Core Safety Profile

Active substance: Benazepril hydrochloride
Pharmaceutical form(s)/strength: Tablets, 5mg + 10mg
P-RMS: IE/H/PSUR/0004/001
Date of FAR: 17.10.2008
4.2 Posology and method of administration

Adults

Hypertension

The usual initial dosage is 10mg given as a single dose which may be titrated to 20mg once daily if necessary. The dosage should be adjusted according to blood pressure response, generally at intervals of 1-2 weeks.

In some patients, the antihypertensive effect may diminish towards the end of the dosing interval, and the total daily dosage should then be divided into two equal doses.

The maximum recommended daily dose in hypertensive patients is 40mg, given as a single dose or two doses.

If benazepril alone does not produce a sufficient fall in blood pressure, another antihypertensive drug e.g. a thiazide-type diuretic or calcium antagonist (initially at a low dose) may be added concomitantly.

In the case of previous diuretic treatment the diuretic should be discontinued for at least 3 days before commencing benazepril and reinstituted subsequently if necessary. If it is not possible to discontinue the diuretic, the initial dose of benazepril should be reduced to 5mg in order to avoid excessive hypotension.

The usual dose of benazepril is recommended in patients with a creatinine clearance of ≥30 mL/min.

In hypertensive patients with a creatinine clearance of <30ml/min

The initial dose is 5mg. The dosage may be increased to up to 10mg daily. For any further reduction in blood pressure a non-thiazide diuretic or another antihypertensive drug should be added.

Abrupt withdrawal of benazepril has not been associated with rapid increases in blood pressure.

Congestive heart failure:

The recommended initial dose is 2.5mg once daily (half of a 5mg tablet). Owing to the risk of a steep fall in blood pressure in response to the first dose, patients taking benazepril for the first time should be closely monitored (see Warnings and Precautions).

The dose may be increased to 5mg once daily after 2-4 weeks if the symptoms of heart failure have not been adequately relieved, provided the patient has not developed symptomatic hypotension or other undesirable effects. Depending on clinical response, the dose may be increased further to 10mg and eventually to 20mg once daily at appropriate intervals. Once daily dosing is generally effective. Some patients may respond better to a twice daily regimen. Controlled clinical trials show that patients with more severe heart failure (NYHA class IV) usually require smaller doses of benazepril than patients with mild to moderate heart failure (NYHA class II and III).

In CHF patients with a creatinine clearance of < 30 mL/min : the daily dose may be increased to 10mg, but the initial low dose given (2.5mg once daily) may prove to be optimal

Hypertensive patients with heart failure

In hypertensive patients with heart failure, a lower initial dose (e.g. 5mg) is recommended (see also 'Precautions').
Progressive chronic renal insufficiency (CRI)

The recommended dose for long-term use to slow the progression of chronic renal disease with or without hypertension is 10mg once daily. Other antihypertensives may be used in combination with benazepril if additional therapy is required to further lower blood pressure.

Elderly

The usual initial dose in hypertension is 5mg once daily which may be titrated to 10mg.

Children

Pediatric patients with hypertension (age 7-16 years, body weight $\geq$ 25kg)

The usual recommended starting dose of benazepril is 0.2 mg/kg (up to a maximum of 10 mg) once daily. Dosage should be adjusted according to blood pressure response. Doses above 0.6 mg/kg (or in excess of 40 mg daily) have not been studied in pediatric patients.

Benazepril tablets are not recommended in pediatric patients who are under seven years of age or for older children who cannot swallow tablets, or for whom the calculated dosage (mg/kg) does not correspond to the available tablet strengths. Treatment with benazepril is not advised in pediatric patients with a glomerular filtration rate $<30$ ml, as there are insufficient data available to support a dosing recommendation in this group. The long-term effects of benazepril on growth and development have not been studied.

The safety and efficacy of benazepril film-coated tablets have not been established in children with CFH and progressive chronic renal insufficiency.

4.3 Contraindications

- Known hypersensitivity to benazepril, to any of the excipients or any other related compounds.
- A history of angioedema associated with previous ACE inhibitor treatment.
- 2nd and 3rd trimester of pregnancy (see Special warnings and precautions for use and Pregnancy and lactation)

4.4 Special warnings and precautions for use

Anaphylactoid and related reactions

Because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including benazepril) may experience a variety of anaphylactoid and related reactions, some of them serious.

Angioedema

Angioneurotic oedema has been reported rarely with ACE inhibitors including benazepril. In some cases symptoms have been observed up to 2 years after initiation of treatment.
Such reactions should be regarded as an indication to discontinue therapy immediately and
the patient closely monitored.

