# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Cilazapril 5 mg film-coated tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mg film-coated tablet contains 5 mg of Cilazapril (as Cilazapril monohydrate).

Excipient(s) with known effect:
Each 5 mg film-coated tablet contains 117.824 mg of lactose monohydrate

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Film-coated tablet.

Pink, oblong presenting a one sided score, weighing approximately 100 mg, film coated tablets.

The tablet can be divided into equal doses.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Cilazapril is indicated for the treatment of hypertension.

Cilazapril is indicated for the treatment of chronic heart failure.

### 4.2 Posology and method of administration

**Posology**

Cilazapril should be administered once daily.

As food intake has no clinically significant influence on absorption, Cilazapril can be administered before or after a meal. The dose should always be taken at about the same time of day.

Hypertension

The initial dose is 1 mg/day. Blood pressure should be assessed, and dosage adjusted individually in accordance with the blood pressure response. The usual dose range of Cilazapril is 2.5 to 5.0 mg once daily.

Patients with a strongly activated renin- angiotensin-aldosterone system (in particular, salt and/or volume depletion, cardiac decompensation, or severe hypertension) may experience an excessive blood pressure fall following the initial dose. A lower starting dose of 0.5 mg once daily is recommended in such patients and the initiation of treatment should take place under medical supervision.

Hypertensive patients receiving diuretics
If possible, the diuretic should be discontinued 2 – 3 days before beginning therapy with Cilazapril to reduce the likelihood of symptomatic hypotension. It may be resumed later if required. The recommended starting dose in these patients is 0.5 mg once daily.

Chronic heart failure
Therapy with Cilazapril should be initiated at a recommended starting dose of 0.5 mg once daily under close medical supervision. This dose should be maintained for about 1 week. If this dose has been well tolerated it may be increased in weekly intervals and according to the clinical status of the patient to 1.0 mg or 2.5 mg. The maximum daily dose for these patients is 5.0 mg. The posology recommendation for cilazapril in chronic heart failure is based on effects on symptomatic improvement, rather than on data showing that cilazapril reduces morbidity and mortality in this patient group (see section 5.1).

**Special populations**

Patients with renal impairment
Reduced dosages are required for patients with renal impairment, depending on their creatinine clearance (see section 4.4).

The following dose schedules are recommended:

**Table 1: Recommended dosage schedule for patients with renal impairment**

| Creatinine clearance | Initial dose of Cilazapril | Maximal dose of Cilazapril |
|---|---|---|
| > 40 ml/min | 1 mg once daily | 5 mg once daily |
| 10 – 40 ml/min | 0.5 mg once daily | 2.5 mg once daily |
| < 10ml/min | Not recommended | |

If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor, they should be discontinued and renal function should be monitored during the first weeks of Cilazapril therapy.

Results from clinical trials showed that clearance of cilazapril was correlated with creatinine clearance in patients with chronic heart failure. The special dosage recommendation should thus be followed in chronic heart failure patients with impaired renal function.

Liver cirrhosis
In patients with liver cirrhosis (but without ascites) who require therapy for hypertension, cilazapril should be dosed with great caution not exceeding 0.5 mg/day

accompanied by a careful monitoring of the blood pressure, because significant hypotension may occur.

Elderly
In the treatment of hypertension Cilazapril should be initiated with a dose between 0.5 mg and 1.0 mg once daily. Thereafter, the maintenance dose must be adapted to individual tolerability, response and clinical status.

In elderly patients with chronic heart failure the recommended starting dose of Cilazapril 0.5 mg must be strictly followed.

Paediatric population: Safety and efficacy in children aged below 18 years have not been established. Therefore, there is no recommendation for administration of cilazapril to children.

Method of administration
Oral use.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or any other angiotensin-converting enzyme (ACE) inhibitor
- Hereditary or idiopathic angioneurotic oedema
- History of angioedema associated with previous ACE inhibitors therapy
- Second and third trimesters of pregnancy (see section 4.4 and 4.6)
- The concomitant use of Cilazapril with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR □ 60 ml/min/1.73m$^2$) (see sections 4.5 and 5.1).
- Concomitant use with sacubitril/valsartan therapy. Cilazapril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).

## 4.4 Special warnings and precautions for use

*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 sections 4.3 and 4.6).
*Hypotension*
ACE inhibitors may cause severe hypotension, especially when starting treatment. Firstdose hypotension is most likely to occur in patients whose renin-angiotensinaldosterone system is activated, such as in renovascular hypertension or other causes of renal hypoperfusion, sodium or volume depletion, or previous treatment with other vasodilators. These conditions can co-exist, particularly in severe heart failure.

