BENAZEPRIL HYDROCHLORIDE- benazepril hydrochloride tablet
DIRECT RX

BENAZEPRIL HYDROCHLORIDE

BOXED WARNING SECTION

WARNING: FETAL TOXICITY

When pregnancy is detected, discontinue benazepril hydrochloride as soon as possible.

Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. See Warnings: Fetal Toxicity

DESCRIPTION SECTION

Benazepril hydrochloride (HCl), USP is a white to off-white crystalline powder, soluble (>100 mg/mL) in water, in ethanol, and in methanol. Its chemical name is benazepril 3-[[1-(ethoxy-carbonyl)-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 C24H28N2O5•HCl, and its molecular weight is 460.96.

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

Benazepril HCl tablets, USP are supplied as white, round, biconvex tablets containing either 5 mg, 10 mg, 20 mg, or 40 mg of benazepril HCl, USP for oral administration. The inactive ingredients are crospovidone, lactose anhydrous, magnesium stearate, microcrystalline cellulose, pregelatinized corn starch and talc.

CLINICAL PHARMACOLOGY SECTION

- Mechanism of Action

  Benazepril and benazeprilat inhibit angiotensin-converting enzyme (ACE) in human subjects and 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 HCl alone for up to 52 weeks had elevations of serum potassium of up to 0.2 mEq/L. Similar patients treated with benazepril HCl and hydrochlorothiazide for up to 24 weeks had no consistent changes in their serum potassium (see PRECAUTIONS).

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

  ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of benazepril HCl 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 (see INDICATIONS AND USAGE).

Pharmacokinetics and Metabolism

Following oral administration of benazepril HCl, peak plasma concentrations of benazepril are reached within 0.5 to 1 hours. The extent of absorption is at least 37% as determined by urinary recovery and is not significantly influenced by the presence of food in the GI tract.

Cleavage of the ester group (primarily in the liver) converts benazepril to its active metabolite, benazeprilat. Peak plasma concentrations of benazeprilat are reached 1 to 2 hours after drug intake in the fasting state and 2 to 4 hours after drug intake in the nonfasting state. The serum protein binding of benazepril is about 96.7% and that of benazeprilat about 95.3%, as measured by equilibrium dialysis; on the basis of in vitro studies, the degree of protein binding should be unaffected by age, hepatic dysfunction, or concentration (over the concentration range of 0.24 to 23.6 μmol/L).

Benazepril is almost completely metabolized to benazeprilat, which has much greater ACE inhibitory activity than benazepril, and to the glucuronide conjugates of benazepril and benazeprilat. Only trace amounts of an administered dose of benazepril HCl can be recovered in the urine as unchanged benazepril, while about 20% of the dose is excreted as benazeprilat, 4% as benazepril glucuronide, and 8% as benazeprilat glucuronide.

The kinetics of benazepril are approximately dose-proportional within the dosage range of 10 mg to 80 mg.

In adults, the effective half-life of accumulation of benazeprilat following multiple dosing of benazepril HCl is 10 to 11 hours. Thus, steady-state concentrations of benazeprilat should be reached after 2 or 3 doses of benazepril HCl given once daily.

The kinetics did not change, and there was no significant accumulation during chronic administration (28 days) of once-daily doses between 5 mg and 20 mg. Accumulation ratios based on AUC and urinary recovery of benazeprilat were 1.19 and 1.27, respectively.

Benazepril and benazeprilat are cleared predominantly by renal excretion in healthy subjects with normal renal function. Nonrenal (i.e., biliary) excretion accounts for approximately 11% to 12% of benazeprilat excretion in healthy subjects. In patients with renal failure, biliary clearance may compensate to an extent for deficient renal clearance.

In patients with renal insufficiency, 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 initial (alpha phase) half-life increase, and time to steady-state may be delayed (see DOSAGE AND ADMINISTRATION).

