PRODUCT MONOGRAPH

pms-BENAZEPRIL
(benazepril hydrochloride)

5 mg, 10 mg and 20 mg Tablets

Angiotensin-Converting Enzyme Inhibitor

Pharmascience Inc.
6111 Royalmount Ave
Bureau 100
Montréal, Québec, Canada
H4P 2T4

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Date of Revision:
February 7, 2007

Control#: 111635

Name of Drug

pms-BENAZEPRIL
(benazepril hydrochloride)
5 mg, 10 mg and 20 mg tablets

Pharmacological Classification

Angiotensin Converting Enzyme Inhibitor

Action and Clinical Pharmacology

pms-BENAZEPRIL (benazepril HC1) is an angiotensin converting enzyme (ACE) inhibitor which is used in the treatment of hypertension.

Benazepril, after hydrolytic bioactivation to benazeprilat, inhibits angiotensin converting enzyme (ACE), a peptidyl dipeptidase catalyzing the conversion of angiotensin I to the vasoconstrictor angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex, leading to sodium resorption and potassium secretion by the distal renal tubules.

Inhibition of ACE results in a decrease in plasma angiotensin II, leading to decreased vasoconstriction and a small decrease in aldosterone secretion and plasma aldosterone concentrations. Although the decrease in aldosterone is small, it can result in small increases in serum potassium. Slight increases in serum potassium have been observed in some hypertensive patients treated with benazepril alone. Essentially no change in mean serum potassium was seen in patients treated with benazepril and a thiazide diuretic (see Precautions).

Removal of inhibition of renin secretion by angiotensin II leads to increased plasma renin activity (due to removal of negative feedback of renin release).

ACE is identical to kininase II. Thus, benazepril may interfere with degradation of the potent peptide vasodilator, bradykinin. Whether increased levels of bradykinin play a role in the therapeutic effects of benazepril is unknown.
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. In particular, benazepril was antihypertensive in all races studied, although it was somewhat less effective in blacks than in nonblacks.

Pharmacokinetics and Metabolism

Following oral administration of pms-BENAZEPRIL, peak plasma concentrations of benazepril are reached within 0.5-1.0 hours. The extent of absorption is at least 37% as determined by urinary recovery of unchanged drug and its metabolites. Following absorption, benazepril is rapidly hydrolyzed to its active metabolite benazeprilat. Peak plasma concentrations of benazeprilat are reached 1-2 hours after drug intake in the fasting state and 2-4 hours after drug intake in the nonfasting state. While the rate of absorption may be slowed by the presence of food in the gastrointestinal tract, the systemic availability of benazeprilat is not affected. Benazeprilat is eliminated predominantly by renal excretion and has an effective accumulation half-life of 10-11 hours. The serum protein binding of benazepril is about 97%, and that of benazeprilat about 95%.

Benazepril is almost completely metabolized to benazeprilat, and to the glucuronide conjugates of benazepril and benazeprilat. Only trace amounts of an administered dose of benazepril 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 (10-40 mg).

The disposition of benazepril and benazeprilat in patients with mild to moderate renal insufficiency (creatinine clearance > 30 mL/min [0.5 mL/s]) is similar to that in patients with normal renal function. In patients with creatinine clearance < 30 mL/min [0.5 mL/s], peak benazeprilat levels and the initial (alpha phase) half-life increase, and time to steady state may be delayed (see Dosage and Administration).

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

Pharmacodynamics

Administration of benazepril to patients with mild to moderate essential hypertension results in a reduction of both supine and standing blood pressure usually with little or no orthostatic change. Symptomatic postural hypotension is infrequent, although it may occur in patients who are salt- and/or volume-depleted **(see Warnings).**

After administration of a single oral dose, the onset of antihypertensive activity occurs at approximately one hour, with maximum reduction of blood pressure achieved by 2-4 hours in most patients. At recommended doses given once daily, antihypertensive effects have persisted for at least 24 hours. In dose-response studies using once daily dosing in mild to moderate essential hypertensive patients, the minimally effective daily dose of benazepril was 10 mg. In studies comparing the same daily dose of benazepril 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.

During chronic therapy, the maximum reduction in blood pressure with any dose is generally achieved after 1-2 weeks. Abrupt withdrawal of benazepril hydrochloride has not been associated with a rapid increase in blood pressure.

When benazepril is given together with thiazide-type diuretics, its blood pressure lowering effect is approximately additive.
Efficacy and safety appear to be the same for elderly (> 65 years of age) and younger adult patients given the same daily dosages.

Indications And Clinical Use

pms-BENAZEPRIL (benazepril HCl) is indicated in the treatment of mild to moderate essential hypertension. It may be used alone or in association with thiazide diuretics.

