 mL/min. No dose adjustment of amlodipine besylate and benazepril hydrochloride is required in patients with creatinine clearance > 30 mL/min (serum creatinine roughly ≤3 mg/dL or 265 µmol/L). [see **WARNINGS AND PRECAUTIONS** (**5.7**), **USE IN SPECIFIC POPULATIONS** (**8.7**) and **CLINICAL PHARMACOLOGY** (**12.3**)].

2.3 Replacement Therapy

Amlodipine besylate and benazepril hydrochloride may be substituted for the titrated components.

3. DOSAGE FORMS AND STRENGTHS

Amlodipine besylate and benazepril hydrochloride capsules are available as follows: 2.5 mg/10 mg, 5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, 10 mg/20 mg, and 10 mg/40 mg.

4. CONTRAINDICATIONS

- Do not co-administer aliskiren with angiotensin receptor blockers, ACE inhibitors, including amlodipine besylate and benazepril hydrochloride in patients with diabetes.
- Amlodipine besylate and benazepril hydrochloride 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, to amlodipine, or to any of the excipients of amlodipine besylate and benazepril hydrochloride.

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 amlodipine besylate and benazepril hydrochloride) 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 amlodipine besylate and benazepril hydrochloride 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 to 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

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

Amlodipine besylate and benazepril hydrochloride can cause symptomatic hypotension. Symptomatic hypotension is most likely to occur in patients who have been volume or salt depleted as a result of diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before starting therapy with benazepril. If hypotension occurs, the patient should be placed in the supine position and if necessary given physiological saline i.v. Treatment with benazepril can be continued once blood pressure and volume have returned to normal.

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 amlodipine besylate and benazepril hydrochloride 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.

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 amlodipine besylate and benazepril hydrochloride as soon as possible [see **USE IN SPECIFIC POPULATIONS** (**8.1**)].

5.6 Hepatitis and Hepatic Failure

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

Monitor renal function periodically in patients treated with amlodipine besylate and benazepril hydrochloride. 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 amlodipine besylate and benazepril hydrochloride. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on amlodipine besylate and benazepril hydrochloride.

5.8 Hyperkalemia

Monitor serum potassium periodically in patients receiving amlodipine besylate and benazepril hydrochloride. 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. . In U.S. placebo-controlled trials of amlodipine besylate and benazepril hydrochloride, 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 amlodipine besylate and benazepril hydrochloride. 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.

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.

Amlodipine besylate and benazepril hydrochloride 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 amlodipine besylate and benazepril hydrochloride doses up to 5 mg/20 mg, 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 amlodipine besylate and benazepril hydrochloride and in 3% of patients treated with placebo.

The most common reasons for discontinuation of therapy with amlodipine besylate and benazepril hydrochloride 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 amlodipine besylate and benazepril hydrochloride are shown in the table below. Cough was the only adverse event with at least possible relationship to treatment that was more common on amlodipine besylate and benazepril hydrochloride (3.3%) than on placebo (0.2%).

PERCENT INCIDENCE IN U.S. PLACEBO-CONTROLLED TRIALS

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

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

The incidence of edema was greater in patients treated with amlodipine monotherapy (5.1%) than in patients treated with amlodipine besylate and benazepril hydrochloride (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 amlodipine besylate and benazepril hydrochloride 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 amlodipine besylate and benazepril hydrochloride.

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, 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) ,leucocytopenia, allergic reaction, hyperglycemia, dysgeusia, hypoestheia, 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.

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

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.

Benazepril

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 amlodipine besylate and benazepril hydrochloride 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, coadministration 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.

Antidiabetic agents: In rare cases, diabetic patients receiving an ACE inhibitor (including benazepril) concomitantly with insulin or oral antidiabetics may develop hypoglycemia. Such patients should therefore be advised about the possibility of hypoglycemic reactions, and should be monitored accordingly.

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 amlodipine besylate and benazepril hydrochloride and other agents that block the RAS.