Hypotension should be treated by placing the patient supine and volume expansion. Cilazapril may be continued once the patient is volume replete, but should be given at a lower dose or discontinued if hypotension persists.
At-risk patients should start treatment with cilazapril under medical supervision, with a low initial dose and careful titration. If possible, diuretic therapy should be discontinued temporarily.
Similar caution should be taken for patients with angina pectoris or cerebrovascular disease, in whom hypotension can cause myocardial or cerebral ischaemia.

*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 section 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.

*Renal impairment*

In patient with renal impairment, the dosage of Cilazapril should be adjusted according to creatinine clearance (see section 4.2). Routine monitoring of potassium and creatinine is part of normal medical practice for these patients. ACE inhibitors have established renoprotective effects, but can cause reversible impairment of renal function in the setting of reduced renal perfusion, whether due to bilateral renal artery stenosis, severe congestive heart failure, volume depletion, hyponatraemia or high dosages of diuretics, and in those receiving treatment with NSAIDs. Preventive measures include withdrawing or temporarily withholding diuretics, beginning therapy with very small doses of ACE inhibitors, and cautious dose titration.
In patients with renal artery stenosis, activation of the renin-angiotensin-aldosterone system helps to maintain renal perfusion by causing constriction of the efferent arteriole. Hence, blockade of angiotensin II formation, and possibly also an increase in the formation of bradykinin, causes efferent arteriolar vasodilation resulting in a reduction in glomerular filtration pressure. Hypotension contributes further to a reduction in renal perfusion (see section 4.4`Hypotension'). As with other agents acting on the reninangiotensin system, there is an increased risk of renal insufficiency, including acute renal failure, when patients with renal artery stenosis are treated with cilazapril. Therefore, caution should be exercised in these patients. If renal failure occurs, treatment should be discontinued.

*Hypersensitivity / angioedema*

Angioedema has been associated with ACE inhibitors, with a reported incidence of 0.10.5%. Angioedema due to ACE inhibitors can present as recurrent episodes of facial swelling, which resolves on withdrawal, or as acute oropharyngeal oedema and airways obstruction, which requires emergency treatment, and may be lifethreatening.

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of cilazapril. Treatment with cilazapril 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.
A variant form is angioedema of the intestine, which tends to occur within the first 24-48 hours of treatment. The risk of angioedema appears to be greater in black-skinned than non-black skinned patients. Patients with a history of angioedema unrelated to ACE inhibitors may be at greater risk.

*Anaphylaxis*

*Haemodialysis*: Anaphylaxis has occurred in patients dialysed with high flux membranes (e.g. AN 69) receiving ACE inhibitors. Consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

*Low-density lipoproteins (LDL) apheresis:* Patients receiving ACE inhibitors during LDL apheresis with dextran sulphate have experienced life-threatening anaphylaxis. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

*Desensitisation:* Anaphylactic reactions can occur in patients undergoing desensitization therapy with wasp or bee venom while receiving an ACE inhibitor. Cilazapril must be stopped before the start of desensitization therapy, and should not be replaced by a β- blocker.

*Hepatic disorders*

Single cases of liver function disorders, such as increased values of liver function tests (transaminases, bilirubin, alkaline phosphatase, gamma GT) and cholestatic hepatitis with or without necrosis have been reported. Patients receiving cilazapril who develop jaundice or marked elevations of hepatic enzymes should discontinue cilazapril and receive appropriate medical follow-up. In patients with liver cirrhosis (but without ascites) who require therapy for hypertension, cilazapril should be initiated at a lower dose and with great caution because significant hypotension may occur (see section 4.2).
In patients with ascites, cilazapril administration is not recommended.

*Neutropenia*

Rarely, neutropenia and agranulocytosis have been associated with ACE inhibitors, especially in patients with renal failure or collagen vascular disease, and those receiving immunosuppressive therapy. Periodic monitoring of leukocyte count is recommended in such patients.

*Serum potassium*

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) or 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).

*Diabetes*

Administration of ACE inhibitors to patients with diabetes may potentiate the blood glucose-lowering effect of oral hypoglycaemic agents or insulin, especially in patients with renal impairment. In such patients, glucose levels should be carefully monitored during initiation of treatment with an ACE inhibitor.