When dialysis was started 2 hours after ingestion of 10 mg of benazepril, approximately 6% of benazeprilat was removed in 4 hours of dialysis. The parent compound, benazepril, was not detected in the dialysate.

In patients with hepatic insufficiency (due to cirrhosis), the pharmacokinetics of benazeprilat are essentially unaltered. The pharmacokinetics of benazepril and benazeprilat do not appear to be influenced by age.

In pediatric patients,

(N=45) hypertensive, age 6 to 16 years, given multiple daily doses of benazepril HCl (0.1 to 0.5 mg/kg), the clearance of benazeprilat for children 6 to 12 years old was 0.35 L/hr/kg, more than twice that of healthy adults receiving a single dose of 10 mg (0.13 L/hr/kg). In adolescents, it was 0.17 L/hr/kg, 27% higher than that of healthy adults. The terminal elimination half-life of benazeprilat in pediatric patients was around 5 hours, one-third that observed in adults.

Pharmacodynamics

Single and multiple doses of 10 mg or more of benazepril HCl cause inhibition of plasma ACE activity by at least 80% to 90% for at least 24 hours after dosing. Pressor responses to exogenous angiotensin I were inhibited by 60% to 90% (up to 4 hours post-dose) at the 10-mg dose.

Clinical Studies

Hypertension

Adult

In single-dose studies, benazepril HCl lowered blood pressure within 1 hour, with peak reductions

achieved 2 to 4 hours after dosing. The antihypertensive effect of a single dose persisted for 24 hours. In multiple-dose studies, once-daily doses of 20 mg to 80 mg decreased seated pressure (systolic/diastolic) 24 hours after dosing by about 6 to 12/4 to 7 mmHg. The trough values represent reductions of about 50% of that seen at peak.

Four dose-response studies using once-daily dosing were conducted in 470 mild-to-moderate hypertensive patients not using diuretics. The minimal effective once-daily dose of benazepril HCl was 10 mg; but further falls in blood pressure, especially at morning trough, were seen with higher doses in the studied dosing range (10 mg to 80 mg). In studies comparing the same daily dose of benazepril HCl given as a single morning dose or as a twice-daily dose, blood pressure reductions at the time of morning trough blood levels were greater with the divided regimen.

The antihypertensive effects of benazepril HCl 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.

Use of benazepril HCl in combination with thiazide diuretics gives a blood-pressure-lowering effect greater than that seen with either agent alone. By blocking the renin-angiotensin-aldosterone axis, administration of benazepril HCl tends to reduce the potassium loss associated with the diuretic.

Pediatric

In a clinical study of 107 pediatric patients, 7 to 16 years of age, with either systolic or diastolic pressure above the 95th percentile, patients were given 0.1 or 0.2 mg/kg then titrated up to 0.3 or 0.6 mg/kg with a maximum dose of 40 mg once daily. After four weeks of treatment, the 85 patients whose blood pressure was reduced on therapy were then randomized to either placebo or benazepril and were followed up for an additional two weeks. At the end of two weeks, blood pressure (both systolic and diastolic) in children withdrawn to placebo rose by 4 to 6 mmHg more than in children on benazepril. No dose-response was observed for the three doses.

INDICATIONS & USAGE SECTION

Benazepril HCl tablets, USP are indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

CONTRAINDICATIONS SECTION

Benazepril HCl, USP is contraindicated in patients who are hypersensitive to benazepril or to any other ACE inhibitor.

Benazepril HCl, USP is also contraindicated in patients with a history of angioedema with or without previous ACE inhibitor treatment.

Do not co-administer aliskiren with angiotensin receptor blockers, ACE inhibitors, including benazepril HCl, USP in patients with diabetes.

Close

WARNINGS SECTION

- 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 benazepril HCl) may be subject to a variety of adverse reactions, some of them serious.

  Head and Neck Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with angiotensin-converting enzyme 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 HCl. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with benazepril HCl should be discontinued and appropriate therapy instituted immediately. Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine injection 1:1000 (0.3 mL to 0.5 mL) should be promptly administered (see ADVERSE REACTIONS).