Do not co-administer aliskiren with amlodipine besylate and benazepril hydrochloride in patients with diabetes. Avoid use of aliskiren with amlodipine besylate and benazepril hydrochloride in patients with renal impairment (GFR <60 ml/min).

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 amlodipine besylate and benazepril hydrochloride 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 amlodipine besylate and benazepril hydrochloride, 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 amlodipine besylate and benazepril hydrochloride for hypotension, oliguria, and hyperkalemia [see **USE IN SPECIFIC**

POPULATIONS (8.4)].

8.2 Labor and Delivery

The effect of amlodipine besylate and benazepril hydrochloride 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 amlodipine besylate and benazepril hydrochloride:

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

In geriatrics, exposure to amlodipine is increased, thus consider lower initial doses of amlodipine besylate and benazepril hydrochloride [see **CLINICAL PHARMACOLOGY** (**12.3**)].

Of the total number of patients who received amlodipine besylate and benazepril hydrochloride in U.S. clinical studies of amlodipine besylate and benazepril hydrochloride, 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 amlodipine besylate and benazepril hydrochloride [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 amlodipine besylate and benazepril hydrochloride. Amlodipine besylate and benazepril hydrochloride capsules are not recommended in patients with severe renal impairment. No dose adjustment of amlodipine besylate and benazepril hydrochloride capsules are needed in patients with mild or moderate impairment of renal function [see **DOSAGE AND ADMINISTRATION** (2.2), **WARNINGS AND PRECAUTION** (5.7) and **CLINICAL PHARMACOLOGY** (12.3)].

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

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 amlodipine besylate and benazepril hydrochloride).

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 amlodipine besylate and benazepril hydrochloride 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.

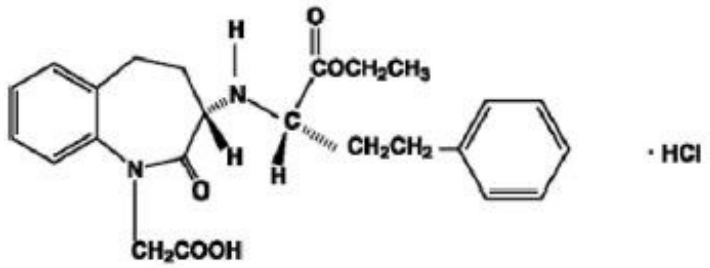
No data are available to suggest physiologic maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of amlodipine, benazepril, or their metabolites. Benazeprilat is only slightly dialyzable; attempted clearance of amlodipine by hemodialysis or hemo-perfusion has not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

Amlodipine besylate and benazepril hydrochloride capsule is a combination of amlodipine besylate and benazepril hydrochloride.

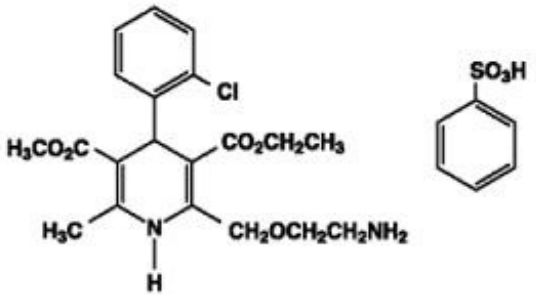
Benazepril hydrochloride is a white to off-white crystalline powder, soluble (>100 mg/mL) in water, in ethanol, and in methanol. Benazepril hydrochloride’s chemical name is 3-[[1-(ethoxycarbonyl)-3-phenyl-(1S)-propyl]amino]-2,3,4,5-tetrahydro-2-oxo-*1H*-1-(3S)-benzazepine-1-acetic acid monohydrochloride;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



Its empirical formula is $C_{24}H_{28}N_2O_5 \cdot HCl$, 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.

Amlodipine besylate and benazepril hydrochloride 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 mg/10 mg, 5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, 10 mg/20 mg and 10 mg/40 mg.

