Public Assessment Report

Decentralised

Cilazapril 0.5mg Film-coated Tablets
Cilazapril 1mg Film-coated Tablets
Cilazapril 2mg Film-coated Tablets
Cilazapril 5mg Film-coated Tablets

Cilazapril monohydrate

UK/H/1431/01-04

PL 31304/0005-8

Symphar SP Z O O
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# Module 1

<table>
<thead>
<tr>
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<th>Cilazapril 0.5mg, 1mg, 2.5mg &amp; 5mg Film-coated Tablets</th>
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<tr>
<td><strong>Type of Application</strong></td>
<td>Complex Abridged Decentralised (Article 10.1)</td>
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<td><strong>Active Substance (INN)</strong></td>
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<td><strong>Pharmacotherapeutic Classification (ATC)</strong></td>
<td>ACE Inhibitors (C09A A08)</td>
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<td><strong>Pharmaceutical Form and Strength</strong></td>
<td>0.5mg, 1mg, 2.5mg &amp; 5mg Film-coated Tablets</td>
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<td><strong>Procedure Numbers</strong></td>
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<td>02/06/2009</td>
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<tr>
<td><strong>MA Number</strong></td>
<td>PL 25124/0014-5</td>
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<tr>
<td><strong>Name and address of MA holder</strong></td>
<td>Symphar SP Z O O, Ul. Wloska 1, 00-777 Warsaw, Poland</td>
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Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Cilazapril 0.5 mg, film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One 0.5 mg film-coated tablet contains 0.5 mg of cilazapril (as cilazapril monohydrate).
Excipient: One 0.5 mg film-coated tablet contains 61.000 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, weighting approx 100 mg, film coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Hypertension
Treatment of essential hypertension.

Heart failure
Treatment of symptomatic heart failure

4.2 Posology and method of administration
Cilazapril should be administered orally in a single daily dose. As with all other medicinal products taken once daily, it should be taken at approximately the same time each day. The absorption of cilazapril is not affected by food.

The maintenance does should be individualized according to patient profile and blood pressure response (see section 4.4).
Essential hypertension

Cilazapril may be used as monotherapy or in combination with other classes of antihypertensive medicinal products.

Hypertensive patients receiving diuretics

Starting dose

The initial recommended dose is 1 mg once a day. Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and/or volume depletion, cardiac decompensation, or severe hypertension) may experience an excessive blood pressure fall following the initial dose. The initiation of treatment should take place under medical supervision.

Maintenance dose

The usual daily dose is 2.5 mg to a maximum of 5 mg administered in a single dose. In general if the desired therapeutic effect cannot be achieved in a period of 3 to 4 weeks on a certain dose level, the dose can be further increased.

If the blood pressure is not adequately controlled with 5 mg Cilazapril once daily, a low dose of a non-potassium-sparing diuretic may be administered concomitantly to enhance the antihypertensive effect.

Hypertensive patients being treated with concomitant diuretic therapy:

Symptomatic hypotension may occur following initiation of therapy with Cilazapril. This is more likely in patients who are being treated currently with diuretics, especially in patients with heart failure, elderly patients (over 75 years) and patients with renal dysfunction. Caution is recommended therefore, since these patients may be volume and/or salt depleted. If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with Cilazapril. In hypertensive patients in whom the diuretic cannot be discontinued, and especially in those on high-dose diuretic therapy, therapy with Cilazapril should be initiated with a 0.5 mg dose.

Renal function and serum potassium should be monitored. The subsequent dosage of cilazapril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed (see section 4.4 and section 4.5). When treatment is initiated in a patient already taking diuretics, it is recommended that the treatment with Cilazapril is started under medical supervision for several hours and until blood pressure is stabilised.

Heart failure

In patients with symptomatic heart failure, Cilazapril should be used as adjunctive therapy to diuretics and, where appropriate, digitalis.

The recommended initial dose is 0.5 mg once daily, initiated under close medical supervision.

If the initial dose is well tolerated, patients should then be titrated to the lowest maintenance dose of 1 mg daily based on clinical response. Further titration within the usual maintenance dose of 1 to 2.5 mg daily should be carried out based on the patient's response, clinical status and tolerability.

The usual maximum dose is 5 mg once daily.

Results from clinical trials showed that clearance of cilazaprilat in patients with chronic heart failure is correlated with creatinine clearance. Thus, in patients with chronic heart failure and
impaired renal function, special dosage recommendations as given under "Impaired renal function" should be followed.

The appearance of hypotension after the initial dose should not preclude careful dose titration of cilazapril, following effective management of the hypotension.

Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with Cilazapril. Renal function and serum potassium should be monitored (see section 4.4).

**Impaired renal function**
Reduced dosages may be required in patients with renal impairment, depending on their creatinine clearance.

The following dose schedules of Cilazapril are recommended:

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Initial dose</th>
<th>Maximal dose</th>
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<tbody>
<tr>
<td>&gt; 40 ml/min</td>
<td>1 mg once daily</td>
<td>5 mg once daily</td>
</tr>
<tr>
<td>10 – 40 ml/min</td>
<td>0.5 mg once daily</td>
<td>2.5 mg once daily</td>
</tr>
<tr>
<td>&lt; 10ml/min</td>
<td>Not recommended</td>
<td></td>
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**Haemodialysis**
In patients requiring haemodialysis, Cilazapril should not be administered on days when dialysis is performed, and the dosage should be adjusted according to blood pressure response.

**Hepatic impairment**
Should patients with liver cirrhosis require treatment with cilazapril, it should be initiated with caution at a dose of 0.5 or 0.25 mg once daily, because significant hypotension may occur (see sections 4.4 and 5.2).

**Elderly**
In the treatment of hypertension Cilazapril should be initiated with between 0.5 mg and 1.0 mg once daily. Thereafter, the maintenance dose may be increased according to individual response.

In the treatment of chronic heart failure Cilazapril should be initiated with a dose of 0.5 mg once daily. The maintenance dose is 1.0 mg to 2.5 mg according to individual tolerability, response and clinical status.

In elderly patients with chronic heart failure the recommended daily starting dose of Cilazapril 0.5 mg must be strictly followed due to the risk of symptomatic hypotension.

**Children and adolescents**
Cilazapril is not recommended for use in children and adolescents below the age of 18 years, due to insufficient data on the safety and efficacy of this medicinal product.
4.3 Contraindications

- Hypersensitivity to cilazapril, any of the excipients 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)

4.4 Special warnings and precautions for use

**Symptomatic hypotension**

Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving Cilazapril, hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (see section 4.5 and section 4.8). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Cilazapril. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of Cilazapril may be necessary.

*Aortic and mitral valve stenosis / hypertrophic cardiomyopathy*

As with other angiotensin-converting enzyme (ACE) inhibitors, Cilazapril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

*Renal function impairment*

In cases of 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.

In patients with heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum
creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. 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 to the above, they should be discontinued and renal function should be monitored during the first weeks of therapy with Cilazapril.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when Cilazapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or ACE inhibitor may be required.

**Proteinuria**

In patients with pre-existing renal impairment proteinuria may occur in rare cases. In clinically relevant proteinuria (greater than 1 g/day) Cilazapril should only be used after a very critical benefit/risk evaluation and with regular monitoring of the clinical and laboratory chemical parameters.

**Hypersensitivity / angioedema**

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including Cilazapril. This may occur at any time during therapy.

In such cases, Cilazapril should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patients. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

ACE inhibitors cause a higher rate of angioedema in Black patients than in non-Black patients.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).

Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain (see section 4.8).

**Anaphylactoid reactions in haemodialysis patients**

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes (e.g. AN 69) and treated concomitantly with an ACE inhibitor. In these patients consideration
should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

Rarely, patients receiving ACE inhibitors during LDL apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Desensitisation

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they have reappeared upon inadvertent re-administration of the medicinal product.

Hepatic failure

High cilazapril plasma concentrations might occur in patients with impaired hepatic function. Very rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving cilazapril who develop jaundice or marked elevations of hepatic enzymes should discontinue Cilazapril and receive appropriate medical follow-up.

Neutropenia/Agranulocytosis

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor. ACE inhibitors should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If Cilazapril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.”

Race

As with other ACE inhibitors, Cilazapril may be less effective in lowering blood pressure in Black patients than in non-Blacks, possibly because of a higher prevalence of low-renin states in the Black hypertensive population.

Cough

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery / anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Cilazapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.
Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including Cilazapril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, or worsening renal function, diabetes mellitus, acute cardiac decompensation, metabolic acidosis, intercurrent events, in particular dehydration, the elderly (age > 70 years) or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes, (especially in those with renal impairment, in whom combined use may lead to significant increases in serum potassium), or those patients taking other medicinal products associated with increases in serum potassium (e.g. heparin). Hyperkalemia can cause serious, sometimes fatal arrhythmias. If concomitant use of the above-mentioned products is deemed appropriate, caution and regular monitoring of serum potassium are recommended (see section 4.5).

Diabetic patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see section 4.5).

Lithium

The combination of lithium and Cilazapril is generally not recommended (see section 4.5).

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).

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.

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

When a diuretic is added to the therapy of a patient receiving cilazapril, the antihypertensive effect is usually additive.

Patients already on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure when cilazapril is added. The possibility of symptomatic hypotension with cilazapril can be minimised by discontinuing the diuretic prior to initiation of treatment with cilazapril (see section 4.4).

Potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes, or other medicinal products associated with increases in serum potassium (e.g. heparin) (see section 4.4, Hyperkalaemia)

Although in clinical trials, serum potassium usually remained within normal limits, hyperkalaemia did occur in some patients. Risk factors for the development of hyperkalaemia
include renal insufficiency, diabetes mellitus, and concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene or amiloride), potassium supplements, potassium-containing salt substitutes or other medicinal products associated with increases in serum potassium (e.g. heparin).

The use of the above-mentioned products, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium.

