

## Summary of Product Characteristics

### 1 NAME OF THE MEDICINAL PRODUCT

Cibacen 10 mg Film Coated Tablets

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg benazepril hydrochloride

Excipients: Each tablet contains 132mg lactose monohydrate

For the full list of excipients, see section 6.1.

### 3 PHARMACEUTICAL FORM

Film-coated tablets.

Dark yellow, round slightly biconvex, film-coated tablets with beveled edges.

### 4 CLINICAL PARTICULARS

#### 4.1 Therapeutic Indications

In the treatment of hypertension as monotherapy or combined with other antihypertensive agents (see sections 4.3, 4.4, 4.5 and 5.1).

As adjunctive therapy in patients with congestive heart failure.

Treatment of patients with mild-to-moderate progressive chronic renal insufficiency, with the exception of those with polycystic kidney disease.

#### 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 Cibacen alone does not produce a sufficient fall in blood pressure, another antihypertensive drug eg. a thiazide-type diuretic or calcium antagonist (initially at a low dose) may be added concomitantly (see sections 4.3, 4.4, 4.5 and 5.1).

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

The usual dose of Cibacen is recommended in patients with a creatinine clearance of  $\geq 30$  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 Cibacen 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 Cibacen 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 Cibacen 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 (eg. 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 Cibacen if additional therapy is required to further lower blood pressure.

*Older patients:*

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

*Paediatric patients with hypertension (age 7-16 years, body weight ≥25kg)*

The usual recommended starting dose of Cibacen is 0.2 mg/kg (up to 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 paediatric studies.

Cibacen tablets are not recommended in paediatric patients who are under seven years of age 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 Cibacen is not advised in paediatric patients with a glomerular filtration rate <30ml, as there are insufficient data available to support a dosing recommendation in this group. The long term effects of Cibacen on growth and development have not been studied.

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

### 4.3 Contraindications

Known hypersensitivity to benazepril or related compounds or any of the excipients of Cibacen (see section 6.1).

A history of angioedema associated with previous ACE inhibitor treatment.

Second and third trimesters of Pregnancy (see Sections 4.4 and 4.6).

The concomitant use of Cibacen with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m<sup>2</sup>) (see sections 4.5 and 5.1).

## 4.4 Special warnings and precautions for use

### Warnings

#### *Anaphylactoid and related reactions*

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

#### *Angioedema*

Angioneurotic oedema has been reported rarely with ACE inhibitors including Cibacen. 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 angioedema while receiving an ACE inhibitor (see also "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 Cibacen. If hypotension occurs, the patient should be placed in the supine position and if necessary given physiological saline IV.

Treatment with Cibacen 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.

*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 antihypertensive 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 Sections 4.3 and 4.6).

*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.

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.

No such adverse effects appear to have occurred after intrauterine ACE inhibitor exposure during the first trimester. This should be made clear to women who have taken ACE inhibitors only during the first trimester. If a patient becomes pregnant, the physician is nevertheless advised to discontinue benazepril as soon as possible.

*Dual blockade of the renin-angiotensin-aldosterone system (RAAS)*

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1). If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

**Precautions***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 Cibacen was associated with increases in blood urea nitrogen, and serum creatinine; these increases were reversible on discontinuation of Cibacen 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 Cibacen was given with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of Cibacen and/or discontinuation of the diuretic may be required. Evaluation of the hypertensive patient should always include assessment of renal function (see Dosage).

#### *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 Cibacen 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 Interactions). 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 Cibacen (*see Dosage and Warnings*).

#### *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.

#### *Ciclosporin and heparin*

Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin and with heparin. Monitoring of serum potassium is recommended.

*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 Cibacen.

*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.

*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.

*mTOR inhibitors*

The risk of angioedema may be increased in patients receiving concomitant ACE inhibitors and mTOR inhibitors (e.g. temsirolimus, sirolimus, everolimus).

*Non-steroidal anti-inflammatory medicinal products (NSAIDs) including acetylsalicylic acid used as an anti-inflammatory agent:*

When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs, attenuation of the antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

*Racecadotril*

Increased risk of angioedema related to concomitant use of benazepril and racecadotril.

Clinical trial data has shown that the dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

## 4.6 Fertility, pregnancy and lactation

### Pregnancy

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see Section 4.4). The use of ACE inhibitors is contraindicated during the 2<sup>nd</sup> and 3<sup>rd</sup> trimesters of pregnancy (see Sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teragenicity 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 antihypertensive treatments which have an established safety profile for use in pregnancy.

When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, and if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, Oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia), (See Section 5.3). Should exposure to ACE inhibitors 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 monitored for hypotension (see Section 4.3 and 4.4).

ACE inhibitors have been reported to cause foetal and neonatal morbidity and death when given to pregnant women.

## Lactation

Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see Section 5.2). Although these concentrations seem to be clinically irrelevant, the use of Cibacen 5mg film-coated tablets in breastfeeding is not recommended for preterm infants and for the first few weeks after delivery, because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience.

In the case of an older infant, the use of Cibacen tablets in a breast-feeding mother may be considered if the treatment is necessary for the mother and the child is observed for any adverse effect.