In using pms-BENAZEPRIL, consideration should be given to the risk of angioedema (see Warnings).
pms-BENAZEPRIL should normally be used in those patients in whom treatment with a diuretic or a beta-blocker was found ineffective or has been associated with unacceptable adverse effects.

pms-BENAZEPRIL can also be tried as an initial agent in those patients in whom use of diuretics and/or betablockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

The safety and efficacy of benazepril in congestive heart failure and renovascular hypertension have not been established and therefore, its use in these conditions is not recommended.

The safety and efficacy of concurrent use of pms-BENAZEPRIL with antihypertensive agents other than thiazide diuretics have not been established.

Contraindications

pms-BENAZEPRIL (benazepril HCl) is contraindicated in patients with known hypersensitivity to this product or any of its components and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

Warnings

Serious Warnings and Precautions

When used in pregnancy, angiotensin converting enzyme (ACE) inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected, pms-BENAZEPRIL should be discontinued as soon as possible.

Angioedema

Angioedema has been reported in patients with ACE inhibitors, including pms-BENAZEPRIL (benazepril HC1). Angioedema associated with laryngeal involvement may be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, pms-BENAZEPRIL should be

discontinued immediately, the patient treated appropriately in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment, although antihistamines may be useful in relieving symptoms. Where there is involvement of tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy (including, but not limited to 0.3 to 0.5 mL of subcutaneous epinephrine solution 1:1000) should be administered promptly (**see Adverse Reactions**).

The incidence of angioedema during ACE inhibitor therapy has been reported to be higher in black patients of African origin than in non-black patients.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see Contraindications).

Hypotension

Occasionally, symptomatic hypotension has occurred after administration of benazepril hydrochloride usually after the first or second dose or when the dose was increased. It is more likely to occur in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In patients with ischemic heart disease or cerebrovascular disease, an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident (**see Adverse Reactions**). Because of the potential fall in blood pressure in these patients, therapy with benazepril should be started under close medical supervision. Such patients should be followed closely for the first weeks of treatment and whenever the dose of benazepril hydrochloride is increased. In patients with severe congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension and has been associated with oliguria, and/or progressive azotemia, and rarely, with acute renal failure and/or death.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has increased after volume expansion. However, lower doses of benzapril hydrochloride and/or reduced concomitant diuretic therapy should be considered.

Neutropenia / Agranulocytosis

Agranulocytosis and bone marrow depression have been caused by ACE inhibitors. Current experience benazepril hydrochloride shows the incidence to be rare and a causal relationship to the administration of benazepril has not been established. Periodic monitoring of white blood cell counts should be considered, especially in patients with collagen vascular disease and/or renal disease.

Use in Pregnancy

ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is detected, benazepril hydrochloride should be discontinued as soon as possible.

Infants with a history of exposure to ACE inhibitors in utero should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for impaired renal function, however, experience with these procedures is limited and they have not been associated with significant clinical benefit.

It is known if benazepril hydrochloride can be removed from the body by hemodialysis.

Human Data: The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function, associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development.

Prematurity, and patent ductus arteriosus and other structural cardiac malformations, as well as neurologic malformations, have also been reported following exposure in the first trimester of pregnancy.

Animal Data: Dose related maternal toxicity was observed in studies of pregnant rats, mice and rabbits at doses of 250 mg/kg, 150 mg/kg and 1 mg/kg respectively. No embryotoxic or teratogenic effects of benazepril were seen at doses up to 250 mg/kg in rats (300 times the maximum recommended dose in humans), 150 mg/kg in mice (90 times the maximum recommended dose in humans) and 5 mg/kg in rabbits (more than 3 times the maximum recommended dose in humans).

Nursing Women:

The presence of concentration of ACE inhibitor have been reported in human milk. Use of ACE inhibitors is not recommended during breast-feeding.

Precautions

Renal Impairment

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensinaldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk.

Use of benazepril hydrochloride should include appropriate assessment of renal function.

Anaphylactoid Reactions During Membrane Exposure

Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g. polyacrylonitrile [PAN]) and treated concomitantly with an ACE inhibitor. Dialysis should be

stopped immediately if symptoms such as nausea, abdominal cramps, burning, angioedema, shortness of breath and severe hypotension occur. Symptoms are not relieved by antihistamines. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agents.

Anaphylactoid Reactions During Desensitization

There have been isolated reports of patients experiencing sustained life threatening anaphylactoid reactions while receiving ACE inhibitors during desensitizing treatment with hymenoptera (bees, wasps) venom. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld for at least 24 hours, but they have reappeared upon inadvertent rechallenge.

Hyperkalemia and Potassium-Sparing Diuretics

Elevated serum potassium (> 5.5 mEq/L) was observed in 1.1% of hypertensive patients in clinical trials treated with benazepril alone and in 0.4% treated with benazepril and hydrochlorothiazide. In most cases these were isolated values, which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in less than 0.1% of hypertensive patients.

Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia (**see Drug Interactions**).

Valvular Stenosis

There is concern on theoretical grounds that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction.

Surgery/Anesthesia

Patients on ACE inhibitors may augment the hypotensive effects of anesthetics and analgesics. 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.