The inactive ingredients of the capsules are crospovidone, hydrophobic fumed silica, lactose anhydrous, magnesium stearate, microcrystalline cellulose, povidone, gelatin, titanium dioxide (not present in 10 mg/20 mg strength), black iron oxide, red iron oxide (present in 5 mg/10 mg, 5 mg/20 mg and 10 mg/ 20 mg strength), yellow iron oxide, (present in 5 mg/10 mg strength), D&C Yellow #10 (present in 5 mg/40 mg strength), FD&C Blue #1 (present in 10 mg/40 mg strength), FD&C Blue #2 (present in 10 mg/20 mg strength), FD&C Green #3 (present in 5 mg/40 mg strength),FD&C Red #40 (present in 10 mg/40 mg strength), FD&C Yellow #6 (present in 5 mg/ 40 mg strength), shellac, propylene glycol, potassium hydroxide.

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 amlodipine besylate and benazepril hydrochloride 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% to 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% to 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.

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.

12.3 Pharmacokinetics

The rate and extent of absorption of benazepril and amlodipine from amlodipine besylate and benazepril hydrochloride aresame as when administered as individual tablets. Absorption from the individual tablets is not influenced by the presence of food in the gastrointestinal tract; food effects on absorption from amlodipine besylate and benazepril hydrochloride have not been studied.

Absorption

Following oral administration of amlodipine besylate and benazepril hydrochloride, peak plasma concentrations of amlodipine are reached in 6 to 12 hours. Absolute bioavailability has been calculated as between 64% and 90%. Following oral administration of amlodipine besylate and benazepril hydrochloride, the peak plasma concentrations of benazepril are reached in 0.5 to 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 to 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.

Distribution

The apparent volume of distribution of amlodipine is about 21 L/kg. *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

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

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 to 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 to 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® (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. 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 to 500 mg/kg/day (6 to 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 amlodipine besylate and benazepril hydrochloride 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 amlodipine besylate and benazepril hydrochloride 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 amlodipine besylate and benazepril hydrochloride 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 amlodipine besylate and benazepril hydrochloride 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 to 8 hours after dosing.

Once-daily doses of benazepril/amlodipine using benazepril doses of 10 to 20 mg and amlodipine doses of 2.5 to 10 mg decreased seated pressure (systolic/diastolic) 24 hours after dosing by about 10 to 25/6 to 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 amlodipine besylate and benazepril hydrochloride 10 mg/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 amlodipine besylate and benazepril hydrochloride 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 amlodipine besylate and benazepril hydrochloride, the maximum reduction in blood pressure with any given dose is generally achieved after 1 to 2 weeks. The antihypertensive effects of amlodipine besylate and benazepril hydrochloride have continued during therapy for at least 1 year. Abrupt withdrawal of amlodipine besylate and benazepril hydrochloride has not been associated with a rapid increase in blood pressure.

16. HOW SUPPLIED/STORAGE AND HANDLING

Amlodipine besylate and benazepril hydrochloride capsules are 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 mg/10 mg, 5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, 10 mg/20 mg and 10 mg/40 mg.

Amlodipine besylate and benazepril hydrochloride capsules, 2.5 mg/10 mg are size '2' capsules with white opaque cap and white opaque body, imprinted with 'LU' (in black ink) on cap and 'E11' (in black ink) on body, containing white to off-white powder and white to off-white, circular tablets, debossed with '1' on one side and plain on the other side.

NDC 68180-755-01 Bottles of 100 capsules

NDC 68180-755-02 Bottles of 500 capsules

NDC 68180-755-03 Bottles of 1000 capsules

Amlodipine besylate and benazepril hydrochloride capsules, 5 mg/10 mg are size '2' capsules with light brown opaque cap and light brown opaque body, imprinted with 'LU' (in black ink) on cap and 'E12' (in black ink) on body, containing white to off-white powder and white to off-white, circular tablets, debossed with '1' on one side and plain on the other side.