*Surgery / anaesthesia*

Anaesthetic agents with blood pressure lowering effects can cause hypotension in patients receiving ACE inhibitors. Hypotension in this setting can be corrected with volume expansion.

*Aortic and mitral valve stenosis / hypertrophic cardiomyopathy*

ACE inhibitors should be used with caution in patients with obstructive cardiac disorders (e.g. mitral stenosis, aortic stenosis, hypertrophic cardiomyopathy), since cardiac output cannot increase to compensate for systemic vasodilation, and there is a risk of severe hypotension.

*Ethnicity*

ACE inhibitors are less effective as antihypertensives in patients with black skin colour. These patients also have a higher risk of angioedema.

*Lactose monohydrate content*

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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

*Lithium*

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased lithium toxicity with ACE inhibitors. Use of Cilazapril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

*Medicines increasing the risk of angioedema*

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 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).

*Other antihypertensive agents*

An additive effect may be observed when cilazapril is administered in combination with other antihypertensive agents.

*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 cilazapril is co-adminitered 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 (see section 4.4). If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

*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.

*Diuretics (thiazide or loop diuretics)*

Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with cilazapril (see section 4.4). The hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake or by initiating therapy with a low dose of cilazapril.

*Angiotensin- receptor antagonists and aliskiren*

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosteronesystem (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).

*Tricyclic antidepressants /Antipsychotics /Anaesthetics/narcotics*

Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

*Non-steroidal anti-inflammatory medicinal products (NSAIDs) including acetylsalicylic acid ≥ 3 g/day*

When ACE inhibitors are administered simultaneously with non-steroidal antiinflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), 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.

*Sympathomimetics*

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

*Antidiabetics*

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicinal products (insulins, oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to 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.

*Others*

No clinically significant interactions were observed when cilazapril and digoxin, nitrates, coumarin anticoagulants, and H2 receptor blockers were concomitantly administered.

## 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 contra-indicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4)

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.

Exposure to ACE inhibitor therapy 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 also section 5.3). Should exposure to an 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 also section 4.3 and 4.4).

*Breastfeeding*

Because no information is available regarding the use of CILAZAPRIL during breastfeeding, CILAZAPRIL is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

## 4.7 Effects on ability to drive and use machines

When driving and operating machines, it should be taken into account that occasionally dizziness and fatigue may occur, especially when starting therapy (see sections 4.4 and 4.8).

## 4.8 Undesirable effects

**(a) Summary of the safety profile**

The most frequent drug-attributable adverse events observed in patients taking ACE inhibitors are cough, skin rash and renal dysfunction. Cough is more common in women and non-smokers. Where the patient can tolerate the cough, it may be reasonable to continue treatment. In some cases, reducing the dose may help.

Treatment-related adverse events severe enough to stop treatment occur in less than 5% of patients receiving ACE inhibitors.

**(b) Tabulated list of adverse reactions**

The following list of adverse reactions is derived from clinical trials and post-marketing data in association with cilazapril and/or other ACE inhibitors. Estimates of frequency are based on the proportion of patients reporting each adverse reaction during cilazapril clinical trials that included a total combined population of 7171 patients. Adverse reactions that were not observed during cilazapril clinical trials but have been reported in association with other ACE inhibitors or derived from postmarketing case reports are classified as `rare'. Frequency categories are as follows:

Very common (≥1/10)
Common (≥1/100, <1/10)
Uncommon (≥1/1,000, <1/100)
Rare (≥1/10,000, <1/1,000)

| **System organ class** | **Common (>1/100, <1/10)** | **Uncommon (>1/1,000, <1/100)** | **Rare (>1/10,000, <1/1,000)** |
|---|---|---|---|
| Blood and lymphatic system disorders | | | Neutropenia, agranulocytosis, thrombocytopenia, anemia |

| | | | |
|---|---|---|---|
| Immune system disorders | | Angioedema (may involve the face, lips, tongue, larynx or gastrointestinal tract) (see section 4.4) | Anaphylaxis (see section 4.4)<br><br>Lupus-like syndrome (symptoms may include vasculitis, myalgia, arthralgia/arthritis, positive antinuclear antibodies, increased erythrocyte sedimentation rate, eosinophilia and leukocytosis) |
| Nervous system disorders | Headache | Dysgeusia | Cerebral ischaemia, transient ischaemic attack, ischaemic stroke<br>Peripheral neuropathy |
| Cardiac disorders | | Myocardial ischaemia, angina pectoris, tachycardia, palpitations | Myocardial infarction, arrhythmia |
| Vascular disorders | Dizziness | Hypotension, Postural hypotension (see section 4.4). Symptoms of hypotension may include syncope, weakness, dizziness and visual impairment. | |
| Respiratory, thoracic and mediastinal disorders | Cough | Dyspnoea, bronchospasm, rhinitis | Interstitial lung disease, bronchitis, sinusitis |
| Gastrointestinal disorders | Nausea | Dry mouth, aphthous stomatitis, | Glossitis, pancreatitis |