Impaired Liver Function

Hepatitis (hepatocellular and/or cholestatic), elevations of liver enzymes and/or serum bilirubin have occurred during therapy with ACE inhibitors in patients with or without pre-existing liver abnormalities. In most cases the changes were reversed on discontinuation of the drug.

Elevations of liver enzymes and/or serum bilirubin have been reported with benazepril (**see Adverse Reactions**). Should the patient receiving pms-BENAZEPRIL experience any unexplained symptoms particularly during the first weeks or months of treatment, it is recommended that a full set of liver function tests and any other necessary investigations be carried out. Discontinuation of pms-BENAZEPRIL should be considered when appropriate.

There are no adequate studies in patients with cirrhosis and/or liver dysfunction. Benazepril hydrochloride should be used with particular caution in patients with pre-existing liver abnormalities. In such patients, baseline liver function tests should be obtained before administration of the drug and close monitoring of response and metabolic effects should apply.

Cough

A dry, persistent cough, which usually disappears only after withdrawal or lowering of the dose benazepril has been reported. Such possibility should be considered as part of the differential diagnosis of the cough.

Pediatric Use

Safety and effectiveness of benazepril hydrochloride in children have not been established, therefore its use in this age group is not recommended.

Use in the Elderly

Although clinical experience has not identified differences in response between the elderly (> 65 years) and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Drug Interactions

Concomitant Diuretic Therapy

Patients concomitantly taking ACE inhibitors and diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy. The possibility of hypotensive effects after the first dose of benazepril hydrochloride can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with benazepril hydrochloride. If it is not possible to discontinue the diuretic, the starting dose of benazepril hydrochloride should be reduced and the patient should be closely observed for several hours following initial dose and until blood pressure has stabilized (**see Warnings and Dosage And Administration**).

Agents Causing Renin Release

The antihypertensive effect of benazepril is augmented by antihypertensive agents that cause renin release (e.g. diuretics).

Agents Increasing Serum Potassium

Since benazepril hydrochloride decreases aldosterone production, increases of serum potassium may occur. Potassium sparing diuretics (e.g. spironolactone, triamterene, amiloride, etc.) or potassium supplements should be given only for documented hypokalemia and with caution and frequent monitoring of serum potassium, since they may lead to a significant increase in serum potassium. Salt substitutes, which contain potassium, should also be used with caution.

Agents Affecting Sympathetic Activity

Agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) may be used with caution. β-adrenergic blocking agents add some further antihypertensive effect to benazepril.

Indomethacin

Indomethacin may diminish the antihypertensive efficacy of concomitantly administered benazepril.

Oral Anticoagulants

Multiple dose interaction studies failed to identify any clinically important effects on the serum concentrations, the degree of protein binding or the anticoagulant effect (measured by prothrombin time) of warfarin and nicoumalone. The bioavailability of benazeprilat was not assessed during the coadministration of benazepril hydrochloride with warfarin or nicoumalone.

Lithium

Increased lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

Hydrochlorothiazide, Chlorthalidone and Furosemide

The bioavailability of benazepril hydrochloride was not altered when single doses were administered concomitantly with the diuretics hydrochlorothiazide, chlorthalidone or furosemide.

Aspirin

No important changes in pharmacokinetic parameters occurred when single doses of benazepril hydrochloride were administered concomitantly with aspirin.

Digoxin

In a single dose interaction study of benazepril hydrochloride with multiple doses of digoxin, no important changes in pharmacokinetic parameters were observed.

Amlodipine/Nifedipine

Benazepril has been used concomitantly with the calcium channel blockers amlodipine and nifedipine, without evidence of clinically important adverse interactions.

Other

In separate single or multiple dose pharmacokinetic interaction studies, the bioavailability of benazepril hydrochloride was not altered by coadministration with propranolol, naproxen, atenolol, nifedipine or cimetidine.

Information for the Patient

Note: As with many other drugs, certain advice to patients being treated with benazepril hydrochloride is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse experiences or intended effects.

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of benazepril hydrochloride. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema, such as swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing. They should immediately stop taking benazepril hydrochloride and consult with their physician.

Hypotension: Patients should be cautioned to report light-headedness, especially during the first few days of benazepril hydrochloride therapy. If actual syncope occurs, the patient should be told to discontinue the drug and consult with their physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with their physician.

Agranulocytosis/Neutropenia: Patients should be told to report promptly to their physician any indication of infection (e.g. sore throat, fever), as this may be a sign of neutropenia.

Impaired Liver Function: Patients should be advised to return to their physician if he/she experiences any symptoms possibly related to liver dysfunction. This would include "viral-like symptoms" in the first weeks to months of therapy (such as fever, malaise, muscle pain, rash or adenopathy which are possible indicators of hypersensitivity reactions), or if abdominal pain, nausea or vomiting, loss of appetite, jaundice, itching or any other unexplained symptoms occur during therapy.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Pregnancy: Since the use of benazepril hydrochloride during pregnancy can cause injury and even death of the developing fetus, patients should be advised to report promptly to their physician if they become pregnant.