NDC 68180-756-01 Bottles of 100 capsules

NDC 68180-756-02 Bottles of 500 capsules

NDC 68180-756-03 Bottles of 1000 capsules

Amlodipine besylate and benazepril hydrochloride capsules, 5 mg/20 mg are size '2' capsules with flesh opaque cap and flesh opaque body, imprinted with 'LU' (in black ink) on cap and 'E13' (in black ink) on body, containing white to off-white powder and white to off-white, circular tablets, debossed with '2' on one side and plain on the other side.

NDC 68180-757-01 Bottles of 100 capsules

NDC 68180-757-02 Bottles of 500 capsules

NDC 68180-757-03 Bottles of 1000 capsules

Amlodipine besylate and benazepril hydrochloride capsules, 5 mg/40 mg are size '2' capsules with dark green cap and white body, imprinted with 'LU' (in black ink) on cap and 'E15' (in black ink) on body, containing white to off-white powder and two white to off-white, circular tablets, debossed with '2' on one side and plain on the other side.

NDC 68180-759-01 Bottles of 100 capsules

NDC 68180-759-02 Bottles of 500 capsules

NDC 68180-759-03 Bottles of 1000 capsules

Amlodipine besylate and benazepril hydrochloride capsules, 10 mg/20 mg are size '2' capsules with purple cap and purple body, imprinted with 'LU' (in black ink) on cap and 'E14' (in black ink) on body, containing white to off-white powder and white to off-white, circular tablets, debossed with '2' on one side and plain on the other side.

NDC 68180-758-01 Bottles of 100 capsules

NDC 68180-758-02 Bottles of 500 capsules

NDC 68180-758-03 Bottles of 1000 capsules

Amlodipine besylate and benazepril hydrochloride capsules, 10 mg/40 mg are size '2' capsules with dark blue cap and white body, imprinted with 'LU' (in black ink) on cap and 'E16' (in black ink) on body, containing white to off-white powder and two white to off-white, circular tablets, debossed with '2' on one side and plain on the other side.

NDC 68180-760-01 Bottles of 100 capsules

NDC 68180-760-02 Bottles of 500 capsules

NDC 68180-760-03 Bottles of 1000 capsules

Storage: Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 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 amlodipine besylate and benazepril hydrochloride 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.

Manufactured for:

Lupin Pharmaceuticals, Inc.

Baltimore, Maryland 21202

United States

Manufactured by:

Lupin Limited

Goa 403 722

INDIA

or

Lupin Limited

Pithampur (M.P.) 454 775

INDIA.

Revised: September 2013 ID# 234155

FDA Approved Patient Labeling

AMLODIPINE BESYLATE AND BENAZEPRIL HYDROCHLORIDE CAPSULES

Read this Patient Information leaflet before you start taking amlodipine besylate and benazepril hydrochloride capsules 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 amlodipine besylate and benazepril hydrochloride capsules?

- Amlodipine besylate and benazepril hydrochloride capsules 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 amlodipine besylate and benazepril hydrochloride capsules, tell your doctor right away.

What is amlodipine besylate and benazepril hydrochloride capsule?

Amlodipine besylate and benazepril hydrochloride capsule 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 amlodipine besylate and benazepril hydrochloride capsules 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. Amlodipine besylate and benazepril hydrochloride capsules can help your blood vessels relax so your blood pressure is lower.

Amlodipine besylate and benazepril hydrochloride capsules have not been studied in children.

Who should not take amlodipine besylate and benazepril hydrochloride capsules?

Don't take amlodipine besylate and benazepril hydrochloride capsules 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 amlodipine besylate and benazepril hydrochloride capsules?