Where swelling is confined to the face, lips and mouth, the condition will usually resolve
without further treatment, although antihistamines may be useful in relieving symptoms. These patients should be followed carefully until the swelling has resolved. However, where there is involvement of the tongue, glottis or larynx, likely to cause airways obstruction, appropriate therapy such as subcutaneous adrenaline (0.5ml 1:1000) should be administered promptly when indicated.

Angioedema with laryngeal oedema can be fatal.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angiodema while receiving an ACE inhibitor (see Contraindications). Other hypersensitivity reactions have been reported.

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.

Anaphylactoid reactions during desensitisation

Two patients undergoing desensitising treatment with Hymenoptera venom while receiving ACE inhibitors had 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 dialysed with high-flux membranes while receiving an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulphate absorption.

Symptomatic hypotension

As with other ACE inhibitors, symptomatic hypotension has been observed in rare cases, typically in patients with volume or salt depletion as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea 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 iv.

Treatment with benazepril can be continued once blood pressure and volume have returned to normal. In patients with severe congestive heart failure, ACE inhibitor therapy can cause excessive hypotension which may be associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure. In such patients, 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.

Agranulocytosis/neutropenia

Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression; such effects occur more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Not enough data are available from clinical trials of benazepril to show whether
or not it causes a similar incidence of agranulocytosis. Monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

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.

Foetal/neonatal morbidity and mortality

ACE inhibitors can cause foetal and neonatal morbidity and death when given to pregnant women.

Several dozen cases have been reported in the world literature. When pregnancy is established, ACE inhibitors should be discontinued as soon as possible.

Pregnancy

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy.

When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started. (see Contraindications and Pregnancy and lactation).

Use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with foetal and neonatal damage, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death.

Oligohydramnios, presumably due to impaired foetal renal function, has been reported. Oligohydramnios in this setting has been associated with foetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these were due to ACE inhibitor exposure.

Impaired renal function

Changes in renal function may occur in susceptible patients. In patients with severe congestive heart failure, whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors may be associated with oliguria and/or progressive azotaemia and (rarely) acute renal failure. In a small study of hypertensive patients with renal artery stenosis in one kidney or bilateral renal artery stenosis, treatment with benazepril was associated with increases in blood urea nitrogen, and serum creatinine; these increases were reversible on discontinuation of benazepril or diuretic therapy, or both. If 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 pre-existing renal vascular disease have developed elevated blood urea nitrogen and serum creatinine levels (usually minor and transient), especially when benazepril was given with a diuretic. This is more likely to occur in
patients with pre-existing renal impairment. Dosage reduction of benazepril and/or discontinuation of the diuretic may be required. Evaluation of the hypertensive patient should always include assessment of renal function (see Posology and method of administration).

**Cough**
Persistent non-productive cough has been reported with ACE inhibitors, presumably due to inhibited degradation of endogenous bradykinin. This cough always resolves after discontinuation of therapy. ACE-inhibitor-induced cough must be considered in the differential diagnosis of cough.

**Surgery/anaesthesia**
The pharmacological action of benazepril may prevent the normal body response to induction of hypotension during anaesthesia or shock. Before surgery the anaesthetist should be informed that the patient is receiving an ACE inhibitor.
During anaesthesia with agents that induce hypotension, ACE inhibitors may block angiotensin II formation secondary to compensatory renin release. Hypotension occurring by this mechanism should be corrected by volume expansion.

**Hyperkalaemia**
During treatment with ACE inhibitors, elevated serum potassium levels have been observed on rare occasions. No discontinuations of benazepril due to hyperkalaemia have been reported in clinical trials in hypertension. Risk factors for development of hyperkalaemia may include renal insufficiency, diabetes mellitus, and concomitant use of agents to treat hypokalaemia (see Interaction with other medicinal products and other forms of interaction). In a trial involving patients with progressive chronic renal disease, some patients discontinued treatment because of hyperkalaemia. In patients with progressive chronic renal disease serum potassium should be monitored.

**Aortic or mitral stenosis**
As with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis.

**Galactose intolerance**
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**4.5 Interaction with other medicinal products and other forms of interaction**

**Diuretics**
Patients on diuretics or fluid-depleted patients may occasionally experience an excessive reduction in blood pressure when therapy with an ACE inhibitor is started. The possibility of hypotensive effects in such patients can be minimised by discontinuing diuretic therapy for at least 3 days before treatment with benazepril (see Posology and method of administration and Special warnings and precautions for use).
Potassium sparing diuretics

Concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium is not recommended in patients receiving ACE inhibitors, since this may lead to significant increases in serum potassium. However, if comedication is considered necessary, frequent monitoring of serum potassium is advisable.