If Cilazapril is given with a potassium-losing diuretic, diuretic-induced hypokalaemia may be ameliorated.

**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).

**Non steroidal anti-inflammatory medicinal products (NSAIDs) including acetylsalicylic acid**

Chronic administration of NSAIDs (including acetylsalicylic acid at anti-inflammatory doses, COX-2 inhibitors and non-selective NSAIDs) may reduce the antihypertensive effect of an ACE inhibitor. NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium and may result in a deterioration of renal function, 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.

**Other antihypertensive agents**

Combination with other antihypertensive agents such as beta-blockers, methyldopa, calcium antagonists, and diuretics may increase the anti-hypertensive efficacy. Concomitant use with glyceryl trinitrate and other nitrates, or other vasodilators, may further reduce blood pressure.

**Tricyclic antidepressants /Antipsychotics /Anaesthetics**

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).

**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.

**Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates**
Cilazapril may be used concomitantly with acetylsalicylic acid (at cardiological doses), thrombolytics, beta-blockers and/or nitrates.

*Immunosuppressants, cytostatics, systemic corticosteroids or procaainamide, allopurinol*

The combination of cilazapril with immunosuppressant medicinal products and/or medicinal products that can cause leucopenia should be avoided.

*Alcohol*

Alcohol enhances the hypotensive effect of cilazapril.

*Antacids*

Antacids (e.g. aluminium hydroxide, magnesium hydroxide, simeticone) may impair absorption of cilazapril and so the administration of both medicinal products should be separated by at least 2 hours.

### 4.6 Pregnancy and lactation

*Pregnancy*

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). It 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.

ACE inhibitor/angiotensin II receptor antagonist exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see 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).

*Lactation*

Because insufficient 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
Cilazapril has no or negligible influence on the ability to drive and use machines.

Although cilazapril is not expected to directly affect the ability to drive or use machines, adverse reactions such as hypotension, dizziness and vertigo may interfere it.

This occurs especially at the start of treatment, when increasing the dosage, when changing over from other preparations and during concomitant use of alcohol, depending on the individual's susceptibility.

4.8 Undesirable effects
The following adverse reactions have been observed during treatment with Cilazapril or other ACE inhibitors (marked with an asterisk) and are ranked under the following frequency convention:

Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, ≤1/100); rare (≥1/10,000, ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated from the available data).

| Blood and lymphatic system disorders | Very rare | Decreased haemoglobin or haematocrit levels, bone marrow depression*, anaemia*, thrombocytopenia*, leucopenia, neutropenia*, agranulocytosis (see section 4.4), haemolytic anaemia*, lymphadenopathy |
| Immune system disorders | Very rare | Auto-immune disease* |
| Metabolism and nutrition disorders | Very rare | Hypoglycaemia* |
| Nervous system disorders | Common | Headache, dizziness |
| Uncommon | Mood changes*, syncope*, sleep disturbances |
| Rare | Depression, jwaesthesia, confusion, taste disturbances |
| Very rare | Neuropathy |
| Cardiovascular disorders | Common | Hypotension, orthostatic or otherwise (including hypotension)* (see section 4.4) |
| Uncommon | Myocardial infarction, cerebrovascular accident, possibly secondary to significant drop in blood pressure in high-risk patients (see section 4.4)*, palpitations, tachycardia*, Raynaud's phenomenon* |
| Very rare | Vasculitis |
| Respiratory, thoracic and mediastinal disorders | Common | Cough |
| Uncommon | Rhinitis, chest pain |
| Rare | Dyspnoea, sinusitis*, bronchitis, allergic alveolitis / eosinophilic pneumonitis*, bronchospasm |
| Gastrointestinal disorders | Common | Nausea, diarrhoea*, vomiting* |
| Uncommon | Abdominal pain, dyspepsia, digestive disorders* |
| Rare | Dry mouth, glossitis |
| Very rare | Pancreatitis, intestinal angioedema* |
| Hepato-biliary disorders |
Very rare | Hepatocellular or cholestatic hepatitis with or without necrosis (severe forms have been observed in exceptional cases), jaundice, hepatic failure*

**Skin and subcutaneous tissue disorders**

Common | Rash

Uncommon | Exanthema, pruritus*

Rare | Hypersensitivity / angioedema: angioedema of the face, extremities, lips, tongue, epiglottis and / or larynx (see section 4.4), urticaria*, alopecia*, psoriasis*

Very rare | Diaphoresis*, pemphigus*, toxic epidermal necrolysis*, Stevens-Johnson syndrome*, erythema multiforme*

A symptom complex involving one or more of the following has been reported with ACE inhibitors: fever, vasculitis, myalgia, arthralgia / arthritis, positive antinuclear antibody (ANA) test, increased sedimentation rate (SR), eosinophilia and leucocytosis. Rash, photosensitisation or other dermatological disorders may occur.

**Musculoskeletal and connective tissue disorders**

Rare | Myalgia, arthralgia

**Renal and urinary disorders**

Rare | Renal impairment, uraemia*

Very rare | Acute renal failure, oliguria / anuria*

**Reproductive system and breast disorders**

Uncommon | Impotence*

Very rare | Gynaecomastia

**General disorders and administration site conditions**

Common | Tiredness

Uncommon | Asthenia*

**Investigations**

Uncommon | Moderately increased plasma urea and creatinine levels, reversible on discontinuation of treatment and most frequently observed in patients with renal artery stenosis, diuretic-treated hypertension, renal impairment. Usually transient hyperkalaemia.

Rare | Proteinuria in patients with glomerular nephropathy, increased serum bilirubin, increased liver enzyme levels (transaminases, bilirubin, alkaline phosphatase, gamma GT), hyponatraemia*

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**4.9 Overdose**

While single doses of up to 160 mg Cilazapril have been administered to normal healthy volunteers without untoward effects on blood pressure, only a few data on overdose are available in patients.

**Symptoms**

Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough. The recommended treatment of overdose is intravenous infusion of normal saline solution.

**Treatment**

After ingestion of an overdose, the patient should be kept under close supervision, preferably in an intensive care unit. Serum electrolytes and creatinine should be monitored frequently. Therapeutic measures depend on the nature and severity of the symptoms. Measurements to
prevent absorption of the drugs (such as gastric lavage, administration of adsorbents and sodium sulphate within 30 minutes after the ingestion of an overdose), and to hasten elimination should be applied if ingestion is recent. If hypotension occurs, the patient should be placed in the shock position and salt and volume supplementation should be given rapidly.

Treatment with angiotensin II should be considered. Bradycardia or extensive vagal reactions should be treated by administering atropine. The use of a pacemaker may be considered. ACE inhibitors may be removed from the circulation by haemodialysis. The use of high-flux polyacrylonitrile membranes should be avoided.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: angiotensin convertase inhibitors, ATC code: C09 AA08

Cilazapril is a selective, long-acting angiotensin-converting enzyme (ACE) inhibitor which suppresses the renin-angiotensin-aldosterone system and 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.

In patients with normal renal function, serum potassium usually remains within the normal range during Cilazapril treatment. In patients concomitantly taking potassium-sparing diuretics, potassium levels may rise.

Hypertension
Cilazapril induces a reduction of both supine and standing systolic and diastolic blood pressure, usually with no orthostatic component. Cilazapril

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 initial dosage seldom achieves the desired therapeutic response. Blood pressure values should be assessed and dosage gradually increased as required. If the maximum recommended dose is not sufficient, it can be combined with non-potassium-sparing diuretics.

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.
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**

In patients with chronic heart failure the renin-angiotensin-aldosterone and the sympathetic nervous systems are generally excessively activated leading to 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 during the treatment.

### 5.2 Pharmacokinetic properties

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.

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

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.

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 fetuses.

ACE inhibitors, as a class, have been shown to induce adverse effect on late fetal development, resulting in fetal 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

0.5 mg: Opadry pink 03B23719: hypromellose 6cp, talc, titanium dioxide (E171), Macrogol 400, iron oxide red (E172), iron oxide yellow (E172).

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.
6.4 Special precautions for storage
Do not store above 25°C.

6.5 Nature and contents of container
Aluminium/Aluminium blisters in a cardboard box.

30 tablets

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
SymPhar Sp. z o.o.
ul. Włoska 1
00-777 Warsaw
Poland

8 MARKETING AUTHORISATION NUMBER(S)
PL 31304/0005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/06/2009

10 DATE OF REVISION OF THE TEXT
02/06/2009
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Cilazapril 1 mg, film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One 1 mg film-coated tablet contains 1 mg of cilazapril (as cilazapril monohydrate).
Excipient: One 1 mg film-coated tablet contains 122.000 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, with the mark C1 engraved on one side, weighting approx 200 mg, film coated tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Hypertension
Treatment of essential hypertension.

Heart failure
Treatment of symptomatic heart failure

4.2 Posology and method of administration
Cilazapril should be administered orally in a single daily dose. As with all other medicinal products taken once daily, it should be taken at approximately the same time each day. The absorption of cilazapril is not affected by food.

The maintenance does should be individualized according to patient profile and blood pressure response (see section 4.4).

Essential hypertension
Cilazapril may be used as monotherapy or in combination with other classes of antihypertensive medicinal products.

Hypertensive patients receiving diuretics

Starting dose
The initial recommended dose is 1 mg once a day. Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and/or volume depletion, cardiac decompensation, or severe hypertension) may experience an excessive blood pressure fall following the initial dose. The initiation of treatment should take place under medical supervision.

**Maintenance dose**

The usual daily dose is 2.5 mg to a maximum of 5 mg administered in a single dose. In general if the desired therapeutic effect cannot be achieved in a period of 3 to 4 weeks on a certain dose level, the dose can be further increased.

If the blood pressure is not adequately controlled with 5 mg Cilazapril once daily, a low dose of a non-potassium-sparing diuretic may be administered concomitantly to enhance the antihypertensive effect.