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 amlodipine besylate and benazepril hydrochloride capsules?"
- **you are breastfeeding.** Amlodipine besylate and benazepril hydrochloride may pass into your milk. Don't breastfeed while you are taking amlodipine besylate and benazepril hydrochloride capsules.
- you have a heart condition
- you have liver problems
- you have kidney problems
- 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 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)

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 amlodipine besylate and benazepril hydrochloride capsules 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®, Lithobid®)
- potassium-containing medicines, potassium supplements or salt substitutes containing potassium;
- ciclosporin, an immunosuppressant medicine used in transplanted patients to reduce the risk of organ rejection;
- 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;
- 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)

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.

How do I take amlodipine besylate and benazepril hydrochloride capsules?

- Take amlodipine besylate and benazepril hydrochloride capsules exactly as your doctor tells you.
- Take amlodipine besylate and benazepril hydrochloride capsules 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 amlodipine besylate and benazepril hydrochloride capsules, call your doctor or Poison Control Center, or go to the emergency room.
- Tell all your doctors or dentist you are taking amlodipine besylate and benazepril hydrochloride capsules 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 amlodipine besylate and benazepril hydrochloride capsules?

Amlodipine besylate and benazepril hydrochloride capsules can cause serious side effects including:

- **serious allergic reactions that can be life threatening.**

Stop amlodipine besylate and benazepril hydrochloride capsules 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
- **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 amlodipine besylate and benazepril hydrochloride capsules. 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 amlodipine besylate and benazepril hydrochloride capsules are:

- dizziness, fainting on standing up
- cough (dry, non-productive, mainly at night, continuing)

- Swelling of the feet, ankles, and hands

These are not all side effects of amlodipine besylate and benazepril hydrochloride capsules. For a complete list, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or at www.fda.gov/medwatch.

How do I store amlodipine besylate and benazepril hydrochloride capsules?

- Store amlodipine besylate and benazepril hydrochloride capsules at room temperature (59 to 86°F).
- Keep amlodipine besylate and benazepril hydrochloride capsules in a closed container in a dry place.
- Keep amlodipine besylate and benazepril hydrochloride capsules and all medicines out of the reach of children.

General Information about amlodipine besylate and benazepril hydrochloride capsules

Doctors can also use medicine for a condition that is not in the patient information leaflet. Take amlodipine besylate and benazepril hydrochloride capsules 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, address medical inquiries to www.lupinpharmaceuticals.com or 1-800-399-2561.

What are the ingredients in amlodipine besylate and benazepril hydrochloride capsules?

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

Inactive ingredients: crospovidone, hydrophobic fumed silica, lactose anhydrous, magnesium stearate, microcrystalline cellulose, povidone, gelatin, titanium dioxide (not present in 10 mg/20 mg strength), black iron oxide, red iron oxide (present in 5 mg/10 mg, 5 mg/20 mg and 10 mg/ 20 mg strength), yellow iron oxide, (present in 5 mg/10 mg strength), D&C Yellow #10 (present in 5 mg/40 mg strength), FD&C Blue #1 (present in 10 mg/40 mg strength), FD&C Blue #2 (present in 10 mg/20 mg strength), FD&C Green #3 (present in 5 mg/40 mg strength),FD&C Red #40 (present in 10 mg/40 mg strength), FD&C Yellow #6 (present in 5 mg/ 40 mg strength), shellac, propylene glycol, potassium hydroxide.

Manufactured for:

Lupin Pharmaceuticals, Inc.

Baltimore, Maryland 21202

United States

Manufactured by:

Lupin Limited

Goa 403 722

INDIA

or

Lupin Limited

Pithampur (M.P.) 454 775

INDIA.