Nursing Women

The presence of concentrations of ACE inhibitor have been reported in human milk. Use of ACE inhibitors is not recommended during breast-feeding.

Adverse Reactions

Benazepril hydrochloride has been evaluated for safety in over 6,000 hypertensive patients. Over 400 elderly patients have participated in controlled hypertension trials. Long-term safety has

been assessed in more than 700 patients treated for 1 year or more. There was no increase in the incidence of adverse reactions in elderly patients given the same daily dose. The overall frequency of adverse reactions was not related to duration of therapy or total daily dose.

The most severe adverse reactions occurring in clinical trials with benazepril hydrochloride were: angioedema (full clinical syndrome, 1 case; edema of lips or face without the other manifestations of angioedema, 0.5%), hypotension (0.3%), postural hypotension (0.4%) and syncope (0.1%). Hypotension or postural dizziness was a cause for discontinuation of therapy in < 0.2% of patients treated with benazepril alone. Myocardial infarction and cerebral vascular accident occurred, possibly secondary to excessive hypotension in high risk patients (see **Warnings**).

The most frequent clinical adverse reactions in placebo-controlled clinical trials with benazepril monotherapy (N=964) were headache (6.2%), dizziness (3.6%), fatigue (2.4%), somnolence (1.6%), postural dizziness (1.5%), nausea (1.3%) and cough (1.2%). Discontinuation of therapy due to adverse experiences was required in 4% of patients treated with benazepril hydrochloride.

Adverse reactions occurring in 1% or more of the 2004 patients in controlled hypertension trials who were treated with benazepril hydrochloride monotherapy, are listed below:

Body System		Patients (N=2004)
Nervous System	Headache	10.2%
	Dizziness	4.2%
	Somnolence	1.1%
	Vertigo	1.1%
Respiratory	Upper respiratory symptoms	5.4%
	Increased cough	3.4%
	Flu symptoms	1.2%
Gastrointestinal	Nausea	2.5%
	Abdominal pain	2.4%
	Diarrhea	2.0%
	Dyspepsia	1.2%
Musculoskeletal	Musculoskeletal pain	2.6%
Other	Fatigue	3.6%
	Rhinitis	2.4%
	Pharyngitis	1.7%
	Back Pain	1.7%
	Chest Pain	1.2%

Clinical adverse reactions occurring in less than 1% of patients treated with benazepril in controlled and uncontrolled clinical trials, and postmarketing experience, are listed below by body system:

Incidence less than 1%

Body as Whole: asthenia

Cardiovascular: excessive hypotension, angina pectoris, palpitations, myocardial infarction, cerebrovascular accident, arrhythmia

Digestive:	constipation, gastritis, vomiting, flatulence, melena, abdominal pain, pancreatitis
Musculoskeletal:	arthritis, arthralgia, myalgia
Nervous:	anxiety, depression, hypertonia, insomnia, nervousness, paresthesia, incoordination, decreased libido.
Respiratory:	dyspnea, asthma, bronchitis
Dermatologic:	apparent hypersensitivity reactions (manifested by dermatitis, pruritus, or rash), photosensitivity, pemphigus, flushing, Stevens-Johnson Syndrome
Special Senses:	tinnitus, taste disorders
Urogenital:	impaired renal function, impotence, urinary frequency
Hematologic:	leucopenia, eosinophilia, hemolytic anemia and thrombocytopenia
Allergic and immune reactions:	angioedema, lip and/or facial edema
Liver:	hepatitis (predominantly cholestatic), cholestatic jaundice

Abnormal Laboratory Findings

Hyperkalemia (see Precautions)

Creatinine, Blood Urea Nitrogen: Increases in serum creatinine (> 150% of baseline) were observed in 2% of patients treated with benazepril hydrochloride alone. Less than 0.1% of these patients developed simultaneous increases in blood urea nitrogen and serum creatinine. Increases are more likely to occur in patients receiving concomitant diuretic therapy than in those on benazepril hydrochloride alone. These increases often reversed on continued therapy.

Neutropenia: Neutrophil counts of less than 1500/mm^3 occurred in 2% of patients treated with benazepril hydrochloride alone. No patient was discontinued from a study because of a low neutrophil or white blood cell (WBC) count. No patient developed a persistent neutrophil count < 1000/mm3 and no patient developed a serious infection in association with a reduced neutrophil or WBC count. No patient treated with benazepril hydrochloride developed agranulocytosis (**see Warnings**).

Hemoglobin: Decreases in hemoglobin (a low value and a decrease of 5 g/dL) occurred in only one of 2014 patients receiving benazepril hydrochloride alone and in 1 of 1357 patients receiving benazepril hydrochloride plus a diuretic.

Hepatic: Elevations of liver enzymes and/or serum bilirubin have occurred (**see Precautions**).