Hypertensive patients being treated with concomitant diuretic therapy:

Symptomatic hypotension may occur following initiation of therapy with Cilazapril. This is more likely in patients who are being treated currently with diuretics, especially in patients with heart failure, elderly patients (over 75 years) and patients with renal dysfunction. Caution is recommended therefore, since these patients may be volume and/or salt depleted.

If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with Cilazapril. In hypertensive patients in whom the diuretic cannot be discontinued, and especially in those on high-dose diuretic therapy, therapy with Cilazapril should be initiated with a 0.5 mg dose.

Renal function and serum potassium should be monitored. The subsequent dosage of cilazapril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed (see section 4.4 and section 4.5). When treatment is initiated in a patient already taking diuretics, it is recommended that the treatment with Cilazapril is started under medical supervision for several hours and until blood pressure is stabilised.

**Heart failure**

In patients with symptomatic heart failure, Cilazapril should be used as adjunctive therapy to diuretics and, where appropriate, digitalis.

The recommended initial dose is 0.5 mg once daily, initiated under close medical supervision.

If the initial dose is well tolerated, patients should then be titrated to the lowest maintenance dose of 1 mg daily based on clinical response. Further titration within the usual maintenance dose of 1 to 2.5 mg daily should be carried out based on the patient's response, clinical status and tolerability.

The usual maximum dose is 5 mg once daily.

Results from clinical trials showed that clearance of cilazaprilat in patients with chronic heart failure is correlated with creatinine clearance. Thus, in patients with chronic heart failure and impaired renal function, special dosage recommendations as given under "Impaired renal function" should be followed.

The appearance of hypotension after the initial dose should not preclude careful dose titration of cilazapril, following effective management of the hypotension.

Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with Cilazapril. Renal function and serum potassium should be monitored (see section 4.4).
Impaired renal function
Reduced dosages may be required in patients with renal impairment, depending on their creatinine clearance.

The following dose schedules of Cilazapril are recommended:

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Initial dose</th>
<th>Maximal dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 40 ml/min</td>
<td>1 mg once daily</td>
<td>5 mg once daily</td>
</tr>
<tr>
<td>10 – 40 ml/min</td>
<td>0.5 mg once daily</td>
<td>2.5 mg once daily</td>
</tr>
<tr>
<td>&lt; 10 ml/min</td>
<td>Not recommended</td>
<td></td>
</tr>
</tbody>
</table>

Haemodialysis
In patients requiring haemodialysis, Cilazapril should not be administered on days when dialysis is performed, and the dosage should be adjusted according to blood pressure response.

Hepatic impairment
Should patients with liver cirrhosis require treatment with cilazapril, it should be initiated with caution at a dose of 0.5 or 0.25 mg once daily, because significant hypotension may occur (see sections 4.4 and 5.2).

Elderly
In the treatment of hypertension Cilazapril should be initiated with between 0.5 mg and 1.0 mg once daily. Thereafter, the maintenance dose may be increased according to individual response.

In the treatment of chronic heart failure Cilazapril should be initiated with a dose of 0.5 mg once daily. The maintenance dose is 1.0 mg to 2.5 mg according to individual tolerability, response and clinical status.

In elderly patients with chronic heart failure the recommended daily starting dose of Cilazapril 0.5 mg must be strictly followed due to the risk of symptomatic hypotension.

Children and adolescents
Cilazapril is not recommended for use in children and adolescents below the age of 18 years, due to insufficient data on the safety and efficacy of this medicinal product.

4.3 Contraindications
- Hypersensitivity to cilazapril, any of the excipients 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)
4.4 Special warnings and precautions for use

Symptomatic hypotension

Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving Cilazapril, hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (see section 4.5 and section 4.8). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Cilazapril. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of Cilazapril may be necessary.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

As with other angiotensin-converting enzyme (ACE) inhibitors, Cilazapril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Renal function impairment

In cases of 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.

In patients with heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. 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 to the above, they should be discontinued and renal function should be monitored during the first weeks of therapy with Cilazapril.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when Cilazapril has been given concomitantly with a diuretic. This is more likely
to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or ACE inhibitor may be required.

**Proteinuria**

In patients with pre-existing renal impairment proteinuria may occur in rare cases. In clinically relevant proteinuria (greater than 1 g/day) Cilazapril should only be used after a very critical benefit/risk evaluation and with regular monitoring of the clinical and laboratory chemical parameters.

**Hypersensitivity / angioedema**

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including Cilazapril. This may occur at any time during therapy.

In such cases, Cilazapril should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patients. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

ACE inhibitors cause a higher rate of angioedema in Black patients than in non-Black patients.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).

Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain (see section 4.8).

**Anaphylactoid reactions in haemodialysis patients**

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes (e.g. AN 69) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

Rarely, patients receiving ACE inhibitors during LDL apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

**Desensitisation**
Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they have reappeared upon inadvertent re-administration of the medicinal product.

**Hepatic failure**

High cilazapril plasma concentrations might occur in patients with impaired hepatic function. Very rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving cilazapril who develop jaundice or marked elevations of hepatic enzymes should discontinue Cilazapril and receive appropriate medical follow-up.

**Neutropenia/Agranulocytosis**

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor. ACE inhibitors should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If Cilazapril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

**Race**

As with other ACE inhibitors, Cilazapril may be less effective in lowering blood pressure in Black patients than in non-Blacks, possibly because of a higher prevalence of low-renin states in the Black hypertensive population.

**Cough**

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

**Surgery / anaesthesia**

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Cilazapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

**Hyperkalaemia**

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including Cilazapril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, or worsening renal function, diabetes mellitus, acute cardiac decompensation, metabolic acidosis, intercurrent events, in particular dehydration, the elderly (age > 70 years) or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes, (especially in those with renal impairment, in whom combined use may lead to significant increases in serum potassium), or
those patients taking other medicinal products associated with increases in serum potassium (e.g. heparin). Hyperkalemia can cause serious, sometimes fatal arrhythmias. If concomitant use of the above-mentioned products is deemed appropriate, caution and regular monitoring of serum potassium are recommended (see section 4.5).

**Diabetic patients**

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see section 4.5).

**Lithium**

The combination of lithium and Cilazapril is generally not recommended (see section 4.5).

**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).

**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.

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

When a diuretic is added to the therapy of a patient receiving cilazapril, the antihypertensive effect is usually additive.

Patients already on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure when cilazapril is added. The possibility of symptomatic hypotension with cilazapril can be minimised by discontinuing the diuretic prior to initiation of treatment with cilazapril (see section 4.4).

Potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes, or other medicinal products associated with increases in serum potassium (e.g. heparin) (see section 4.4, Hyperkalaemia)

Although in clinical trials, serum potassium usually remained within normal limits, hyperkalaemia did occur in some patients. Risk factors for the development of hyperkalaemia include renal insufficiency, diabetes mellitus, and concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene or amiloride), potassium supplements, potassium-containing salt substitutes or other medicinal products associated with increases in serum potassium (e.g. heparin).

The use of the above-mentioned products, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium.
If Cilazapril is given with a potassium-losing diuretic, diuretic-induced hypokalaemia may be ameliorated.

**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).

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

Chronic administration of NSAIDs (including acetylsalicylic acid at anti-inflammatory doses, COX-2 inhibitors and non-selective NSAIDs) may reduce the antihypertensive effect of an ACE inhibitor. NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium and may result in a deterioration of renal function, 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.

**Other antihypertensive agents**

Combination with other antihypertensive agents such as beta-blockers, methyldopa, calcium antagonists, and diuretics may increase the anti-hypertensive efficacy. Concomitant use with glyceryl trinitrate and other nitrates, or other vasodilators, may further reduce blood pressure.

**Tricyclic antidepressants/Antipsychotics/Anaesthetics**

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).

**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.

**Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates**

Cilazapril may be used concomitantly with acetylsalicylic acid (at cardiological doses), thrombolytics, beta-blockers and/or nitrates.

**Immunosuppressants, cytostatics, systemic corticosteroids or procainamide, allopurinol**
The combination of cilazapril with immunosuppressant medicinal products and/or medicinal products that can cause leucopenia should be avoided.

**Alcohol**

Alcohol enhances the hypotensive effect of cilazapril.

**Antacids**

Antacids (e.g. aluminium hydroxide, magnesium hydroxide, simeticone) may impair absorption of cilazapril and so the administration of both medicinal products should be separated by at least 2 hours.

### 4.6 Pregnancy and lactation

#### Pregnancy

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). It 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.

ACE inhibitor/angiotensin II receptor antagonist exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see 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).

#### Lactation

Because insufficient 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

Cilazapril has no or negligible influence on the ability to drive and use machines.
Although cilazapril is not expected to directly affect the ability to drive or use machines, adverse reactions such as hypotension, dizziness and vertigo may interfere it. This occurs especially at the start of treatment, when increasing the dosage, when changing over from other preparations and during concomitant use of alcohol, depending on the individual's susceptibility.