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

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 (a procedure dependent upon devices not approved in the United States).

Hypotension

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

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 or azotemia and, rarely, with acute renal failure and death. In such patients, benazepril HCl therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of benazepril or diuretic is increased.

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

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 benazepril HCl 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 benazepril HCl, 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 benazepril HCl for hypotension, oliguria, and hyperkalemia [see Precautions, Pediatric Use].

No teratogenic effects of benazepril HCl were seen in studies of pregnant rats, mice, and rabbits. On a mg/m2 basis, the doses used in these studies were 60 times (in rats), 9 times (in mice), and more than 0.8 times (in rabbits) the maximum recommended human dose (assuming a 50-kg woman). On a mg/kg basis these multiples are 300 times (in rats), 90 times (in mice), and more than 3 times (in rabbits) the maximum recommended human dose.

Hepatic Failure

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

PRECAUTIONS SECTION

- General

Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors, including benazepril HCl, may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. In a small study of hypertensive patients with renal artery stenosis in a solitary kidney or bilateral renal artery stenosis, treatment with benazepril HCl was associated with increases in blood urea nitrogen and serum creatinine; these increases were reversible upon discontinuation of benazepril HCl or diuretic therapy, or both. When such patients are treated with ACE inhibitors, renal function should be monitored during the first few weeks of therapy. Some 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 HCl has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of benazepril HCl and/or discontinuation of the diuretic may be required. Evaluation of the hypertensive patient should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

Hyperkalemia: In clinical trials, hyperkalemia (serum potassium at least 0.5 mEq/L greater than the upper limit of normal) occurred in approximately 1% of hypertensive patients receiving benazepril HCl. In most cases, these were isolated values which resolved despite continued therapy. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with benazepril HCl (see Drug Interactions).

Cough:

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

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

Information for Patients

Pregnancy: Female patients of childbearing age should be told about the consequences of exposure to benazepril HCl 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.
Angioedema: Angioedema, including laryngeal edema, can occur at any time with treatment with ACE inhibitors. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, or tongue, or difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.
Symptomatic Hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first days of therapy, and it should be reported to the prescribing physician. Patients should be told that if syncope occurs, benazepril HCl should be discontinued until the prescribing physician has been consulted.
All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.
Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.
Neutropenia: Patients should be told to promptly report any indication of infection (e.g., sore throat, fever), which could be a sign of neutropenia.
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 benazepril HCl. The possibility of hypotensive effects with benazepril HCl can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with benazepril HCl. If this is not possible, the starting dose should be reduced (see DOSAGE AND ADMINISTRATION).
Potassium Supplements and Potassium-Sparing Diuretics: Concomitant use with benazepril HCl may effect potassium levels. Monitor potassium periodically.
Oral Anticoagulants: Interaction studies with warfarin and acenocoumarol failed to identify any clinically important effects on the serum concentrations or clinical effects of these anticoagulants.
Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors (including benazepril) during therapy with lithium. Monitor lithium levels when used concomitantly with benazepril HCl.
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.
Anti-diabetics: In rare cases, diabetic patients receiving an ACE inhibitor (including benazepril) concomitantly with insulin or oral anti-diabetics may develop hypoglycemia. Such patients should therefore be advised about the possibility of hypoglycemic reactions and should be monitored accordingly.
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) 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 hypertension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Most patients receiving the combination of two RAS inhibitors do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function and electrolytes in patients on benazepril HCl and other agents that affect the