Other: Elevations of uric acid and blood glucose have been reported, as have scattered incidents of hyponatremia and proteinuria.

Symptoms And Treatment Of Overdosage

No data are available on overdosage in humans.

The most likely clinical manifestation of overdosage would be symptoms attributable to severe hypotension, for which the usual treatment is intravenous infusion of normal saline solution.

If ingestion is recent, then emesis should be induced. Although the active metabolite, benazeprilat, is only slightly dialysable, renal dialysis may be useful in overdosed patients with severely impaired renal function.

Dosage And Administration

Dosage of pms-BENAZEPRIL (benazepril HCl) must be individualized. Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation and salt restriction. The dosage of other antihypertensive agents being used with pms-BENAZEPRIL may need to be adjusted.

Monotherapy: The recommended initial dose of pms-BENAZEPRIL is 10 mg once daily. Dosage should be adjusted according to blood pressure response, generally, at intervals of at least two weeks.

The usual maintenance dose is 20 mg daily. The maximum daily dose of pms-BENAZEPRIL is 40 mg.

In some patients treated once daily, the antihypertensive effect may diminish towards the end of the dosing interval. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, either twice daily administration with the same total daily dose, or an increase in dose should be considered.

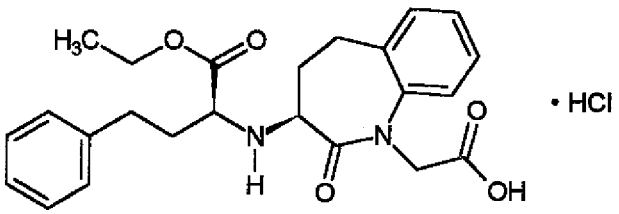
If blood pressure is not controlled with pms-BENAZEPRIL alone, a diuretic may be added. After the addition of a diuretic, it may be possible to reduce the dose of pms-BENAZEPRIL.

Concomitant Diuretic Therapy: Symptomatic hypotension occasionally may occur following the initial dose of pms-BENAZEPRIL and is more likely in patients who are currently being treated with a diuretic. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with pms-BENAZEPRIL to reduce the likelihood of hypotension (**see Warnings**). If the diuretic cannot be discontinued, an initial dose of 5 mg pms-BENAZEPRIL should be used with careful medical supervision for several hours and until blood pressure has stabilized. The dosage of pms-BENAZEPRIL should subsequently be titrated (as described above) to the optimal response.

Dosage Adjustment in Renal Impairment: The usual dose of pms-BENAZEPRIL is recommended for patients with a creatinine clearance > 30 mL/min [0.5 mL/s]. For patients with severe renal impairment (creatinine clearance of < 30 mL/min [0.5 mL/s]), the initial daily dose is 5 mg. Titration must be individualized. The dosage may be titrated upwards to 10 mg/day. For further reductions in blood pressure the addition of a diuretic or another antihypertensive should be considered or alternatively, the dose of pms-BENAZEPRIL can be increased.

Pharmaceutical Information

Drug Substance



Benazepril Hydrochloride

Chemical Name: 3-[(1-(Ethoxycarbonyl)-3-phenyl-(1S)-propyl) amino]-2,3,4,5-tetrahydro-2-oxo-1H-l-(3S)-benzazepine-l-acetic acid monohydrochloride

Molecular Formula: $C_{24}H_{22}N_20_5$ x HC1

Molecular Weight: 460.96

Description: Practically odourless, white to off-white crystalline powder.

Solubility: Freely soluble in methanol and ethanol, soluble in water and phosphate buffer (pH 7), slightly soluble in dichloromethane and ethyl acetate, practically insoluble in cyclohexane.

pKa: 3.1 and 5.3 (when in water)

Melting Point: 180.5-181.6°C.

Composition:

pms-BENAZEPRIL 5 mg, 10 mg and 20 mg film-coated tablets also contain cellulose compounds, colloidal silicon dioxide, corn starch, hydrogenated castor oil, iron oxide, lactose, polyethylene glycol, povidone, talc and titanium dioxide.

Stability and Storage Recommendations:

Protect from heat (i.e., store at 15°C - 30°C) and humidity.

Availability Of Dosage Forms

pms-BENAZEPRIL 5 mg Tablets

Light yellow, capsule-shaped, biconvex film-coated tablets. Fully bisected on both sides. Available in bottles of 100.

pms-BENAZEPRIL 10 mg Tablets
Dark yellow, capsule-shaped, biconvex film-coated tablets. Fully bisected on both sides. Available in bottles of 100.

pms-BENAZEPRIL 20 mg Tablets
Reddish-orange, capsule-shaped, biconvex film-coated tablets. Fully bisected on both sides. Available in bottles of 100.

Information For The Consumer

Serious Warning and Precautions

pms- BENAZEPRIL should not be used during pregnancy. If you discover that you are pregnant while taking pms-BENAZEPRIL, stop the medication and please contact your physician as soon as possible.