### 4.8 Undesirable effects

The following adverse reactions have been observed during treatment with Cilazapril or other ACE inhibitors (marked with an asterisk) and are ranked under the following frequency convention:

- Very common (≥1/10)
- Common (≥1/100, <1/10)
- Uncommon (≥1/1,000, ≤1/100)
- Rare (≥1/10,000, ≤1/1,000)
- Very rare (≤1/10,000)
- Not known (cannot be estimated from the available data)

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased haemoglobin or haematocrit levels, bone marrow depression*, anaemia*, thrombocytopenia*, leucopenia, neutropenia*, agranulocytosis (see section 4.4), haemolytic anaemia*, lymphadenopathy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immune system disorders</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auto-immune disease*</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycaemia*</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache, dizziness</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood changes*, syncope*, sleep disturbances</td>
<td></td>
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<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression, jxaesthesia, confusion, taste disturbances</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th>Very rare</th>
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<tbody>
<tr>
<td>Neuropathy</td>
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<table>
<thead>
<tr>
<th>Cardiovascular disorders</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension, orthostatic or otherwise (including hypotension)* (see section 4.4)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiovascular disorders</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction, cerebrovascular accident, possibly secondary to significant drop in blood pressure in high-risk patients (see section 4.4)<em>, palpitations, tachycardia</em>, Raynaud's phenomenon*</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiovascular disorders</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasculitis</td>
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<table>
<thead>
<tr>
<th>Respiratory, thoracic and mediastinal disorders</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
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<table>
<thead>
<tr>
<th>Respiratory, thoracic and mediastinal disorders</th>
<th>Uncommon</th>
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</thead>
<tbody>
<tr>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory, thoracic and mediastinal disorders</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea, sinusitis*, bronchitis, allergic alveolitis / eosinophilic pneumonitis*, bronchospasm</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, diarrhoea*, vomiting*</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain, dyspepsia, digestive disorders*</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth, glossitis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatitis, intestinal angioedema*</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepato-biliary disorders</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular or cholestatic hepatitis with or without necrosis (severe forms have been observed in exceptional cases), jaundice, hepatic failure*</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td></td>
</tr>
</tbody>
</table>
### Overdose

While single doses of up to 160 mg Cilazapril have been administered to normal healthy volunteers without untoward effects on blood pressure, only a few data on overdose are available in patients.

#### Symptoms

Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, Bradycardia, dizziness, anxiety and cough. The recommended treatment of overdose is intravenous infusion of normal saline solution.

#### Treatment

After ingestion of an overdose, the patient should be kept under close supervision, preferably in an intensive care unit. Serum electrolytes and creatinine should be monitored frequently. Therapeutic measures depend on the nature and severity of the symptoms. Measurements to prevent absorption of the drugs (such as gastric lavage, administration of adsorbents and sodium sulphate within 30 minutes after the ingestion of an overdose), and to hasten elimination should be applied if ingestion is recent. If hypotension occurs, the patient should be placed in the shock position and salt and volume supplementation should be given rapidly.

### Adverse reactions

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Exanthema, pruritus*</td>
</tr>
<tr>
<td>Rare</td>
<td>Hypersensitivity / angioedema: angioedema of the face, extremities, lips, tongue, epiglottis and / or larynx (see section 4.4), urticaria*, alopecia*, psoriasis*</td>
</tr>
<tr>
<td>Very rare</td>
<td>Diaphoresis*, pemphigus*, toxic epidermal necrolysis*, Stevens-Johnson syndrome*, erythema multiforme*</td>
</tr>
<tr>
<td></td>
<td>A symptom complex involving one or more of the following has been reported with ACE inhibitors: fever, vasculitis, myalgia, arthralgia / arthritis, positive antinuclear antibody (ANA) test, increased sedimentation rate (SR), eosinophilia and leucocytosis. Rash, photosensitisation or other dermatological disorders may occur.</td>
</tr>
</tbody>
</table>

#### Musculoskeletal and connective tissue disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Myalgia, arthralgia</td>
</tr>
</tbody>
</table>

#### Renal and urinary disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Renal impairment, uraemia*</td>
</tr>
<tr>
<td>Very rare</td>
<td>Acute renal failure, oliguria / anuria*</td>
</tr>
</tbody>
</table>

#### Reproductive system and breast disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Impotence*</td>
</tr>
<tr>
<td>Very rare</td>
<td>Gynaecomastia</td>
</tr>
</tbody>
</table>

#### General disorders and administration site conditions

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Tiredness</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Asthenia*</td>
</tr>
</tbody>
</table>

#### Investigations

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Moderately increased plasma urea and creatinine levels, reversible on discontinuation of treatment and most frequently observed in patients with renal artery stenosis, diuretic-treated hypertension, renal impairment. Usually transient hyperkalaemia.</td>
</tr>
<tr>
<td>Rare</td>
<td>Proteinuria in patients with glomerular nephropathy, increased serum bilirubin, increased liver enzyme levels (transaminases, bilirubin, alkaline phosphatase, gamma GT), hyponatraemia*</td>
</tr>
</tbody>
</table>
Treatment with angiotensin II should be considered. Bradycardia or extensive vagal reactions should be treated by administering atropine. The use of a pacemaker may be considered. ACE inhibitors may be removed from the circulation by haemodialysis. The use of high-flux polyacrylonitrile membranes should be avoided.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: angiotensin convertase inhibitors, ATC code: C09 AA08

Cilazapril is a selective, long-acting angiotensin-converting enzyme (ACE) inhibitor which suppresses the renin-angiotensin-aldosterone system and 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.

In patients with normal renal function, serum potassium usually remains within the normal range during Cilazapril treatment. In patients concomitantly taking potassium-sparing diuretics, potassium levels may rise.

Hypertension
Cilazapril induces a reduction of both supine and standing systolic and diastolic blood pressure, usually with no orthostatic component. Cilazapril

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 initial dosage seldom achieves the desired therapeutic response. Blood pressure values should be assessed and dosage gradually increased as required. If the maximum recommended dose is not sufficient, it can be combined with non-potassium-sparing diuretics.

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.

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

In patients with chronic heart failure the renin-angiotensin-aldosterone and the sympathetic nervous systems are generally excessively activated leading to 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 during the treatment.

5.2 Pharmacokinetic properties

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.

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

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.

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 postnatal 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 $^{14}$C-cilazapril to pregnant mice, rats and monkeys, radioactivity was measured in the fetuses.

ACE inhibitors, as a class, have been shown to induce adverse effect on late fetal development, resulting in fetal 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 pink 03B23719: hypromellose 6cp, talc, titanium dioxide (E171), Macrogol 400, iron oxide red (E172), iron oxide yellow (E172).

#### 6.2 Incompatibilities

Not applicable.

#### 6.3 Shelf life

3 years.

#### 6.4 Special precautions for storage

Do not store above 25°C.
6.5  Nature and contents of container
Aluminium/Aluminium blisters in a cardboard box.

30 tablets

6.6  Special precautions for disposal
No special requirements

7  MARKETING AUTHORISATION HOLDER
SymPhar Sp. z o.o.
ul. Włoska 1
00-777 Warsaw
Poland

8  MARKETING AUTHORISATION NUMBER(S)
PL 31304/0006

9  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/06/2009

10  DATE OF REVISION OF THE TEXT
02/06/2009
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Cilazapril 2.5 mg, film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One 2.5 mg film-coated tablet contains 2.5 mg of cilazapril (as cilazapril monohydrate).
Excipient: One 2.5 mg film-coated tablet contains 58.912 mg of lactose monohydrate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet

Brown, oblong presenting a one sided score, film coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Hypertension
Treatment of essential hypertension.

Heart failure
Treatment of symptomatic heart failure

4.2 Posology and method of administration
Cilazapril should be administered orally in a single daily dose. As with all other medicinal products taken once daily, it should be taken at approximately the same time each day. The absorption of cilazapril is not affected by food.

The maintenance doses should be individualized according to patient profile and blood pressure response (see section 4.4).

Essential hypertension
Cilazapril may be used as monotherapy or in combination with other classes of antihypertensive medicinal products.

Hypertensive patients receiving diuretics

Starting dose
The initial recommended dose is 1 mg once a day. Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and/or volume depletion, cardiac decompensation, or severe hypertension) may experience an excessive blood pressure fall following the initial dose. The initiation of treatment should take place under medical supervision.

Maintenance dose
The usual daily dose is 2.5 mg to a maximum of 5 mg administered in a single dose. In general if the desired therapeutic effect cannot be achieved in a period of 3 to 4 weeks on a certain dose level, the dose can be further increased.

If the blood pressure is not adequately controlled with 5 mg Cilazapril once daily, a low dose of a non-potassium-sparing diuretic may be administered concomitantly to enhance the anti-hypertensive effect.

Hypertensive patients being treated with concomitant diuretic therapy:
Symptomatic hypotension may occur following initiation of therapy with Cilazapril. This is more likely in patients who are being treated currently with diuretics, especially in patients with heart failure, elderly patients (over 75 years) and patients with renal dysfunction. Caution is recommended therefore, since these patients may be volume and/or salt depleted. If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with Cilazapril In hypertensive patients in whom the diuretic cannot be discontinued, and especially in those on high-dose diuretic therapy, therapy with Cilazapril should be initiated with a 0.5 mg dose.

Renal function and serum potassium should be monitored. The subsequent dosage of cilazapril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed (see section 4.4 and section 4.5). When treatment is initiated in a patient already taking diuretics, it is recommended that the treatment with Cilazapril is started under medical supervision for several hours and until blood pressure is stabilised.

Heart failure
In patients with symptomatic heart failure, Cilazapril should be used as adjunctive therapy to diuretics and, where appropriate, digitalis.

The recommended initial dose is 0.5 mg once daily, initiated under close medical supervision.

If the initial dose is well tolerated, patients should then be titrated to the lowest maintenance dose of 1 mg daily based on clinical response. Further titration within the usual maintenance dose of 1 to 2.5 mg daily should be carried out based on the patient's response, clinical status and tolerability.

The usual maximum dose is 5 mg once daily.

Results from clinical trials showed that clearance of cilazaprilat in patients with chronic heart failure is correlated with creatinine clearance. Thus, in patients with chronic heart failure and impaired renal function, special dosage recommendations as given under "Impaired renal function" should be followed.

The appearance of hypotension after the initial dose should not preclude careful dose titration of cilazapril, following effective management of the hypotension.

Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with Cilazapril. Renal function and serum potassium should be monitored (see section 4.4).
Impaired renal function
Reduced dosages may be required in patients with renal impairment, depending on their creatinine clearance.