| | | | |
|---|---|---|---|
| | | decreased appetite, diarrhoea, vomiting | |
| Hepatobiliary disorders | | | Abnormal liver function test (including transaminases, bilirubin, alkaline phosphatase, gamma GT)<br>Cholestatic hepatitis with or without necrosis |
| Skin and subcutaneous tissue disorders | | Rash, maculopapular rash | Psoriaform dermatitis, psoriasis (exacerbation), lichen planus, exfoliative dermatitis, urticaria, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous pemphigoid, pemphigus, Karposi's sarcoma, vasculitis/purpura, photosensitivity reactions, alopecia, onycholysis |
| Musculoskeletal and connective tissue disorders | | Muscle cramps, myalgia, arthralgia | |

| | | | |
|---|---|---|---|
| | | | Renal impairment, acute renal failure (see section 4.4), blood creatinine increased, blood urea Increased Hyperkalaemia, hyponatraemia, proteinuria, nephrotic syndrome, nephritis |
| Reproductive system and breast disorders | | Impotence | Gynaecomastia |
| General disorders and administration site conditions | Fatigue | Excess sweating, flushing, asthenia, sleep disorder | |

**(c) Description of selected adverse events**

Hypotension and postural hypotension may occur when starting treatment or increasing dose, especially in at-risk patients (see section 4.4). Renal impairment and acute renal failure are more likely in patients with severe heart failure, renal artery stenosis, preexisting renal disorders or volume depletion (see section 4.4).

Hyperkalaemia is most likely to occur in patients with renal impairment and those taking potassium sparing diuretics or potassium supplements.

The events of cerebral ischaemia, transient ischaemic attack and ischaemic stroke reported rarely in association with ACE inhibitors may be related to hypotension in patients with underlying cerebrovascular disease. Similarly, myocardial ischaemia may be related to hypotension in patients with underlying ischaemic heart disease.

Headache is a commonly reported adverse event, although the incidence of headache is greater in patients receiving placebo than in those receiving ACE inhibitors.

**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 the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

## 4.9 Overdose

*Symptoms*
Limited data are available for overdosage in humans. Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough.

*Management*
The recommended treatment of overdose is intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. If hypotension occurs, the patient should be placed in the shock. If available, treatment with angiotensin II should be considered.

Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

If indicated, cilazaprilat, the active form of cilazapril, may be removed from the general irculation by haemodialysis (see section 4.4).

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: angiotensin convertase inhibitors, ATC code: C09 AA08

Mechanism of action
Cilazapril is a specific, long-acting angiotensin-converting enzyme (ACE) inhibitor which suppresses the renin-angiotensin-aldosterone system and thereby the conversion of the inactive angiotensin I to angiotensin II, which is a potent vasoconstrictor. At recommended doses, the effect of Cilazapril in hypertensive patients and in patients with chronic heart failure is maintained for up to 24 hours.

Clinical efficacy and safety
*Hypertension*
Cilazapril induces a reduction of both supine and standing systolic and diastolic blood pressure, usually with no orthostatic component. It is effective in all degrees of essential hypertension as well as in renal hypertension. The anti-hypertensive effect of Cilazapril is usually apparent within the first hour after administration, with maximum effect observed between three and seven hours after dosing. In general the heart rate (pulse) remains unchanged. Reflex tachycardia is not induced by the drug, although small, clinically insignificant alterations of heart rate may occur. In some patients the anti-hypertensive effect of the drug diminishes toward the end of the dosage interval.

The anti-hypertensive effect of Cilazapril is maintained during long-term therapy. No rapid increases in blood pressure have been observed after abrupt withdrawal of Cilazapril.

In hypertensive patients with moderate or severe renal impairment, the glomerular filtration rate and renal blood flow remain in general unchanged with Cilazapril despite a clinically significant blood pressure reduction.