RAS.
Do not co-administer aliskiren with benazepril HCl in patients with diabetes. Avoid use of aliskiren with benazepril HCl in patients with renal impairment (GFR <60 ml/min).
Other:
Benazepril HCl has been used concomitantly with beta-adrenergic-blocking agents, calcium-channel-blocking agents, diuretics, digoxin, and hydralazine, without evidence of clinically important adverse interactions. Benazepril, like other ACE inhibitors, has had less than additive effects with beta-adrenergic blockers, presumably because both drugs lower blood pressure by inhibiting parts of the renin-angiotensin system.
The pharmacokinetics of benazepril are not affected by the following drugs: 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 (cimetidine kinetics were not studied).
Carcinogenesis, Mutagenesis, Impairment of Fertility
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 weights, this dose is 110 times the maximum recommended human dose. When compared on the basis of body surface areas, 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 (with or without metabolic activation), in an in vitro test for forward mutations in cultured mammalian cells, or in a nucleus anomaly test. In doses of 50 to 500 mg/kg/day (6 to 60 times the maximum recommended human dose based on mg/m2 comparison and 37 to 375 times the maximum recommended human dose based on a mg/kg comparison), Benazepril HCl had no adverse effect on the reproductive performance of male and female rats.
Nursing Mothers
Minimal amounts of unchanged benazepril and of benazeprilat are excreted into the breast milk of lactating women treated with benazepril. A newborn child ingesting entirely breast milk would receive less than 0.1% of the mg/kg maternal dose of benazepril and benazeprilat.
Geriatric Use
Of the total number of patients who received benazepril in U.S. clinical studies of benazepril HCl, 18% were 65 or older while 2% were 75 or older. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.
Benazepril and benazeprilat are substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.
Pediatric Use
Neonates with a history of in utero exposure to benazepril HCl:
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 with another ACE inhibitor, but experience is limited.
The antihypertensive effects of benazepril HCl have been evaluated in a double-blind study in pediatric patients 7 to 16 years of age (see CLINICAL PHARMACOLOGY: Pharmacodynamics,Hypertension). The pharmacokinetics of benazepril HCl have been evaluated in pediatric patients 6 to 16 years of age (see CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism). Benazepril HCl was generally well tolerated and adverse effects were similar to those described in adults. (See ADVERSE REACTIONS: Pediatric Patients). The long-term effects of benazepril on growth and development have not been studied. Infants below the age of 1 year should not be given benazepril HCl because of the risk of effects on kidney development.

Treatment with benazepril HCl is not recommended in pediatric patients less than 6 years of age (see ADVERSE REACTIONS), and in children with glomerular filtration rate <30 mL/min as there are insufficient data available to support a dosing recommendation in these groups. (See CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism,In Pediatric Patients and DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS SECTION

- Benazepril HCl has been evaluated for safety in over 6000 patients with hypertension; over 700 of these patients were treated for at least one year. The overall incidence of reported adverse events was comparable in benazepril HCl and placebo patients.

  The reported side effects were generally mild and transient, and there was no relation between side effects and age, duration of therapy, or total dosage within the range of 2 to 80 mg. Discontinuation of therapy because of a side effect was required in approximately 5% of U.S. patients treated with benazepril HCl and in 3% of patients treated with placebo.

  The most common reasons for discontinuation were headache (0.6%) and cough (0.5%) (see PRECAUTIONS, Cough).

  The side effects considered possibly or probably related to study drug that occurred in U.S. placebo-controlled trials in more than 1% of patients treated with benazepril HCl are shown below.

PATIENTS IN U.S. PLACEBO-CONTROLLED STUDIES

	BENAZEPRIL HCl (N=964)		PLACEBO (N=496)	
	N	%	N	%
Headache	60	6.2	21	4.2
Dizziness	35	3.6	12	2.4
Somnolence	15	1.6	2	0.4
Postural Dizziness	14	1.5	1	0.2

Other adverse experiences reported in controlled clinical trials (in less than 1% of benazepril patients or with less than 1% difference in incidence between benazepril or placebo treatment), and rarer events seen in post-marketing experience, include the following (in some, a causal relationship to drug use is uncertain):

Dermatologic: Stevens-Johnson syndrome, pemphigus, apparent hypersensitivity reactions (manifested by dermatitis, pruritus, or rash), photosensitivity, and flushing.