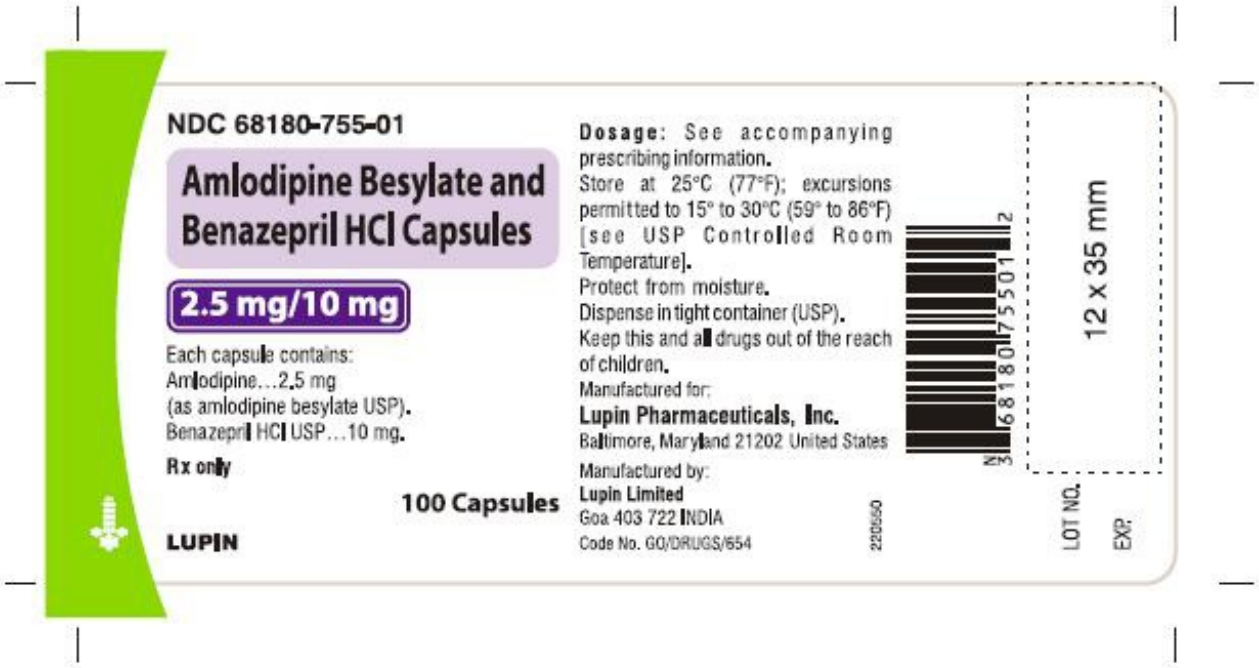
Revised: September 2013 ID#: 234156

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

Amlodipine Besylate and Benazepril Hydrochloride Capsules

2.5 mg/10 mg – Bottle of 100s

NDC 68180-755-01 bottles of 100



Amlodipine Besylate and Benazepril Hydrochloride Capsules

5 mg/10 mg – Bottle of 100s

NDC 68180-756-01 bottles of 100

Amlodipine Besylate and Benazepril Hydrochloride Capsules

5 mg/20 mg – Bottle of 100s

NDC 68180-757-01 bottles of 100

Amlodipine Besylate and Benazepril Hydrochloride Capsules

5 mg/40 mg – Bottle of 100s

NDC 68180-759-01 bottles of 100

Amlodipine Besylate and Benazepril Hydrochloride Capsules

10 mg/20 mg – Bottle of 100s

NDC 68180-758-01 bottles of 100

Amlodipine Besylate and Benazepril Hydrochloride Capsules

10 mg/40 mg – Bottle of 100s

NDC 68180-760-01 bottles of 100

AMLODIPINE BESYLATE AND BENAZEPRIL HYDROCHLORIDE

amlodipine besylate and benazepril hydrochloride capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:68180-755
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AMLODIPINE BESYLATE (AMLODIPINE)	AMLODIPINE	2.5 mg
BENAZEPRIL HYDROCHLORIDE (BENAZEPRILAT)	BENAZEPRIL HYDROCHLORIDE	10 mg

