Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cibacen 5 mg Film Coated Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5mg benazepril hydrochloride.

Excipients: Each tablet contains 142mg lactose monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablets.

Light-yellow, ovaloid, slightly biconvex film-coated tablets scored on both sides.

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 (creatinine clearance 30-60 mL/min), with the exception of those with polycystic kidney disease.

See sections 4.3, 4.4, 4.5 and 5.1.

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 2-3 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 5mgin order to avoid excessive hypotension (see section 4.4 Special warnings and precautions for use).

The usual dose of Cibacen is recommended in patients with a creatinine clearance of ≥30mL/min. Abrupt withdrawal of Cibacen has not been associated with rapid increases in blood pressure.

Inhypertensivepatientswithacreatinineclearanceof<30ml/min:

Adults

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.

Congestiveheartfailure:

Adults

The recommended initial dose is 2.5mg once daily (half of a 5 mg 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 section 4.4 Special warnings and precautions for use*)*.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 unacceptable adverse effects. Depending on the clinical response, the dose may be increased further to 10 mg 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 (see section 5.2 Pharmacokinetic properties).

Hypertensivepatientswithheart failure:

In hypertensive patients with heart failure, a lower initial dose (e.g. 5mg) is recommended *(seealso'Precautions')*.

Progressivechronicrenalinsufficiency(CRI):

Adults

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.

Special Populations

Elderly

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

Children

Paediatricpatientswithhypertension(age7-16years,bodyweight≥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 patients.

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

Cibacen is contraindicated for patients with:

- 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 sacubitril/valsartan therapy is contraindicated. Cibacen must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.4 and 4.5).

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^2) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

Warnings

Anaphylactoidandrelatedreactions
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 adverse 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. In cases of angioedema, Cibacen should be immediately discontinued and appropriate therapy and monitoring be provided until complete and sustained resolution of signs and symptoms.
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 (0.5miL 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 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.

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see section 4.3). Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of Cibacen . Treatment with Cibacen must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking an ACE inhibitor.

Anaphylactoidreactionsduringdesensitisation
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.

Anaphylactoidreactionsduringmembraneexposure
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.

Symptomatichypotension
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 i.v..

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 Cibacen 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 Cibacen 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.

Hepatitisandhepatic 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/neonatalmorbidityandmortality
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 stopped immediately.

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.

The use of ACE inhibitors is not recommended during the first trimester of pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately.

Precautions
Impairedrenal/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 *(seeDosage).*

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
ACE inhibitors can cause hyperkalemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function and/or in patients taking potassium supplements (including salt substitutes), potassium-sparing diuretics, trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole and especially aldosterone antagonists or angiotensin-receptor blockers, hyperkalemia can occur. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored (see section 4.5).

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 section 4.5 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.

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

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

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 close 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.

4.5 Interaction with other medicinal products and other forms of interactions

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 sections 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use).*

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes
Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with cilazapril. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Care should also be taken when Cibacen is co-administered with other agents that increase serum potassium, such as trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole) as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Therefore, the combination of cilazapril with the above-mentioned drugs is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Medicines increasing the risk of angioedema
The concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema. Sacubitril/valsartan must not be started until 36 hours after taking the last dose of Cibacen therapy. Cibacen therapy must not be started until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.4).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk for angioedema (see section 4.4).

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 NSAIDs including aspirin. In a controlled clinical trial, indomethacin has not been shown to interfere with the antihypertensive effects of Cibacen.

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.

Anti-diabeticagents
In rare cases, diabetic patients receiving an ACE inhibitor (including Cibacen) concomitantly with insulin or oral antidiabetics may develop hypoglycaemia.
Such patients should therefore be advised about the possibility of hypoglycaemic reactions, and should be monitored accordingly.

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.

The pharmacokinetics of benazepril are not affected by the following drugs: hydrochlorothiazide, furosemide, chlorthalidone, digoxin, propranolol, atenolol, nifedipine, amlodipine, naproxen, acetylsalicylic acid, or cimetidine. Likewise, the administration of benazepril does not substantially affect the pharmacokinetics of these medications with the exception of possibly increased plasma levels of digoxin (cimetidine kinetics were not studied).

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

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

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 2nd and 3rd 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 being conclusive; however a small increase in risk cannotbe excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have anestablished safety profilefor use in pregnancy. When pregnancyis 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 Preclinical safety data). 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 sections 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 benazepril 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 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.

Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories:; very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥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.

Blood and lymphatic system disorders:
Very rare: haemolytic anaemia, thrombocytopenia
Frequency not known: Agranulocytosis, neutropenia (see section 4.4 Special warnings and precautions for use: Agranulocytosis/neutropenia).

Immune system disorders
Rare: Angioedema, lip oedema: face oedema
Frequency not known: Anaphylactoid reactions (see section 4.4 Special warnings and precautions for use: Anaphylactoid and related reactions)

Metabolism and nutrition disorders

Frequency not known: Hyperkalaemia

Psychiatric disorders
Rare: Insomnia, nervousness and paraesthesia

Nervous system disorders
Common: headache, dizziness,
Rare: somnolence,
Very rare: Dysgeusia

Ear and labyrinth disorders:
Very rare: tinnitus

Cardiacdisorders:
Common: palpitations, orthostatic symptoms.
Rare: orthostatic hypotension, chest pain, angina pectoris, arrhythmia.
Very rare: myocardial infarction.

Vascular disorders
Common: Flushing

Respiratory, thoracic and mediastinal disorders
Common: cough, symptoms of upper respiratory tract infection.

Gastrointestinaldisorders:
Common: gastrointestinal disorder.
Rare: diarrhoea, constipation, nausea, vomiting, abdominal pain.
Very rare: pancreatitis.
Frequency not known: Small bowel angioedema

Hepatobiliary disorders:
Rare: hepatitis (predominantly cholestatic), cholestatic jaundice (see section 4.4 Special warnings and precautions for use: Hepatic failure)

Skin and subcutaneous tissue disorders:
Common: rash, flushing, pruritis, photosensitivity reaction.
Rare: Pemphigus.
Very rare: Stevens-Johnson syndrome.

Musculoskeletaland connective tissue disorders:
Rare: arthralgia, arthritis, myalgia.

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 Special warnings and precautions for use: Impaired renal function*).*

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)

Laboratoryfindings:
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 Special warnings and precautions for use).

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; E-mail: medsafety@hpra.ie.

4.9 Overdose

Signsandsymptoms:
Although there is -limited experience of overdosage with Cibacen, 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 (see section 4.4 Special warnings and precautions for use). In the case of marked hypotension, give normal saline solution i.v.

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 95th percentile, patients were given 0.1 or 0.2 mg/kg benazepril hydrochloride then titrated up to 0.3 pr 0.6 mg/kg with a maximum dose of 40 mg once daily.

During the dose escalation phase subject 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

Two years.

6.4 Special precautions for storage

Do not store above 25ºC.
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

Mylan IRE Healthcare Limited
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8 MARKETING AUTHORISATION NUMBER

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