Your doctor has decided to use pms-BENAZEPRIL (benazepril HC1) to treat your high blood pressure. Here are some things to know about pms-BENAZEPRIL in order to use it safely, and get the most benefit.

Patients who have high blood pressure are often unaware of any signs of this problem. In fact, many feel quite normal. Yet, if high blood pressure is not treated, it can cause serious problems such as heart disease, blood vessel disease, stroke or kidney disease. Some patients have to take medicine to control high blood pressure for the rest of their lives. It is very important that you take your medicine exactly as directed and keep regular appointments with your doctor even if you feel well.

pms-BENAZEPRIL (benazepril HCL) belongs to a class of drugs known as Angiotensin Converting Enzyme (ACE) inhibitors. pms-BENAZEPRIL (benazepril HCL) helps to control high blood pressure by preventing your body from producing a substance (angiotensin) that increases blood pressure.

Using PMS-BENAZEPRIL safely

What does your doctor need to know about you?

To decide whether you can take pms-BENAZEPRIL safely, your doctor must know whether you have certain medical conditions. Before taking pms-BENAZEPRIL, make sure your doctor knows if you have:

- allergic reactions to drugs
- kidney disease
- previously taken medications, especially diuretics ("water pills")
- other medical problems.

Are you pregnant or breast-feeding or thinking of becoming pregnant?

Taking pms-BENAZEPRIL during pregnancy can cause injury and even death to your baby. This medicine should not be used during pregnancy. If you become pregnant while taking pms-BENAZEPRIL, stop the medication and report to your doctor as soon as possible. It is possible that pme-BENAZEPRIL passes into breast milk. You should not breast-feed while taking pms-BENAZEPRIL.

What about taking other drugs at the same time?

Please give your doctor precise information on any other drugs you may be taking, especially other drugs that lower blood pressure, drugs serving to remove fluids (diuretics, "water pills") or potassium supplements (e.g., SLOW K®).

Salt substitute preparations

You should not take any salt substitutes containing potassium while using pms-BENAZEPRIL. Read the label of these products to see if they contain potassium.

What are the side effects?

Along with its intended action, any medication, including pms-BENAZEPRIL, may cause side effects. Most people do not have any problems with side effects, but if they do occur they may require medical attention.

During the first few days of pms-BENAZEPRIL therapy, some patients may experience light-headedness or dizziness. If this happens to you it should be reported to your doctor. If your dizziness is severe and causes fainting, stop taking pms-BENAZEPRIL and contact your doctor. Dizziness or light-headedness may also occur during your pms-BENAZEPRIL therapy if you experience an extreme loss of body water due to excessive sweating, inadequate fluid intake, vomiting or diarrhea.

In rare instances, patients who have been given an ACE inhibitor drug have developed swelling of the face, lips, tongue, ankles, wrists, or difficulty swallowing or breathing. In the event that you develop any of these symptoms, you should stop taking pms-BENAZEPRIL and contact your doctor immediately.

The following reactions may also occur at the start of treatment with pms-BENAZEPRIL: tiredness, drowsiness, nervousness, difficulty sleeping, feelings of anxiety, headache, stomach upset, palpitations, hot flushes and noises in the ears. These reactions often go away within 1-2 weeks of treatment. However, if these or any other problems appear and do not go away during treatment, you should report them to your doctor.

Please tell your doctor if any of the following happens:

- a sign of infection (e.g., sore throat, fever)
- "viral-like" symptoms (e.g., fever, a feeling of illness, muscle pain, rash, enlargement of glands), abdominal pain, nausea, vomiting, loss of appetite, jaundice (yellowing of skin and/or eyes), itching or any other unexplained symptoms that occur in the first weeks to months of therapy
- coughing, sore throat, sinusitis
- sad mood (depression)
- pain in the chest.

Sometimes drugs for the treatment of high blood pressure may adversely affect your powers of concentration. Make sure you know how you react to pms-BENAZEPRIL before you drive, use

machines or do other tasks that require you to be alert.

How to take pms-BENAZEPRIL

Always take your dose of pms-BENAZEPRIL as directed by your doctor. Never change the dose unless told to do so. You can take your pms-BENAZEPRIL before, during or after a meal since food will not decrease its effectiveness.

pms-BENAZEPRIL will not cure high blood pressure, but it does help to control it. You must continue to take pms-BENAZEPRIL as directed if you expect to lower your blood pressure and keep it down. It is important that your doctor check your progress at regular visits to make sure that this medicine is working the way it should.

To help you to remember to take your medicine, try to take it at the same time each day. If you miss a dose, try to take the missed dose as soon as possible. If it is less than 10 hours until your next dose anyway, skip the missed dose and then go back to your regular dosing schedule. Do not take two doses at the same time.

Storage

Protect your tablets from heat (store at 15°C - 30°C) and humidity.