Lithium

Increased serum 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.

Indomethacin

It has been shown that the hypotensive effect of ACE inhibitors may be reduced when administered concomitantly with indomethacin, although indomethacin has not been shown to interfere with the antihypertensive effects of benazepril.

Anti-diabetic agents

Concomitant administration of ACE-inhibitors and anti-diabetic medicines (insulin, oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with the risk of hypoglycaemia. This phenomenon may be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

4.6 Pregnancy and lactation

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see Special warnings and precautions for use). The use of ACE inhibitors is contraindicated during the 2nd and 3rd trimester of pregnancy (see Contraindications and Special warnings and precautions for use).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

ACE inhibitor therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See Preclinical safety data). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see Contraindications and Special warnings and precautions for use).

ACE inhibitors have been reported to cause foetal and neonatal and death when given to pregnant women.
Pregnancy should be excluded before the start of treatment and avoided during treatment. Benazepril and benazeprilat have been found in breast milk, at a maximum concentration of 0.3% of that found in the plasma. The fraction of benazeprilat reaching the systemic circulation of an infant is negligible.

However, although any adverse effects on breast fed infants are very unlikely, use of benazepril is not recommended in breast-feeding women.

4.7 Effects an ability to drive and use machines
As with other antihypertensive drugs, it is advisable to exercise caution when driving or operating machines.

4.8 Undesirable effects
Frequency estimate: very rare 0.01%; rare 0.01% to 0.1%; uncommon 0.1% to 1%; common 1% to 10%; very common 10%.

Benazepril has been found to be well tolerated. Adverse reactions associated with benazepril and other ACE inhibitors are listed below. The adverse experience profile for pediatric patients appears to be similar to that seen in adult patients.

There is no information about the long-term administration to pediatric patients and its effects on growth, puberty and general development.

The pharmacokinetic data were derived from a limited number of patients.

Cardiovascular system
Common: palpitations, orthostatic symptoms.
Rare: symptomatic hypotension, chest pain, angina pectoris, arrhythmias.
Very rare: myocardial infarction.

Gastrointestinal tract:
Common: non-specific gastrointestinal disorders.
Rare: diarrhoea, constipation, nausea, vomiting, abdominal pain.
Very rare: pancreatitis.

Skin:
Common: rash, flushing, pruritis, photosensitivity.
Rare: There have been rare reports of pemphigus in patients receiving ACE inhibitors.
Very rare: Stevens-Johnson syndrome.

Liver and biliary duct:
Rare: hepatitis (predominantly cholestatic, cholestatic jaundice (see Special warnings and precautions for use).
Urogenital system:
Common: urinary frequency.
Rare: increase in blood urea nitrogen, increase in serum creatinine.
Very rare: impaired renal function (see Special warnings and precautions for use).

Respiratory tract:
Common: cough, respiratory tract symptoms.

Central nervous system:
Common: headache, dizziness, fatigue.
Rare: somnolence, insomnia, nervousness and paraesthesia.

Blood:
Very rare: haemolytic anaemia, thrombocytopenia (see Special warnings and precautions for use).

Sense organs:
Very rare: tinnitus and dysguesia.

Allergic and immune reactions:
Rare: Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx (see Special warnings and precautions for use).

Musculoskeletal system:
Rare: arthralgia, arthritis, myalgia.

Laboratory findings:
As with other ACE inhibitors, minor increases in blood urea nitrogen (BUN) and serum creatinine, which were reversible on discontinuation of therapy have been observed in 0.1% of patients with essential hypertension treated with benazepril alone. Increases are more likely to occur in patients also receiving diuretics or in patients with renal artery stenosis (see Special warnings and precautions for use).
The following events of unknown frequency have been reported during post marketing use of benazepril: small bowel angioedema, anaphylactoid reactions, hyperkalaemia, agranulocytosis and neutropenia (see Special warnings and precautions for use).

4.9 Overdose
Signs and symptoms:
Although there is no experience of overdosage with benazepril, the main sign to be expected is marked hypotension.
**Treatment:**

If ingestion is recent, induce vomiting. although the active metabolite benazeprilat is only slightly dialysable, dialysis might be considered in overdosed patients with severely impaired renal function to support normal elimination. In the case of marked hypotension, give normal saline solution iv.