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS LACTOSE	
GELATIN	
SILICON DIOXIDE	
CELLULOSE, MICROCRYSTALLINE	
CROSPOVIDONE	
SHELLAC	
POVIDONE	
POTASSIUM HYDROXIDE	
MAGNESIUM STEARATE	
PROPYLENE GLYCOL	
TITANIUM DIOXIDE	
FERROSOFERRIC OXIDE	

Product Characteristics

Color	WHITE (White Opaque Cap and White Opaque Body)	**Score**	no score
Shape	CAPSULE	**Size**	18mm
Flavor		**Imprint Code**	LU;E11
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68180-755-02	500 in 1 BOTTLE		
2	NDC:68180-755-03	1000 in 1 BOTTLE		
3	NDC:68180-755-01	100 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date

ANDA	ANDA078466	02/05/2010	

AMLODIPINE BESYLATE AND BENAZEPRIL HYDROCHLORIDE

amlodipine besylate and benazepril hydrochloride capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:68180-756
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AMLODIPINE BESYLATE (AMLODIPINE)	AMLODIPINE	5 mg
BENAZEPRIL HYDROCHLORIDE (BENAZEPRILAT)	BENAZEPRIL HYDROCHLORIDE	10 mg

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS LACTOSE	
FERRIC OXIDE YELLOW	
GELATIN	
SILICON DIOXIDE	
CELLULOSE, MICROCRYSTALLINE	
CROSPOVIDONE	
SHELLAC	
POVIDONE	
POTASSIUM HYDROXIDE	
MAGNESIUM STEARATE	
PROPYLENE GLYCOL	
TITANIUM DIOXIDE	
FERROSOFERRIC OXIDE	
FERRIC OXIDE RED	

Product Characteristics

Color	BROWN (Light Brown Opaque Cap and Light Brown Opaque Body)	**Score**	no score
Shape	CAPSULE	**Size**	18mm
Flavor		**Imprint Code**	LU;E12
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68180-756-02	500 in 1 BOTTLE		
2	NDC:68180-756-01	100 in 1 BOTTLE		
3	NDC:68180-756-03	1000 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078466	02/05/2010	

AMLODIPINE BESYLATE AND BENAZEPRIL HYDROCHLORIDE

amlodipine besylate and benazepril hydrochloride capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:68180-757
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AMLODIPINE BESYLATE (AMLODIPINE)	AMLODIPINE	5 mg
BENAZEPRIL HYDROCHLORIDE (BENAZEPRILAT)	BENAZEPRIL HYDROCHLORIDE	20 mg

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS LACTOSE	
GELATIN	
SILICON DIOXIDE	
CELLULOSE, MICROCRYSTALLINE	
CROSPOVIDONE	
SHELLAC	
POVIDONE	
POTASSIUM HYDROXIDE	
MAGNESIUM STEARATE	
PROPYLENE GLYCOL	
TITANIUM DIOXIDE	
FERROSOFERRIC OXIDE	
FERRIC OXIDE RED	

Product Characteristics

Color	PINK (Flesh Opaque Cap and Flesh Opaque Body)	**Score**	no score
Shape	CAPSULE	**Size**	18mm
Flavor		**Imprint Code**	LU;E13
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68180-757-01	100 in 1 BOTTLE		
2	NDC:68180-757-02	500 in 1 BOTTLE		
3	NDC:68180-757-03	1000 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078466	02/05/2010	

AMLODIPINE BESYLATE AND BENAZEPRIL HYDROCHLORIDE

amlodipine besylate and benazepril hydrochloride capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:68180-758
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AMLODIPINE BESYLATE (AMLODIPINE)	AMLODIPINE	10 mg
BENAZEPRIL HYDROCHLORIDE (BENAZEPRILAT)	BENAZEPRIL HYDROCHLORIDE	20 mg