The following dose schedules of Cilazapril are recommended:

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Initial dose</th>
<th>Maximal dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 40 ml/min</td>
<td>1 mg once daily</td>
<td>5 mg once daily</td>
</tr>
<tr>
<td>10 – 40 ml/min</td>
<td>0.5 mg once daily</td>
<td>2.5 mg once daily</td>
</tr>
<tr>
<td>&lt; 10 ml/min</td>
<td>Not recommended</td>
<td></td>
</tr>
</tbody>
</table>

Haemodialysis
In patients requiring haemodialysis, Cilazapril should not be administered on days when dialysis is performed, and the dosage should be adjusted according to blood pressure response.

Hepatic impairment
Should patients with liver cirrhosis require treatment with cilazapril, it should be initiated with caution at a dose of 0.5 or 0.25 mg once daily, because significant hypotension may occur (see sections 4.4 and 5.2).

Elderly
In the treatment of hypertension Cilazapril should be initiated with between 0.5 mg and 1.0 mg once daily. Thereafter, the maintenance dose may be increased according to individual response.

In the treatment of chronic heart failure Cilazapril should be initiated with a dose of 0.5 mg once daily. The maintenance dose is 1.0 mg to 2.5 mg according to individual tolerability, response and clinical status.

In elderly patients with chronic heart failure the recommended daily starting dose of Cilazapril 0.5 mg must be strictly followed due to the risk of symptomatic hypotension.

Children and adolescents
Cilazapril is not recommended for use in children and adolescents below the age of 18 years, due to insufficient data on the safety and efficacy of this medicinal product.

4.3 Contraindications
- Hypersensitivity to cilazapril, any of the excipients 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)
4.4 Special warnings and precautions for use

Symptomatic hypotension

Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving Cilazapril, hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (see section 4.5 and section 4.8). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Cilazapril. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of Cilazapril may be necessary.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

As with other angiotensin-converting enzyme (ACE) inhibitors, Cilazapril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Renal function impairment

In cases of 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.

In patients with heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. 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 to the above, they should be discontinued and renal function should be monitored during the first weeks of therapy with Cilazapril.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when Cilazapril has been given concomitantly with a diuretic. This is more likely
to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or ACE inhibitor may be required.

**Proteinuria**

In patients with pre-existing renal impairment proteinuria may occur in rare cases. In clinically relevant proteinuria (greater than 1 g/day) Cilazapril should only be used after a very critical benefit/risk evaluation and with regular monitoring of the clinical and laboratory chemical parameters.

**Hypersensitivity / angioedema**

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including Cilazapril. This may occur at any time during therapy.

In such cases, Cilazapril should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patients. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

ACE inhibitors cause a higher rate of angioedema in Black patients than in non-Black patients.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).

Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain (see section 4.8).

**Anaphylactoid reactions in haemodialysis patients**

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes (e.g. AN 69) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

Rarely, patients receiving ACE inhibitors during LDL apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

**Desensitisation**
Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they have reappeared upon inadvertent re-administration of the medicinal product.

**Hepatic failure**

High cilazapril plasma concentrations might occur in patients with impaired hepatic function. Very rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving cilazapril who develop jaundice or marked elevations of hepatic enzymes should discontinue Cilazapril and receive appropriate medical follow-up.

**Neutropenia/Agranulocytosis**

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor. ACE inhibitors should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If Cilazapril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

**Race**

As with other ACE inhibitors, Cilazapril may be less effective in lowering blood pressure in Black patients than in non-Blacks, possibly because of a higher prevalence of low-renin states in the Black hypertensive population.

**Cough**

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

**Surgery / anaesthesia**

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Cilazapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

**Hyperkalaemia**

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including Cilazapril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, or worsening renal function, diabetes mellitus, acute cardiac decompensation, metabolic acidosis, intercurrent events, in particular dehydration, the elderly (age > 70 years) or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes, (especially in those with renal impairment, in whom combined use may lead to significant increases in serum potassium), or
those patients taking other medicinal products associated with increases in serum potassium (e.g. heparin). Hyperkalemia can cause serious, sometimes fatal arrhythmias. If concomitant use of the above-mentioned products is deemed appropriate, caution and regular monitoring of serum potassium are recommended (see section 4.5).

Diabetic patients
In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see section 4.5).

Lithium
The combination of lithium and Cilazapril is generally not recommended (see section 4.5).

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).

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.

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
When a diuretic is added to the therapy of a patient receiving cilazapril, the antihypertensive effect is usually additive.

Patients already on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure when cilazapril is added. The possibility of symptomatic hypotension with cilazapril can be minimised by discontinuing the diuretic prior to initiation of treatment with cilazapril (see section 4.4).

Potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes, or other medicinal products associated with increases in serum potassium (e.g. heparin) (see section 4.4, Hyperkalaemia)

Although in clinical trials, serum potassium usually remained within normal limits, hyperkalaemia did occur in some patients. Risk factors for the development of hyperkalaemia include renal insufficiency, diabetes mellitus, and concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene or amiloride), potassium supplements, potassium-containing salt substitutes or other medicinal products associated with increases in serum potassium (e.g. heparin).

The use of the above-mentioned products, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium.
If Cilazapril is given with a potassium-losing diuretic, diuretic-induced hypokalaemia may be ameliorated.

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).

**Non steroidal anti-inflammatory medicinal products (NSAIDs) including acetylsalicylic acid > 3 g/day**
Chronic administration of NSAIDs (including acetylsalicylic acid at anti-inflammatory doses, COX-2 inhibitors and non-selective NSAIDs) may reduce the antihypertensive effect of an ACE inhibitor. NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium and may result in a deterioration of renal function, 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.

**Other antihypertensive agents**
Combination with other antihypertensive agents such as beta-blockers, methyldopa, calcium antagonists, and diuretics may increase the anti-hypertensive efficacy. Concomitant use with glyceryl trinitrate and other nitrates, or other vasodilators, may further reduce blood pressure.

**Tricyclic antidepressants /Antipsychotics /Anaesthetics**
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).

**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.

**Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates**
Cilazapril may be used concomitantly with acetylsalicylic acid (at cardiological doses), thrombolytics, beta-blockers and/or nitrates.

**Immunosuppressants, cytostatics, systemic corticosteroids or procainamide, allopurinol**
The combination of cilazapril with immunosuppressant medicinal products and/or medicinal products that can cause leucopenia should be avoided.

*Alcohol*

Alcohol enhances the hypotensive effect of cilazapril.

*Antacids*

Antacids (e.g. aluminium hydroxide, magnesium hydroxide, simeticone) may impair absorption of cilazapril and so the administration of both medicinal products should be separated by at least 2 hours.

### 4.6 Pregnancy and lactation

#### Pregnancy

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). It 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.

ACE inhibitor/angiotensin II receptor antagonist exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see 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).

#### Lactation

Because insufficient 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

Cilazapril has no or negligible influence on the ability to drive and use machines.
Although cilazapril is not expected to directly affect the ability to drive or use machines, adverse reactions such as hypotension, dizziness and vertigo may interfere it. This occurs especially at the start of treatment, when increasing the dosage, when changing over from other preparations and during concomitant use of alcohol, depending on the individual's susceptibility.

### 4.8 Undesirable effects
The following adverse reactions have been observed during treatment with Cilazapril or other ACE inhibitors (marked with an asterisk) and are ranked under the following frequency convention:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common (≥1/10); common (≥1/100, &lt;1/10); uncommon (≥1/1,000, ≤1/100); rare (≥1/10,000, ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated from the available data).</td>
<td></td>
</tr>
</tbody>
</table>

### Blood and lymphatic system disorders
- Very rare: Decreased haemoglobin or haematocrit levels, bone marrow depression*, anaemia*, thrombocytopenia*, leucopenia, neutropenia*, agranulocytosis (see section 4.4), haemolytic anaemia*, lymphadenopathy

### Immune system disorders
- Very rare: Auto-immune disease*

### Metabolism and nutrition disorders
- Very rare: Hypoglycaemia*

### Nervous system disorders
- Common: Headache, dizziness
- Uncommon: Mood changes*, syncope*, sleep disturbances
- Rare: Depression, jwaesthesia, confusion, taste disturbances
- Very rare: Neuropathy

### Cardiovascular disorders
- Common: Hypotension, orthostatic or otherwise (including hypotension)* (see section 4.4)
- Uncommon: Myocardial infarction, cerebrovascular accident, possibly secondary to significant drop in blood pressure in high-risk patients (see section 4.4)*, palpitations, tachycardia*, Raynaud's phenomenon*
- Very rare: Vasculitis

### Respiratory, thoracic and mediastinal disorders
- Common: Cough
- Uncommon: Rhinitis, chest pain
- Rare: Dyspnoea, sinusitis*, bronchitis, allergic alveolitis / eosinophilic pneumonitis*, bronchospasm

### Gastrointestinal disorders
- Common: Nausea, diarrhoea*, vomiting*
- Uncommon: Abdominal pain, dyspepsia, digestive disorders*
- Rare: Dry mouth, glossitis
- Very rare: Pancreatitis, intestinal angioedema*

### Hepato-biliary disorders
- Very rare: Hepatocellular or cholestatic hepatitis with or without necrosis (severe forms have been observed in exceptional cases), jaundice, hepatic failure*

### Skin and subcutaneous tissue disorders
- Common: Rash
<table>
<thead>
<tr>
<th>Frequency</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Exanthema, pruritus*</td>
</tr>
<tr>
<td>Rare</td>
<td>Hypersensitivity / angioedema: angioedema of the face, extremities, lips, tongue, epiglottis and / or larynx (see section 4.4), urticaria*, alopecia*, psoriasis*</td>
</tr>
<tr>
<td>Very rare</td>
<td>Diaphoresis*, pemphigus*, toxic epidermal necrolysis*, Stevens-Johnson syndrome*, erythema multiforme*</td>
</tr>
<tr>
<td></td>
<td>A symptom complex involving one or more of the following has been reported with ACE inhibitors: fever, vasculitis, myalgia, arthralgia / arthritis, positive antinuclear antibody (ANA) test, increased sedimentation rate (SR), eosinophilia and leucocytosis. Rash, photosensitisation or other dermatological disorders may occur.</td>
</tr>
</tbody>
</table>