Gastrointestinal: Nausea, pancreatitis, constipation, gastritis, vomiting, and melena.

Hematologic: Thrombocytopenia and hemolytic anemia.

Neurologic and Psychiatric: Anxiety, decreased libido, hypertonia, insomnia, nervousness, and paresthesia.

Other: Fatigue, asthma, bronchitis, dyspnea, sinusitis, urinary tract infection, frequent urination, infection, arthritis, impotence, alopecia, arthralgia, myalgia, asthenia, sweating.

Another potentially important adverse experience, eosinophilic pneumonitis, has been attributed to other ACE inhibitors.

Pediatric Patients:

The adverse experience profile for pediatric patients appears to be similar to that seen in adult patients.

Clinical Laboratory Test Findings

Hemoglobin: Decreases in hemoglobin (a low value and a decrease of 5 g/dL) were rare, occurring in only 1 of 2,014 patients receiving benazepril HCl alone and in 1 of 1,357 patients receiving benazepril HCl plus a diuretic. No U.S. patients discontinued treatment because of decreases in

hemoglobin.
Other (causal relationships unknown): Elevations of uric acid, blood glucose, serum bilirubin, and liver enzymes (see WARNINGS) have been reported, as have scattered incidents of hyponatremia, electrocardiographic changes, eosinophilia, and proteinuria.

OVERDOSAGE SECTION

Single oral doses of 3 g/kg benazepril were associated with significant lethality in mice. Rats, however, tolerated single oral doses of up to 6 g/kg. Reduced activity was seen at 1 g/kg in mice and at 5 g/kg in rats. Human overdoses of benazepril have not been reported, but the most common manifestation of human benazepril overdosage is likely to be hypotension, which can be associated with electrolyte disturbances and renal failure.

Laboratory determinations of serum levels of benazepril and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of benazepril overdose.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of benazepril and its metabolites. Benazepril is only slightly dialyzable, but dialysis might be considered in overdosed patients with severely impaired renal function (see WARNINGS).

Angiotensin II could presumably serve as a specific antagonist-antidote in the setting of benazepril overdose, but angiotensin II is essentially unavailable outside of scattered research facilities. Because the hypotensive effect of benazepril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat benazepril overdose by infusion of normal saline solution.

If ingestion is recent, activated charcoal should be considered. Gastric decontamination (e.g., vomiting, gastric lavage) may be considered in individual cases, in the early period after ingestion.

Patients should be closely monitored for blood pressure and clinical symptoms. Supportive management should be employed to ensure adequate hydration and to maintain systemic blood pressure.

In the case of marked hypotension, physiological saline solution should be administered intravenously; depending on the clinical situation the use of vasopressors (e.g., catecholamines i.v.) may be considered.

DOSAGE & ADMINISTRATION SECTION

Hypertension

Adults

The recommended initial dose for patients not receiving a diuretic is 10 mg once a day. The usual maintenance dosage range is 20 mg to 40 mg per day administered as a single dose or in two equally divided doses. A dose of 80 mg gives an increased response, but experience with this dose is limited. The divided regimen was more effective in controlling trough (pre-dosing) blood pressure than the same dose given as a once-daily regimen. Dosage adjustment should be based on measurement of peak (2 to 6 hours after dosing) and trough responses. If a once-daily regimen does not give adequate trough response, an increase in dosage or divided administration should be considered. If blood pressure is not controlled with benazepril HCl tablets, USP alone, a diuretic can be added.

Total daily doses above 80 mg have not been evaluated.

Concomitant administration of benazepril HCl tablets, USP with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics can lead to increases of serum potassium (see PRECAUTIONS).

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally can

occur following the initial dose of benazepril HCl tablets, USP. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued two to three days prior to beginning therapy with benazepril HCl tablets, USP (see WARNINGS). Then, if blood pressure is not controlled with benazepril HCl tablets, USP alone, diuretic therapy should be resumed.