Always remember

Your doctor has prescribed pms-BENAZEPRIL for you after a careful review of your medical condition. Use it only as directed and do not give it to anyone else. If you require more information, consult your doctor or pharmacist. Keep this and all medication out of the reach of children. If you suspect you are experiencing side effects, stop taking the tablets, and notify your doctor.

Pharmacology

Benazepril HC1 exhibited antihypertensive activity in spontaneously hypertensive and renal hypertensive rats in oral doses ranging from 0.1 to 10 mg/kg. Antihypertensive efficacy was evident in renal hypertensive dogs receiving 3.0 mg/kg P.O. of benazepril HCI. In these rat and dog models, blood pressure reductions were detected as early as 1.5 to 2 hours after the first dose and activity persisted up to 24 hours after dosage. The antihypertensive efficacy gradually increased up to the second or third day of dosage when benazepril was given once daily. In the hypertensive rat studies, no tolerance to the antihypertensive action was evident with daily dosage continued up to 4 weeks. There was a gradual return to initial levels when treatment was discontinued.
In hemodynamic studies in dogs, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance, with an increase in cardiac output and renal blood flow and little or no change in heart rate.

In spontaneous hypertensive rats, blood flow to various tissue beds (kidney, heart, and selected brain and gastrointestinal regions) was unaffected by benazepril.

Characterization of the ACE inhibitory activity of benazepril and benazeprilat was provided directly by studies with the isolated enzyme or tissues containing the enzyme. Indirect evidence of enzyme inhibition was provided by prevention of the effects of angiotensin I on contraction of isolated smooth muscle preparations and on pressor responses of rats and dogs.

In a study in dogs, benazepril was shown to potentiate the hypotensive effect of an injection of bradykinin, the degradation of which is catalyzed by ACE.

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.

Benazepril passes the blood-brain barrier only to an extremely low extent, as evidenced by studies in rats with 14C-labelied benazepril, in which the lowest concentration of radioactivity was found in the brain (0.14 .tg/g compared to blood concentrations of 3-4.5 p.g/g). Multiple doses of benazepril HCI resulted in relatively high concentrations for a short period of time in liver and excretory organs (renal and biliary excretion). No particular tissue affinity was observed except for a slight increase in concentration in the lung, due to slower elimination in that organ. Some placental passage occurend when the drug was admiunistered to pregnant rats.

Toxicology

Acute Toxicity

Species	Route	Sex	LD_{50} (mg/kg)
Mouse	P.O.	♂	3350-4019
		♀	3160
	I.V.	♂	562
		♀	537
	S.C.	♂	> 3200
		♀	> 3600
Rat	P.O.	♂	> 5000
	I.V.	♂	432
		♀	483
	S.C.	♂	3400
		♀	4200

Signs of toxicity in rodents include ptosis, reduced activity, exophthalmus, bradypnea, clonic spasms and dyspnea.

Intravenous doses of 2.5 mg/kg induced no adverse affects in the female beagle. Emesis and anorexia were noted in beagles given oral doses ^{3} 250 mg/kg and ^{3} 500 mg/kg respectively. One dog was found dead on the fifth day post-dose after daily signs of emesis, anorexia, nasal discharge and reduced activity.

Long-Term Toxicity Studies of Benazepril

Species	Duration	Sex	Route	Daily doses	Results
Rat	13 wks	♀&♂	P.O.	0, 1, 10, 100, 1000 mg/kg	Salivation at high dose. ↓ food consumption & body weight gain in ♂ ≥ 10 mg/kg, ♀ ≥ 100 mg/kg. Urinary effects in ♂ ≥ 10 mg/kg. Anemia in high dose ♂ + ♀. ↑ inorganic phosphorous in high dose ♂ and ♀ & ↑ BUN in high dose ♂. ↑ K^+ in ♂ at doses ≥ 10 mg/kg. ↓ total protein & albumin in ♂ at doses ≥100 mg/kg. A ↓ absolute and relative weight of liver, heart and thyroid in ♂ and ↑ relative kidney weights in ♀ at doses ≥100 mg/kg. ↑ PAS & granules in JG-cells ≥10 mg/kg. Most effects reversible after 5 weeks. No gross changes attributed to treatment at autopsy.
Rat	6 months	♀&♂	P.O.	0, 15, 50, 150 mg/kg	↓ body weight gain in ♂ ≥ 50 mg/kg. ↑ BUN, ↓ ACE at doses ≥ 50 mg/kg. Organ weight effects (heart & liver ↓; kidney ↑) at all dose levels. ↑ serum K^+ in 150 mg/kg ♂. Focal tubular cortical renal lesions in high dose ♂ & ♀.
Rat	52 weeks	♀&♂	Diet	0, 10, 50, 250 mg/kg	No compound related mortalities. ↓ erythroid parameters ≥50 mg/kg. ↑ in mean percent reticulocytes in ♀ at 250 mg/kg. ↑ in mean serum K^+ in ♂ at ≥50 mg/kg and Cl^- in ♂ or ♀ at ≥ 10 mg/kg. ↑ BUN at ≥ 50 mg/kg. At all doses: ↓ food consumption & body weight gain, JG-cell & arteriolar hypertrophy, and ↓ senile nephropathy. ↓ in mean absolute and/or relative heart weight. ↓ kidney and liver weights in all ♂ and high dose ♀.↑ prostate weights in at ♂ at ≥ 50 mg/kg and thymus at ≥ 250mg/kg.
Dog	13 weeks	♀&♂	P.O (gavage)	0, 1, 10, 30, 100 → 150 mg/kg (dose ↑ on test day 50)	No mortalities and related compound effects only at high dose. Emesis and anorexia. ↑ body weight gain ♂. ↑ SGPT, BUN, creatinine. ↓ heart weights without ECG or microscopic changes. No microscopic pathological changes.
Dog	12 months	♀&♂	P.O. (capsule)	0, 15, 50, 150 mg/kg	No mortality and no clinical signs related to compound. ↓ food consumption & body weight gain in ♂ ≥50 mg/kg. ↑ BUN and erythroid parameters at some time points at ≥ 50 mg/kg. ↑ HR at ≥150 mg/kg. Splenic hemosiderosis and slight renal cortical tubular basophilia and interstitial inflammation at 150 mg/kg. JG and arteriolar hypertrophy at all doses. All effects showed reversibility after 1 month.