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS LACTOSE	
FD&C BLUE NO. 2	
GELATIN	
SILICON DIOXIDE	
CELLULOSE, MICROCRYSTALLINE	
CROSPOVIDONE	
SHELLAC	
POVIDONE	
POTASSIUM HYDROXIDE	
MAGNESIUM STEARATE	
PROPYLENE GLYCOL	
FERROSOFERRIC OXIDE	
FERRIC OXIDE RED	

Product Characteristics

Color	PURPLE (Purple Cap and Purple Body)	**Score**	no score
Shape	CAPSULE	**Size**	18mm
Flavor		**Imprint Code**	LU;E14

Contains	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68180-758-03	1000 in 1 BOTTLE		
2	NDC:68180-758-02	500 in 1 BOTTLE		
3	NDC:68180-758-01	100 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078466	02/05/2010	

AMLODIPINE BESYLATE AND BENAZEPRIL HYDROCHLORIDE

amlodipine besylate and benazepril hydrochloride capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:68180-759
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AMLODIPINE BESYLATE (AMLODIPINE)	AMLODIPINE	5 mg
BENAZEPRIL HYDROCHLORIDE (BENAZEPRILAT)	BENAZEPRIL HYDROCHLORIDE	40 mg

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS LACTOSE	
D&C YELLOW NO. 10	
FD&C GREEN NO. 3	
FD&C YELLOW NO. 6	
GELATIN	
SILICON DIOXIDE	
CELLULOSE, MICROCRYSTALLINE	
CROSPOVIDONE	
SHELLAC	
POVIDONE	
POTASSIUM HYDROXIDE	
MAGNESIUM STEARATE	
PROPYLENE GLYCOL	
TITANIUM DIOXIDE	
FERROSOFERRIC OXIDE	

Product Characteristics

Color	GREEN (dark green cap) , WHITE (white body)	**Score**	no score
Shape	CAPSULE	**Size**	18mm
Flavor		**Imprint Code**	LU;E15
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68180-759-02	500 in 1 BOTTLE		
2	NDC:68180-759-01	100 in 1 BOTTLE		
3	NDC:68180-759-03	1000 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078466	07/05/2011	

AMLODIPINE BESYLATE AND BENAZEPRIL HYDROCHLORIDE

amlodipine besylate and benazepril hydrochloride capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:68180-760
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AMLODIPINE BESYLATE (AMLODIPINE)	AMLODIPINE	10 mg
BENAZEPRIL HYDROCHLORIDE (BENAZEPRILAT)	BENAZEPRIL HYDROCHLORIDE	40 mg

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS LACTOSE	
FD&C BLUE NO. 1	
FD&C RED NO. 40	
GELATIN	
SILICON DIOXIDE	
CELLULOSE, MICROCRYSTALLINE	
CROSPOVIDONE	
SHELLAC	
POVIDONE	
POTASSIUM HYDROXIDE	

MAGNESIUM STEARATE	
PROPYLENE GLYCOL	
TITANIUM DIOXIDE	
FERROSOFERRIC OXIDE	

Product Characteristics

Color	BLUE (dark blue cap) , WHITE (white body)	**Score**	no score
Shape	CAPSULE	**Size**	18mm
Flavor		**Imprint Code**	LU;E16
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68180-760-02	500 in 1 BOTTLE		
2	NDC:68180-760-01	100 in 1 BOTTLE		
3	NDC:68180-760-03	1000 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078466	07/05/2011	

Labeler - Lupin Pharmaceuticals, Inc. (089153071)

Registrant - LUPIN LIMITED (675923163)

Establishment

Name	Address	ID/FEI	Business Operations
LUPIN LIMITED		677600414	Manufacture(68180-755, 68180-756, 68180-757, 68180-758, 68180-759, 68180-760)

Establishment

Name	Address	ID/FEI	Business Operations
LUPIN LIMITED		863645527	Manufacture(68180-755, 68180-756, 68180-757, 68180-758, 68180-759, 68180-760)

Revised: 9/2013 Lupin Pharmaceuticals, Inc.