If the diuretic cannot be discontinued, an initial dose of 5 mg benazepril HCl tablets, USP should be used to avoid excessive hypotension.

Pediatrics

In children, doses of benazepril HCl tablets, USP between 0.1 and 0.6 mg/kg once daily have been studied, and doses greater than 0.1 mg/kg were shown to reduce blood pressure (see Pharmacodynamics). Based on this, the recommended starting dose of benazepril HCl tablets, USP is 0.2 mg/kg once per day as monotherapy. Doses above 0.6 mg/kg (or in excess of 40 mg daily) have not been studied in pediatric patients.

For pediatric patients who cannot swallow tablets, or for whom the calculated dosage (mg/kg) does not correspond to the available tablet strengths for benazepril HCl tablets, USP, follow the suspension preparation instructions below to administer benazepril HCl as a suspension.

Treatment with benazepril HCl tablets, USP is not advised for children below the age of 6 years (see PRECAUTIONS, Pediatric Use) and in pediatric patients with glomerular filtration rate <30 mL, as there are insufficient data available to support a dosing recommendation in these groups.

For Hypertensive Patients with Renal Impairment

For patients with a creatinine clearance <30 mL/min/1.73 m2 (serum creatinine >3 mg/dL), the recommended initial dose is 5 mg benazepril HCl tablets, USP once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 40 mg (see WARNINGS).

Preparation of Suspension (for 150 mL of a 2 mg/mL suspension)

Add 75 mL of Ora-Plus®* oral suspending vehicle to an amber polyethylene terephthalate (PET) bottle containing fifteen benazepril HCl tablets, USP 20 mg tablets, and shake for at least 2 minutes. Allow the suspension to stand for a minimum of 1 hour. After the standing time, shake the suspension for a minimum of 1 additional minute. Add 75 mL of Ora-Sweet®* oral syrup vehicle to the bottle and shake the suspension to disperse the ingredients. The suspension should be refrigerated at 2° to 8°C (36° to 46°F) and can be stored for up to 30 days in the PET bottle with a child-resistant screw-cap closure. Shake the suspension before each use.

*Ora-Plus® and Ora-Sweet® are registered trademarks of Paddock Laboratories, Inc. Ora-Plus® contains carrageenan, citric acid, methylparaben, microcrystalline cellulose, carboxymethylcellulose sodium, potassium sorbate, simethicone, sodium phosphate monobasic, xanthan gum, and water. Ora-Sweet® contains citric acid, berry citrus flavorant, glycerin, methylparaben, potassium sorbate, sodium phosphate monobasic, sorbitol, sucrose, and water.

HOW SUPPLIED SECTION

Benazepril HCl tablets, USP, 5 mg, are supplied as white, biconvex, round, uncoated tablets, debossed with “51” on one side and “A” on the other side.

They are available as follows:

Bottles of 30: NDC 65162-751-03

Bottles of 100: NDC 65162-751-10

Bottles of 500: NDC 65162-751-50

Benazepril HCl tablets, USP, 10 mg, are supplied as white, biconvex, round, uncoated tablets, debossed

with “52” on one side and “A” on the other side.

They are available as follows:

Bottles of 30: NDC 65162-752-03

Bottles of 100: NDC 65162-752-10

Bottles of 500: NDC 65162-752-50

Benazepril HCl tablets, USP, 20 mg, are supplied as white, biconvex, round, uncoated tablets, debossed with “53” on one side and “A” on the other side.

They are available as follows:

Bottles of 30: NDC 65162-753-03

Bottles of 100: NDC 65162-753-10

Bottles of 500: NDC 65162-753-50

Benazepril HCl tablets, USP, 40 mg, are supplied as white, biconvex, round, uncoated tablets, debossed with “54” on one side and “A” on the other side.