As with other ACE inhibitors, the blood pressure-lowering effect of Cilazapril in Black patients may be less pronounced than in non-Blacks. However, racial

differences in response are no longer evident when Cilazapril is administered in combination with hydrochlorothiazide.

*Chronic heart failure*
No clinical trials have been carried out which prove the effect of cilazapril on morbidity and mortality in heart failure.

In patients with chronic heart failure, the renin-angiotensin-aldosterone and the sympathetic nervous systems are generally activated, leading to enhanced systemic vasoconstriction and to the promotion of sodium and water retention. By suppressing the renin-angiotensin- aldosterone system, Cilazapril improves loading conditions in the failing heart by reducing systemic vascular resistance (afterload) and pulmonary capillary wedge pressure (preload) in patients on diuretics and/or digitalis.

Furthermore, the exercise tolerance of these patients increases significantly thus showing an improvement in quality of life. The haemodynamic and clinical effects occur promptly and persist.

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

The concomitant use of aliskiren with an ACE-inhibitor or an angiotensin II receptor blocker is contraindicated in patients with type 2 diabetes mellitus or renal impairment (GFR □ 60ml/min/1.73m2).

## 5.2 Pharmacokinetic properties

Absorption
Cilazapril is efficiently absorbed and rapidly converted to the active form, Cilazaprilat. Ingestion of food immediately prior to Cilazapril administration, delays and reduces the absorption to a minor extent which, however, is therapeutically irrelevant. The bioavailability of Cilazaprilat after oral administration of Cilazapril

approximates 60% based on urinary recovery data. Maximum serum concentrations are reached within two hours after drug administration and are directly related to dosage.

Elimination
Cilazaprilat is eliminated unchanged by the kidneys, with an effective half-life of nine hours after once-daily dosing with Cilazapril.

*Special populations*

Renal impairment
In patients with renal impairment, higher plasma concentrations of Cilazaprilat are observed than in patients with normal renal function, since drug clearance is reduced when creatinine clearance is lower. There is no elimination in patients with complete renal failure, but haemodialysis reduces concentrations of Cilazapril and Cilazaprilat to a limited extent.

Elderly
In elderly patients whose renal function is normal for age, plasma concentrations of Cilazaprilat may be up to 40% higher and the clearance up to 20% lower than in younger patients. Similar changes in the pharmacokinetics occur in patients with moderate to severe liver cirrhosis.

Chronic heart failure
In patients with chronic heart failure the clearance of Cilazaprilat is correlated with the creatinine clearance. Thus, dosage adjustments do not go beyond those recommended for patients with impaired renal functions (see section 4.2) should not be necessary.

### 5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

In chronic oral toxicity studies (rats and monkeys), the target organ is the kidney, with reversible damage.

In fertility and general reproduction performance testing in rats, dosing with 50 mg/kg/day of CILAZAPRIL resulted in greater implantation losses, less viable fetuses, smaller pups, and dilatation of the renal pelvis in the pups. No teratogenic effects or adverse effects on post- natal pup development were observed in rats and Cynomolgus monkeys during embryotoxicity testing. In the rats, however, at a dose of 400 mg/kg/day, renal cavitation was observed in the pups. In peri- and post-natal toxicity testing in rats, dosing with 50 mg/kg/day resulted in greater pup mortality, smaller pups, and delayed unfolding of the pinna. On administration of 14C-CILAZAPRIL to pregnant mice, rats and monkeys, radioactivity was measured in the foetuses.

ACE inhibitors, as a class, have been shown to induce adverse effect on late foetal development, resulting in foetal death and congenital effects in rodents and rabbits: renal lesions and an increase in peri- and post-natal mortality have been observed.

## 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

*Tablet core*

Lactose monohydrate

Maize starch

Hypromellose 3cp

Talc

Sodium stearyl fumarate

*Film -Coating*

Opadry brown 03B26857: hypromellose 6cp, talc, titanium dioxide (E171), Macrogol 400, iron oxide red (E172).

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

3 years

## 6.4 Special precautions for storage

Do not store above 25ºC.

## 6.5 Nature and contents of container

Aluminium/Aluminium blisters in a cardboard box.

28 tablets

### 6.6 Special precautions for disposal

No special requirements

## 7 MARKETING AUTHORISATION HOLDER

Activase Pharmaceuticals Limited,
11 Boumpoulinas, 3rd Floor,
P.C. 1060, Nicosia
Cyprus

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 28444/0117

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

02/06/2009

## 10 DATE OF REVISION OF THE TEXT

29/10/2025