### Musculoskeletal and connective tissue disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Myalgia, arthralgia</td>
</tr>
</tbody>
</table>

### Renal and urinary disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Renal impairment, uraemia*</td>
</tr>
<tr>
<td>Very rare</td>
<td>Acute renal failure, oliguria / anuria*</td>
</tr>
</tbody>
</table>

### Reproductive system and breast disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Impotence*</td>
</tr>
<tr>
<td>Very rare</td>
<td>Gynaecomastia</td>
</tr>
</tbody>
</table>

### General disorders and administration site conditions

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Tiredness</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Asthenia*</td>
</tr>
</tbody>
</table>

### Investigations

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Moderately increased plasma urea and creatinine levels, reversible on discontinuation of treatment and most frequently observed in patients with renal artery stenosis, diuretic-treated hypertension, renal impairment. Usually transient hyperkalaemia.</td>
</tr>
<tr>
<td>Rare</td>
<td>Proteinuria in patients with glomerular nephropathy, increased serum bilirubin, increased liver enzyme levels (transaminases, bilirubin, alkaline phosphatase, gamma GT), hyponatraemia*</td>
</tr>
</tbody>
</table>

### 4.9 Overdose

While single doses of up to 160 mg Cilazapril have been administered to normal healthy volunteers without untoward effects on blood pressure, only a few data on overdose are available in patients.

#### Symptoms

Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough. The recommended treatment of overdose is intravenous infusion of normal saline solution.

#### Treatment

After ingestion of an overdose, the patient should be kept under close supervision, preferably in an intensive care unit. Serum electrolytes and creatinine should be monitored frequently. Therapeutic measures depend on the nature and severity of the symptoms. Measurements to prevent absorption of the drugs (such as gastric lavage, administration of adsorbents and sodium sulphate within 30 minutes after the ingestion of an overdose), and to hasten elimination should be applied if ingestion is recent. If hypotension occurs, the patient should be placed in the shock position and salt and volume supplementation should be given rapidly.
Treatment with angiotensin II should be considered. Bradycardia or extensive vagal reactions should be treated by administering atropine. The use of a pacemaker may be considered. ACE inhibitors may be removed from the circulation by haemodialysis. The use of high-flux polyacrylonitrile membranes should be avoided.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: angiotensin convertase inhibitors, ATC code: C09 AA08

Cilazapril is a selective, long-acting angiotensin-converting enzyme (ACE) inhibitor which suppresses the renin-angiotensin-aldosterone system and 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.

In patients with normal renal function, serum potassium usually remains within the normal range during Cilazapril treatment. In patients concomitantly taking potassium-sparing diuretics, potassium levels may rise.

Hypertension
Cilazapril induces a reduction of both supine and standing systolic and diastolic blood pressure, usually with no orthostatic component. Cilazapril
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 initial dosage seldom achieves the desired therapeutic response. Blood pressure values should be assessed and dosage gradually increased as required. If the maximum recommended dose is not sufficient, it can be combined with non-potassium-sparing diuretics.

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.

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

In patients with chronic heart failure the renin-angiotensin-aldosterone and the sympathetic nervous systems are generally excessively activated leading to 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 during the treatment.

5.2 Pharmacokinetic properties

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.

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

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.

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 $^{14}$C-cilazapril to pregnant mice, rats and monkeys, radioactivity was measured in the fetuses.

ACE inhibitors, as a class, have been shown to induce adverse effect on late fetal development, resulting in fetal 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 25°C.

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
SymPhar Sp. z o.o.
ul. Włoska 1
00-777 Warsaw
Poland

8 MARKETING AUTHORISATION NUMBER(S)
PL 31304/0007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/06/2009

10 DATE OF REVISION OF THE TEXT
02/06/2009
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Cilazapril 5 mg, film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One 5 mg film-coated tablet contains 5 mg of cilazapril (as cilazapril monohydrate).
Excipient: One 5 mg film-coated tablet contains 117.825 mg of lactose monohydrate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet

Brown, oblong presenting a one sided score, with the mark C5 engraved on one side, weighting approx 200mg film coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Hypertension
Treatment of essential hypertension.
Heart failure
Treatment of symptomatic heart failure

4.2 Posology and method of administration
Cilazapril should be administered orally in a single daily dose. As with all other medicinal products taken once daily, it should be taken at approximately the same time each day. The absorption of cilazapril is not affected by food.

The maintenance does should be individualized according to patient profile and blood pressure response (see section 4.4).

Essential hypertension
Cilazapril may be used as monotherapy or in combination with other classes of antihypertensive medicinal products.

Hypertensive patients receiving diuretics
Starting dose

The initial recommended dose is 1 mg once a day. Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and/or volume depletion, cardiac decompensation, or severe hypertension) may experience an excessive blood pressure fall following the initial dose. The initiation of treatment should take place under medical supervision.

Maintenance dose

The usual daily dose is 2.5 mg to a maximum of 5 mg administered in a single dose. In general if the desired therapeutic effect cannot be achieved in a period of 3 to 4 weeks on a certain dose level, the dose can be further increased.

If the blood pressure is not adequately controlled with 5 mg Cilazapril once daily, a low dose of a non-potassium-sparing diuretic may be administered concomitantly to enhance the anti-hypertensive effect.

Hypertensive patients being treated with concomitant diuretic therapy:

Symptomatic hypotension may occur following initiation of therapy with Cilazapril. This is more likely in patients who are being treated currently with diuretics, especially in patients with heart failure, elderly patients (over 75 years) and patients with renal dysfunction. Caution is recommended therefore, since these patients may be volume and/or salt depleted. If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with Cilazapril In hypertensive patients in whom the diuretic cannot be discontinued, and especially in those on high-dose diuretic therapy, therapy with Cilazapril should be initiated with a 0.5 mg dose.

Renal function and serum potassium should be monitored. The subsequent dosage of cilazapril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed (see section 4.4 and section 4.5). When treatment is initiated in a patient already taking diuretics, it is recommended that the treatment with Cilazapril is started under medical supervision for several hours and until blood pressure is stabilised.

Heart failure

In patients with symptomatic heart failure, Cilazapril should be used as adjunctive therapy to diuretics and, where appropriate, digitalis.

The recommended initial dose is 0.5 mg once daily, initiated under close medical supervision.

If the initial dose is well tolerated, patients should then be titrated to the lowest maintenance dose of 1 mg daily based on clinical response. Further titration within the usual maintenance dose of 1 to 2.5 mg daily should be carried out based on the patient's response, clinical status and tolerability.

The usual maximum dose is 5 mg once daily.

Results from clinical trials showed that clearance of cilazaprilat in patients with chronic heart failure is correlated with creatinine clearance. Thus, in patients with chronic heart failure and impaired renal function, special dosage recommendations as given under "Impaired renal function" should be followed.

The appearance of hypotension after the initial dose should not preclude careful dose titration of cilazapril, following effective management of the hypotension.

Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with Cilazapril. Renal function and serum potassium should be monitored (see section 4.4).
Impaired renal function
Reduced dosages may be required in patients with renal impairment, depending on their creatinine clearance.

The following dose schedules of Cilazapril are recommended:

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Initial dose</th>
<th>Maximal dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 40 ml/min</td>
<td>1 mg once daily</td>
<td>5 mg once daily</td>
</tr>
<tr>
<td>10 – 40 ml/min</td>
<td>0.5 mg once daily</td>
<td>2.5 mg once daily</td>
</tr>
<tr>
<td>&lt; 10ml/min</td>
<td>Not recommended</td>
<td></td>
</tr>
</tbody>
</table>

Haemodialysis
In patients requiring haemodialysis, Cilazapril should not be administered on days when dialysis is performed, and the dosage should be adjusted according to blood pressure response.

Hepatic impairment
Should patients with liver cirrhosis require treatment with cilazapril, it should be initiated with caution at a dose of 0.5 or 0.25 mg once daily, because significant hypotension may occur (see sections 4.4 and 5.2).

Elderly
In the treatment of hypertension Cilazapril should be initiated with between 0.5 mg and 1.0 mg once daily. Thereafter, the maintenance dose may be increased according to individual response.

In the treatment of chronic heart failure Cilazapril should be initiated with a dose of 0.5 mg once daily. The maintenance dose is 1.0 mg to 2.5 mg according to individual tolerability, response and clinical status.

In elderly patients with chronic heart failure the recommended daily starting dose of Cilazapril 0.5 mg must be strictly followed due to the risk of symptomatic hypotension.

Children and adolescents
Cilazapril is not recommended for use in children and adolescents below the age of 18 years, due to insufficient data on the safety and efficacy of this medicinal product.

4.3 Contraindications
- Hypersensitivity to cilazapril, any of the excipients 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)

4.4 Special warnings and precautions for use
Symptomatic hypotension

Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving Cilazapril, hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (see section 4.5 and section 4.8). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Cilazapril. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of Cilazapril may be necessary.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

As with other angiotensin-converting enzyme (ACE) inhibitors, Cilazapril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Renal function impairment

In cases of 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.

In patients with heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. 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 to the above, they should be discontinued and renal function should be monitored during the first weeks of therapy with Cilazapril.
Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when Cilazapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or ACE inhibitor may be required.

Proteinuria

In patients with pre-existing renal impairment proteinuria may occur in rare cases. In clinically relevant proteinuria (greater than 1 g/day) Cilazapril should only be used after a very critical benefit/risk evaluation and with regular monitoring of the clinical and laboratory chemical parameters.

Hypersensitivity / angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including Cilazapril. This may occur at any time during therapy.

In such cases, Cilazapril should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patients. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

ACE inhibitors cause a higher rate of angioedema in Black patients than in non-Black patients.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).

Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain (see section 4.8).

Anaphylactoid reactions in haemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes (e.g. AN 69) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

Rarely, patients receiving ACE inhibitors during LDL apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.
**Desensitisation**

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they have reappeared upon inadvertent re-administration of the medicinal product.

**Hepatic failure**

High cilazapril plasma concentrations might occur in patients with impaired hepatic function. Very rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving cilazapril who develop jaundice or marked elevations of hepatic enzymes should discontinue Cilazapril and receive appropriate medical follow-up.

**Neutropenia/Agranulocytosis**

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor. ACE inhibitors should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procaainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If Cilazapril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.”

**Race**

As with other ACE inhibitors, Cilazapril may be less effective in lowering blood pressure in Black patients than in non-Blacks, possibly because of a higher prevalence of low-renin states in the Black hypertensive population.

**Cough**

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

**Surgery / anaesthesia**

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Cilazapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

**Hyperkalaemia**

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including Cilazapril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, or worsening renal function, diabetes mellitus, acute cardiac decompensation, metabolic acidosis, intercurrent events, in particular dehydration, the elderly (age > 70 years) or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes, (especially in those with renal
impairment, in whom combined use may lead to significant increases in serum potassium), or those patients taking other medicinal products associated with increases in serum potassium (e.g. heparin). Hyperkalemia can cause serious, sometimes fatal arrhythmias. If concomitant use of the above-mentioned products is deemed appropriate, caution and regular monitoring of serum potassium are recommended (see section 4.5).

**Diabetic patients**

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see section 4.5).

**Lithium**

The combination of lithium and Cilazapril is generally not recommended (see section 4.5).

**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).

**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.

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**

When a diuretic is added to the therapy of a patient receiving cilazapril, the antihypertensive effect is usually additive.

Patients already on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure when cilazapril is added. The possibility of symptomatic hypotension with cilazapril can be minimised by discontinuing the diuretic prior to initiation of treatment with cilazapril (see section 4.4).

Potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes, or other medicinal products associated with increases in serum potassium (e.g. heparin) (see section 4.4, Hyperkalaemia)

Although in clinical trials, serum potassium usually remained within normal limits, hyperkalaemia did occur in some patients. Risk factors for the development of hyperkalaemia include renal insufficiency, diabetes mellitus, and concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene or amiloride), potassium supplements, potassium-containing salt substitutes or other medicinal products associated with increases in serum potassium (e.g. heparin).

The use of the above-mentioned products, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium.
If Cilazapril is given with a potassium-losing diuretic, diuretic-induced hypokalaemia may be ameliorated.

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).

Non steroidal anti-inflammatory medicinal products (NSAIDs) including acetylsalicylic acid > 3 g/day
Chronic administration of NSAIDs (including acetylsalicylic acid at anti-inflammatory doses, COX-2 inhibitors and non-selective NSAIDs) may reduce the antihypertensive effect of an ACE inhibitor. NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium and may result in a deterioration of renal function, 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.

Other antihypertensive agents
Combination with other antihypertensive agents such as beta-blockers, methyldopa, calcium antagonists, and diuretics may increase the anti-hypertensive efficacy. Concomitant use with glyceryl trinitrate and other nitrates, or other vasodilators, may further reduce blood pressure.

Tricyclic antidepressants /Antipsychotics /Anaesthetics
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).

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.

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates
Cilazapril may be used concomitantly with acetylsalicylic acid (at cardiological doses), thrombolytics, beta-blockers and/or nitrates.

Immunosuppressants, cytostatics, systemic corticosteroids or procainamide, allopurinol
The combination of cilazapril with immunosuppressant medicinal products and/or medicinal products that can cause leucopenia should be avoided.

Alcohol

Alcohol enhances the hypotensive effect of cilazapril.

Antacids

Antacids (e.g. aluminium hydroxide, magnesium hydroxide, simeticone) may impair absorption of cilazapril and so the administration of both medicinal products should be separated by at least 2 hours.

4.6 Pregnancy and lactation

Pregnancy

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). It 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.

ACE inhibitor/angiotensin II receptor antagonist exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see 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).

Lactation

Because insufficient 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

Cilazapril has no or negligible influence on the ability to drive and use machines.
Although cilazapril is not expected to directly affect the ability to drive or use machines, adverse reactions such as hypotension, dizziness and vertigo may interfere it.

This occurs especially at the start of treatment, when increasing the dosage, when changing over from other preparations and during concomitant use of alcohol, depending on the individual's susceptibility.

4.8 Undesirable effects

The following adverse reactions have been observed during treatment with Cilazapril or other ACE inhibitors (marked with an asterisk) and are ranked under the following frequency convention:

Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, ≤1/100); rare (≥1/10,000, ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated from the available data).

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Immune system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Very rare</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiovascular disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Uncommon</td>
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<tr>
<td>Very rare</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory, thoracic and mediastinal disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Rare</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Very rare</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepato-biliary disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Frequency</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Very rare</td>
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</tbody>
</table>

A symptom complex involving one or more of the following has been reported with ACE inhibitors: fever, vasculitis, myalgia, arthralgia / arthritis, positive antinuclear antibody (ANA) test, increased sedimentation rate (SR), eosinophilia and leucocytosis. Rash, photosensitisation or other dermatological disorders may occur.

**Musculoskeletal and connective tissue disorders**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Myalgia, arthralgia</td>
</tr>
</tbody>
</table>

**Renal and urinary disorders**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Renal impairment, uraemia*</td>
</tr>
<tr>
<td>Very rare</td>
<td>Acute renal failure, oliguria / anuria*</td>
</tr>
</tbody>
</table>

**Reproductive system and breast disorders**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Impotence*</td>
</tr>
<tr>
<td>Very rare</td>
<td>Gynaecomastia</td>
</tr>
</tbody>
</table>

**General disorders and administration site conditions**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Tiredness</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Asthenia*</td>
</tr>
</tbody>
</table>

**Investigations**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Moderately increased plasma urea and creatinine levels, reversible on discontinuation of treatment and most frequently observed in patients with renal artery stenosis, diuretic-treated hypertension, renal impairment. Usually transient hyperkalaemia.</td>
</tr>
<tr>
<td>Rare</td>
<td>Proteinuria in patients with glomerular nephropathy, increased serum bilirubin, increased liver enzyme levels (transaminases, bilirubin, alkaline phosphatase, gamma GT), hyponatraemia*</td>
</tr>
</tbody>
</table>

### 4.9 Overdose

While single doses of up to 160 mg Cilazapril have been administered to normal healthy volunteers without untoward effects on blood pressure, only a few data on overdose are available in patients.

**Symptoms**

Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, Bradycardia, dizziness, anxiety and cough. The recommended treatment of overdose is intravenous infusion of normal saline solution.

**Treatment**

After ingestion of an overdose, the patient should be kept under close supervision, preferably in an intensive care unit. Serum electrolytes and creatinine should be monitored frequently. Therapeutic measures depend on the nature and severity of the symptoms. Measurements to prevent absorption of the drugs (such as gastric lavage, administration of adsorbents and sodium sulphate within 30 minutes after the ingestion of an overdose), and to hasten elimination should be applied if ingestion is recent. If hypotension occurs, the patient should be placed in the shock position and salt and volume supplementation should be given rapidly.
Treatment with angiotensin II should be considered. Bradycardia or extensive vagal reactions should be treated by administering atropine. The use of a pacemaker may be considered. ACE inhibitors may be removed from the circulation by haemodialysis. The use of high-flux polyacrylonitrile membranes should be avoided.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: angiotensin convertase inhibitors, ATC code: C09 AA08

Cilazapril is a selective, long-acting angiotensin-converting enzyme (ACE) inhibitor which suppresses the renin-angiotensin-aldosterone system and 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.

In patients with normal renal function, serum potassium usually remains within the normal range during Cilazapril treatment. In patients concomitantly taking potassium-sparing diuretics, potassium levels may rise.

Hypertension
Cilazapril induces a reduction of both supine and standing systolic and diastolic blood pressure, usually with no orthostatic component. Cilazapril

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 initial dosage seldom achieves the desired therapeutic response. Blood pressure values should be assessed and dosage gradually increased as required. If the maximum recommended dose is not sufficient, it can be combined with non-potassium-sparing diuretics.

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.

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

In patients with chronic heart failure the renin-angiotensin-aldosterone and the sympathetic nervous systems are generally excessively activated leading to 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 during the treatment.

5.2 Pharmacokinetic properties
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.

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

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.

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 \(^{14}\)C-cilazapril to pregnant mice, rats and monkeys, radioactivity was measured in the fetuses.

ACE inhibitors, as a class, have been shown to induce adverse effect on late fetal development, resulting in fetal 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 25°C.
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
SymPhar Sp. z o.o.
ul. Włoska 1
00-777 Warsaw
Poland

8 MARKETING AUTHORISATION NUMBER(S)
PL 31304/0008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
02/06/2009

10 DATE OF REVISION OF THE TEXT
02/06/2009
Module 3

Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

- PRODUCT NAME, 0.5 mg, film-coated tablets
- PRODUCT NAME, 1 mg film-coated tablets
- PRODUCT NAME, 2.5 mg film-coated tablets
- PRODUCT NAME, 5 mg film-coated tablets

(Cilaprazil)

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get worse, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What PRODUCT NAME is and what it is used for
2. Before you take PRODUCT NAME
3. How to take PRODUCT NAME
4. Possible side effects
5. How to store PRODUCT NAME
6. Further information

1. WHAT PRODUCT NAME IS AND WHAT IT IS USED FOR

PRODUCT NAME belongs to the group of medicines called angiotensin converting enzyme inhibitors (ACE-inhibitors), which reduce blood pressure. They also make it easier for the heart to pump blood around the body.