Reproduction and Teratology Studies

No adverse effects on reproductive performance were observed in male and female rats treated with 50 to 500 mg/kg/day of benazepril HC1 during gestational days 6 through 15 or from 14 days premating to 21 days postpartum.

No direct embryotoxic, fetotoxic or teratogenic effects were seen in rats, mice or rabbits treated during gestational days 6 to 15 (mice and rats) or 7 to 19 (rabbits) with oral doses up to 500

mg/kg/day, 150 mg/kg/day and 5 mg/kg/day, respectively. Fetal effects consisted of developmental delays secondary to maternal toxicity (decreased food consumption and body weight). Postnatal growth of rat pups was reduced at maternal doses ^{3} 250 mg/kg/day. Maternal toxicity with mortality occurred in rabbits at doses of 0.1 mg/kg/day or more.

Carcinogenicity Studies

No evidence of a tumorigenic effect was seen when benazepril HC1 was administered for 104 weeks to rats at a dose of up to 150 mg/kg/day. No evidence of carcinogenicity was seen when benazepril was administered for up to 104 weeks to mice at the same dose.

Mutagenicity Studies

Benazepril was not mutagenic when tested in the Ames microbial mutagen test with or without metabolic activation. The following genotoxicity studies with benazepril were negative: an in vitro test for forward mutations in cultured mammalian cells, a nucleus anomaly test, and a sister chromatid exchange study in chinese hamsters.

Bibliography

FITZPATRICK MA, and JULIUS S.
Hemodynamic effects of angiotensin-converting enzyme inhibitors in essential hypertension: a review.
J Cardio Pharm 1985; 7: S35-539

KAISER G, ACKERMANN R, BRECHBUEHLER S, and DIETERLE W.
Pharmacokinetics and pharmacodynamics of the ACE inhibitor benazepril hydrochloride in the elderly.
Eur J Clin Pharmacol 1990; 38: 379-385

KAISER G, ACKERMANN R, and SIOUFI A.
Pharmacokinetics of a new angiotensin-converting enzyme inhibitor, benazepril hydrochloride, in special populations.
Am Heart J 1989; 117 (3): 746-751

McFATE SMITH W, and GOMEZ HJ.
The use of benazepril in hypertensive patients age 55 and over.
Clin Cardiol 1991; 14 (8, Suppl IV): 79-82

NUSSBERGER J, DE GASPARO M, JUILLERAT L, GUYENNE TT, MOOSER V, WAEBER B, and BRUNNER HR.
Rapid measurement of total and active renin: plasma concentrations during acute and sustained converting enzyme inhibition with CGS 14824A.
Clin Exp Hypertens [A] 1987; 9 (8/9): 1353-1366

WAEBER G, FASANELLA D'AMORE T, NUSSBERGER J, WAEBER B, and BRUNNER HR.
Effect on blood pressure and the renin-angiotensin system of repeated doses of the converting enzyme inhibitor CGS 14824A.
Eur J Clin Pharmacol 1987; 31 (6): 643-646

WHALEN JJ.
Definition of the effective dose of the converting-enzyme inhibitor benazepril. Am Heart J. 1989; 117 (3): 728-734

YAMAMOTO S, TAKEMORI E, HASEGAWA Y, KURODA K, NAKAO K, INUKAI T, SAKONJYO H, NISHIMURA T, and NISHIMORI T.
General pharmacology of the novel angiotensin converting enzyme inhibitor benazepril hydrochloride. Effects on cardiovascular, visceral and renal functions and on hemodynamics.
Arzneimittelforschung 1991; 41 (9): 913-923

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