## 4.7 Effects on 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

Cibacen has been found to be well tolerated. The adverse experience profile for paediatric patients appears to be similar to that seen in adult patients.

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

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

Adverse reactions associated with Cibacen and other ACE inhibitors are ranked under the heading of frequency, the most frequent first, using the following convention; very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

### *Cardiovascular disorders:*

Common: palpitations, orthostatic symptoms.

Rare: orthostatic hypotension, chest pain, angina pectoris, arrhythmia.

Very rare: myocardial infarction.

### *Gastrointestinal disorders:*

Common: gastrointestinal disorders.

Rare: diarrhoea, constipation, nausea, vomiting, abdominal pain.

Very rare: pancreatitis.

### *Vascular disorders*

Common: Flushing

### *Immune system disorders*

Rare: Angioedema, lip oedema: face oedema, extremities, lips, tongue, glottis and/or larynx (see sections (see section 4.4 Special warnings and precautions for use))

*Psychiatric disorders*

Rare: Insomnia, nervousness and paraesthesia

*Skin and subcutaneous tissue disorders:*

Common: rash, flushing, pruritis, photosensitivity reaction.

Rare: Pemphigus

Very rare: Stevens-Johnson syndrome.

*Hepatobiliary disorders:*

Rare: hepatitis (predominantly cholestatic, cholestatic jaundice

(see section 4.4 Special warnings and precautions for use)

*Renal and urinary disorders:*

Common: Pollakiuria.

Rare: increase in blood urea nitrogen, increase in serum creatinine.

Very rare: impaired renal function (see Section 4.4 Precautions).

*Respiratory thoracic and mediastinal disorders*

Common: cough, symptoms of upper respiratory tract infections.

*Nervous system disorders:*

Common: headache, dizziness,

Rare: somnolence,

Very rare: Dysgeusia

*Blood and lymphatic system disorders:*

Very rare: haemolytic anaemia, thrombocytopenia

(see also (see section 4.4 Special warnings and precautions for use)).

*Ear and labyrinth disorders:*

Very rare: tinnitus.

*Musculoskeletal and connective tissue disorders:*

Rare: arthralgia, arthritis, myalgia.

*General disorders and administration site conditions*

Common: fatigue

The following adverse events of unknown frequency have been reported during postmarketing use of benazepril: small bowel angioedema, anaphylactoid reactions, hyperkalaemia, agranulocytosis, neutropenia (see section 4.4 Special warnings and precautions for use)

*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 Cibacen alone. Increases are more likely to occur in patients also receiving diuretics or in patients with renal artery stenosis (see Section 4.4 Precautions).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: [www.hpra.ie](http://www.hpra.ie); Email: [medsafety@hpra.ie](mailto:medsafety@hpra.ie).



## 4.9 Overdose

### *Signs and symptoms:*

Although there is limited experience of overdosage with benazepril, the main sign to be expected is marked hypotension, which can be associated with electrolyte disturbances and renal failure.

### *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.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

ATC Code: CO9A A07

Cibacen is a prodrug. The active metabolite, benazeprilat, is an inhibitor of angiotensin converting enzyme and hence reduces the conversion of angiotensin I to angiotensin II.

Since Cibacen inhibits the production of angiotensin II it is effective in hypertension by reducing vasoconstriction and aldosterone production. Cibacen diminishes the reflex-induced sympathetic increase in heart rate which occurs in response to vasodilation.

Like other ACE inhibitors, Cibacen also inhibits degradation of the vasodilator bradykinin by kininase; this inhibition may contribute to the antihypertensive effect.

Cibacen reduces sitting, supine and standing blood pressure in all grades of hypertension. In most patients, an antihypertensive effect is seen after about 1 hour following a single oral dose and maximum reduction of blood pressure is achieved within 2-4 hours. The antihypertensive effects last for at least 24 hours after administration. During repeated administration the maximum reduction in blood pressure with each dose is generally reached after 1 week and continues during long-term therapy.

In patients pretreated with digitalis and a diuretic, Cibacen brought about an increase in cardiac output and exercise tolerance, and a reduction in pulmonary wedge pressure, systemic vascular resistance and blood pressure. Heart rate was slightly reduced. Treatment with Cibacen in CHF patients also lessened fatigue, rales, oedema and improved NYHA class. Clinical trials have shown improvement in haemodynamic variables for 24 hours with once-daily dosing.

A double-blind, placebo-controlled trial has shown that Cibacen reduced the risk of increased serum creatinine or the need for dialysis. These beneficial effects were accompanied by a reduction in blood pressure and a marked decrease in proteinuria. Patients with polycystic kidney disease did not experience slowing of the loss of renal function when treated with Cibacen. However, Cibacen can still be used to treat hypertension in such patients.

In a clinical study of 107 paediatric patients, 7 to 16 years of age, with either systolic or diastolic pressure above the 95<sup>th</sup> percentile, patients were given 0.1 or 0.2 mg/kg benazepril hydrochloride then titrated up to 0.3 or 0.6 mg/kg with a maximum dose of 40 mg once daily.