They are available as follows:

Bottles of 30: NDC 65162-754-03

Bottles of 100: NDC 65162-754-10

Bottles of 500: NDC 65162-754-50

Storage: Store at 20º to 25°C (68° to 77ºF); excursions permitted to 15º to 30°C (59º to 86°F) [See USP Controlled Room Temperature]. Protect from moisture.

Dispense in tight container as defined in the USP.

To report SUSPECTED ADVERSE REACTIONS, contact Amneal Pharmaceuticals at (1-877-835-5472) or www.amneal.com or FDA at 1-800-FDA-1088 or www.fda.gove/medwatch

Manufactured by:

Amneal Pharmaceuticals of NY

Hauppauge, NY 11788

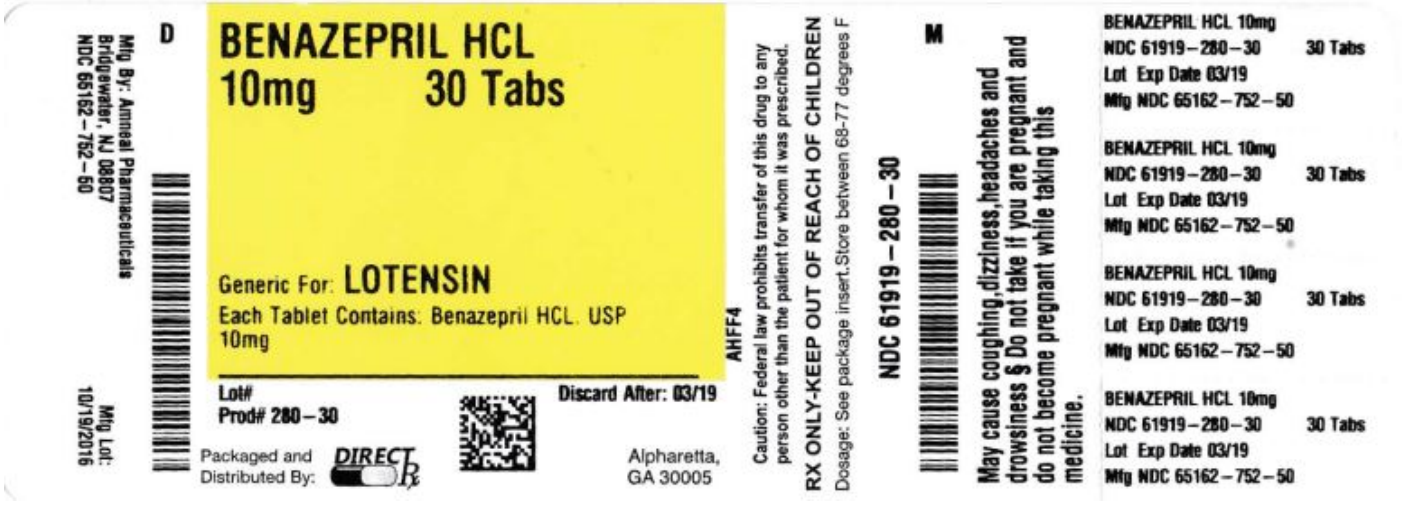
Distributed by:

Amneal Pharmaceuticals

Glasgow, KY 42141

Rev. 01-2015-00

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL



BENAZEPRIL HYDROCHLORIDE

benazepril hydrochloride tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:61919-280(NDC:65162-752)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
BENAZEPRIL HYDROCHLORIDE (UNII: N1SN99T69T) (BENAZEPRILAT - UNII:JRM708L703)	BENAZEPRIL HYDROCHLORIDE	10 mg

Product Characteristics			
Color	white	**Score**	no score
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	52;A
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:61919-280-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	01/01/2014	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076820	01/01/2014	

Labeler - DIRECT RX (079254320)

Establishment

Name	Address	ID/FEI	Business Operations
DIRECT RX		079254320	relabel(61919-280) , repack(61919-280)

Revised: 1/2020

DIRECT RX