During the dose escalation phase subjects were to receive low dose benazepril hydrochloride for 8 days, medium dose for 7 days and high dose for 14 days. Hereafter SSBP was significantly decreased from baseline by 10.8 mmHg for all subjects and for subjects in both weight groups. SDBP also was significantly decreased by 9.3 mmHg for all subjects.

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.

The mean increase in SSBP was significantly greater in the placebo group (7.9 mmHg) compared to the medium dose (1.0 mmHg), but not in the low dose (3.9 mmHg) or high dose (2.2 mmHg) groups. Thus, no dose-response was observed for the three doses.

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

## 5.2 Pharmacokinetic properties

Benazepril is rapidly absorbed and converted to the active metabolite benazeprilat which reaches peak plasma levels at 1.5 hours. The half-life for accumulation of benazeprilat is 10-11 hours and steady-state levels are reached after 2-3 days. The pharmacokinetics are not altered by multiple dosing. Absorption of the drug is delayed by food but the effect is not of clinical significance.

About 95% of benazepril and benazeprilat bind to human serum proteins (mainly albumin). Binding is not affected by age. The steady-state distribution volume of benazeprilat is about 9 litres.

Elimination of benazeprilat is via the kidneys and bile, renal excretion being the main route in patients with normal renal function. Elimination is biphasic with an initial half-life of about 3 hours and a terminal half-life of about 22 hours.

In patients with renal insufficiency, the rate of elimination of benazeprilat is reduced. Where renal impairment is severe, dosage reduction is recommended (see 'Dosage and Administration'). Regular haemodialysis starting at least 2 hours after administration of benazepril hydrochloride does not significantly affect plasma concentrations of benazepril and benazeprilat, which means that no additional dose needs to be given after dialysis. Only a small amount of benazeprilat is removed from the body by dialysis.

Because elimination is slightly slower in CHF patients, steady-state trough concentrations of benazeprilat tend to be higher in this group than in healthy subjects or hypertensive patients.

In patients with moderate hepatic dysfunction due to cirrhosis, pharmacokinetic parameters of benazeprilat are not affected.

In paediatric patients, (N=45) hypertensive, aged 7 to 16 years, given multiple daily doses of benazepril hydrochloride (0.1 to 0.5 mg/kg), the clearance of benazeprilat for children 7 to 12 years old was 0.35 L/h/kg, more than twice that of healthy adults receiving a single dose of 10 mg (0.13 L/h/kg). In adolescents (aged 13 to 16 years), it was 0.17 L/h/kg, 27% higher than that of healthy adults. The terminal elimination half-life of benazeprilat in paediatric patients was around 5 hours, one third that observed in adults.

#### Lactation:

In nine women given an oral dose of 20 mg of benazepril daily for 3 days (time postpartum not stated), peaks milk levels of 0.9µg/L of benazepril at 1 hour after the dose and 2µg/L of its active metabolite benazeprilat at 1.5 hours after the dose were detected. It is estimated that the breastfed infant would receive a daily dose less than 0.14% of the maternal weight-adjusted dose of benazepril.

## 5.3 Preclinical safety data

#### *Reproduction toxicity studies:*

No adverse effects on reproductive performance were observed in male and female rats treated with up to 500mg/kg/day of benazepril hydrochloride.

No direct embryotoxic, fetotoxic, or teratogenic effects were seen in mice treated with up to 150mg/kg/day, rats treated with up to 500mg/kg/day, and rabbits treated with up to 5mg/kg/day.

#### *Mutagenicity:*

In a series of in vitro and in vivo tests no mutagenic potential was detected.

#### *Carcinogenicity:*

No evidence of a tumorigenic effect was seen when benazepril hydrochloride was administered to rats in doses of up to 150mg/kg/day (250 times the maximum recommended total human dose). No evidence of carcinogenicity was seen when benazepril hydrochloride was administered for 104 weeks to mice in the same doses.

No non-clinical studies have been conducted with the purpose of investigating potential juvenile toxicity of benazepril HC1.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

#### Core

Colloidal anhydrous silica  
Lactose monohydrate  
Microcrystalline cellulose  
Hydrogenated castor oil  
Pregelatinised maize starch  
Crospovidone

#### Coating

Hypromellose  
Yellow iron oxide (E172)  
Macrogol 8000  
Talc  
Titanium dioxide (E171)

### 6.2 Incompatibilities

Not applicable.

### **6.3 Shelf life**

Three years.

### **6.4 Special precautions for storage**

Do not store above 25°C.

Store in the original package to protect from moisture.

### **6.5 Nature and contents of container**

PVC/PE/PVDC blister packs with aluminium foil of 28 tablets (2 strips of 14 contained in a cardboard outer carton).

### **6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product**

No special requirements.

## **7 MARKETING AUTHORISATION HOLDER**

Meda Health Sales Ireland Ltd  
Unit 34/35  
Block A  
Dunboyne Business Park  
Dunboyne  
Co. Meath  
Ireland

## **8 MARKETING AUTHORISATION NUMBER**

PA1332/001/002

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 16 June 1999

Date of last renewal: 16 June 2009

## **10 DATE OF REVISION OF THE TEXT**

December 2016