PRODUCT NAME is used to treat the following:
- high blood pressure (hypertension)
- heart failure (a condition where the heart is unable to pump enough blood to meet the body’s needs)

2. BEFORE YOU TAKE

Do not take PRODUCT NAME.
• if you are allergic to cilazapril, other ACE inhibitors or any other ingredient of the tablet.
• if you have previously suffered from swelling of the face, lips, throat or tongue, when treated with other ACE inhibitors (e.g. enalapril), or due to hereditary or unknown reason.
• If you are more than 3 months pregnant
• If you are breast feeding

Take special care with <PRODUCT NAME>:

<PRODUCT NAME> is not generally recommended if the followig apply, so ask to your doctor before starting to take this medicine or to continue taking this medicine:
• If you are also taking lithium (used to treat mental health problems), potassium-sparing diuretics (“water tablets”), potassium supplements of potassium-containing salts substitutes
• If you have narrow arteries to your kidneys (renal artery stenosis) or only have one functioning kidney
• If jaundice occurs during treatment. You must stop taking this medicine and contact your doctor
• If you have high levels of potassium in your blood

When starting to take this medicine, it is important to note that an excessive decrease of blood pressure might occur, especially if you suffer from heart failure, ischaemic heart disease (angina) or disorders of the blood vessels in the brain (cerebrovascular conditions such as previous stroke).

Tell your doctor before you start to take this medicine:
• If you are on a salt restricted diet or are taking diuretics (“water tablets”).
• If you are over 70 years old.
• If you have abnormal levels of water and minerals in your body (fluid/electrolyte imbalance). Possible signs are: dry mouth, thirst, weakness, lethargy, drowsiness, restlessness, myalgia or cramps, muscle fatigue, a drop in blood pressure, low urine output, tachycardia, anorexia and vomiting
• If you have recently suffered from vomiting and/or diarrhoea
• If you have heart muscle diseases (hypertrophic cardiomyopathy) or narrowing of the aortic valve (aortic stenosis) or heart failure
• If you have or have had liver or kidney problems, or you are undergoing haemodialysis
• If you suffer from diabetes
• If you suffer from connective tissue diseases (e.g. lupus erythematosus, an inflammatory disease of the skin, intestine, joints, kidney and heart), use medicines to suppress the immune system (immunosuppressants) or are being treated with allopurinal (a medicine against gout) or procainamide (a medicine for irregular heart beat)
• If you need to have an anaesthetic or major surgery
• If you have to undergo LDL apheresis (removal of cholesterol from the blood by a machine)
• If you have to undergo desensitisation therapy to some insect venoms

Furthermore, this medicine might cause a dry cough. This will disappear after the treatment is stopped.

Taking other medicines:
Talk to your doctor if you are taking or have recently taken any of the following:

Symphar, Cilaprazil 0.5mg, 1mg, 2.5mg and 5mg Tablets
Lithium salts, which are used to treat mental health problems (see 'Take special care with Cilazapril')
- Potassium-sparing diuretics ("water tablets"), such as spironolactone, triamterene, potassium canrenoate or amiloride
- Potassium salts
- Other medicines to treat high blood pressure, such as beta-blockers (e.g. bisoprolol), calcium channel blockers (e.g. verapamil), methylspas, aurates (e.g. glyceryl trinitrate), vasodilators (e.g. minoxidil)
- Other diuretics ("water tablets")
- Medicines known as sympathomimetics e.g. salbutamol, ephedrine and some medicines for colds, coughs or flu symptoms
- Non-steroidal anti-inflammatory drugs (NSAIDs), which are used to reduce pain and inflammation, e.g. acetylsalicylic acid (aspirin) or ibuprofen
- Epsiparin to prevent and disperse blood clots
- Immunosuppressants such as ciclosporin or tacrolimus, which are used following organ transplant
- Corticosteroids, such as beclomethasone or prednisolone, which are sometimes used to suppress inflammation caused by allergic reactions
- Allopurinol, which is used to treat gout
- Procainamide, which is used to treat abnormal heart rhythms
- Drugs used to treat diabetes, such as insulin, sulphonylamides or metformin
- Antacids, which are used for the relief of indigestion. Doses of cilazapril and antacids should be taken 3 hours apart
- Antidepressants such as imipramine
- Medicines used to treat psychotic illnesses, such as chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine, amitriptyline, nortriptyline, imipramine, droperidol, haloperidol or pimozide

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**Taking <PRODUCT NAME> with food and drink**
You should avoid consuming alcohol whilst on this medicine, as the blood pressure-lowering effect could be increased.

**Pregnancy and breast-feeding**
You must not take <PRODUCT NAME> after the third month of pregnancy and it is not generally recommended to take it during the first 3 months of pregnancy. If you are pregnant or are trying to become pregnant, talk to your doctor before taking this medicine.
Do not breast-feed while taking <PRODUCT NAME>. Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines**
Your medicine may occasionally cause light-headedness, low blood pressure or dizziness. If affected, do not drive or operate machinery.

**Important information about some of the ingredients of <PRODUCT NAME>**
This product contains lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

A. HOW TO TAKE <PRODUCT NAME>

Always take <PRODUCT NAME> exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Your doctor will decide on the right starting dose for you and on any increase in the dose depending on your condition and whether you are taking any other medicines. Do not change your dosage unless your doctor tells you to do so. <PRODUCT NAME> may be used on its own or with other medicines which lower blood pressure.

The usual dosage is as follows:

**High blood pressure:**
- The usual starting dose is 1 mg once daily. In some cases, your doctor may feel that you should start on a lower dose.
- If you are elderly, your doctor will probably start you on 0.5 or 1 mg a day.
- If you have kidney or liver problems, your doctor may start you on a lower dose than normal.
- If you are already taking diuretics ("water tablets"), your doctor may stop you taking the diuretic at all for 2 or 3 days before you start to take <PRODUCT NAME>. Your doctor may prescribe a starting dose of 0.5 mg of Cilaprazil.
- Your doctor will probably increase your dose to between 2.5 and 5 mg a day depending on your response.

**Heart Failure:**
- The usual starting dose is 0.5 mg once daily.
- If you are elderly, your doctor will probably start you on 0.5 mg a day.
- If you have kidney or liver problems, your doctor may start you on a lower dose than normal.
- Your doctor will probably increase your dose to at least 1 mg a day depending on your response.
- The usual maximum dose is 5 mg once daily.

You should swallow <PRODUCT NAME> film-coated tablets with a drink at around the same time each day.

**Children and adolescents:**
- <PRODUCT NAME> should not be used for children and adolescents below 18 years due to a lack of data on safety and efficacy.

If you take more <PRODUCT NAME> than you should
If you (or someone else) swallow a lot of tablets all together or if you think a child has swallowed any of the tablets, contact your nearest hospital casualty department or your doctor immediately.
An overdose is likely to cause low blood pressure, dizziness, hyperventilation, low or high heart rate, palpitations, nausea and feeling sleepy and confused. Please take this leaflet, any remaining tablets and the container with you to the hospital or doctor so that they know which tablets were consumed.

If you forget to take <PRODUCT NAME>
Do not take a double dose to make up for a forgotten tablet. Take your next dose at the normal time.

If you stop taking <PRODUCT NAME>
The treatment of hypertension and heart failure is a long-term treatment and interruption of treatment must be discussed with the doctor. Interruption or stopping your treatment could cause your blood pressure to increase, or it could cause your symptoms to recur if you are being treated for heart failure.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, <PRODUCT NAME> can cause side effects although not everybody gets them.

The following side effects have been reported at the approximate frequencies shown.

If you experience the following, stop taking <PRODUCT NAME> and tell your doctor immediately or go to the casualty department at your nearest hospital:

* A severe allergic reaction (tach, itching, swelling of the face, lips, mouth or throat that may cause difficulty in swallowing or breathing)

This is a serious but rare (affecting fewer than one person in 1,000 but more than one person in 10,000) side effect, which occurs more frequently in Black-patients than in non-Blacks. You may need urgent medical attention or hospitalisation.

* Jaundice (yellowing of the skin and whites of the eyes caused by liver or blood problems) (see 2. Before you take Cilaprazil. Take special care with Cilaprazil).

This is a serious but very rare side effect which occurs in fewer than one person in 10,000.
If you experience the following, contact your doctor immediately:

* An infection with symptoms such as fever and serious deterioration of your general condition, or fever with local infections symptoms such as sore throat/lymph nodes/mouth or urinary problems; cilaprazil may cause a reduction in the number of white blood cells and your resistance to infection may be decreased.

This is a very rare side effect, which occurs in fewer than one person in 10,000. A blood test will be taken to check possible reduction of white blood cells (agranulocytosis). It is important to inform your doctor about your medicines.

The following side effect have also been reported:
Common side effects (affecting fewer than one person in 10 but more than one person in 100):
- Headache, dizziness
- Low blood pressure, which may be characterised by light-headedness, weakness, or dizziness when you stand up
- Cough (see 2. Before you take <Product name>, take special care with <Product name>)
- Nasal, dizziness, vomiting
- Fast
- Tiredness

Uncommon (affecting fewer than one person in 100 but more than one person in 1,000):
- Mood changes, fainting, sleep disturbances
- Hair loss, stroke, palpitations, excessively fast heartbeat, transiently reduced blood flow to the limbs (which may be associated with coldness, pallor or numbness of the affected limb)
- Runny nose, chest pain
- Abdominal pain, indigestion, digestive disorders
- Rash with fever, itching
- Impotence
- Weakening
- Increase in the amount of urine or creatinine in the blood
- High blood potassium levels

Rare (affecting fewer than one person in 1,000 but more than one person in 10,000):
- Depression, pain and needles, confusion, taste disturbances
- Shortness of breath, difficulty breathing which may be associated with wheezing, rhinitis, allergic lung problems, paroxysms
- Dry mouth, inflammation of the tongue
- Allergic (hypersensitivity) reactions, including angioedema (which is characterised by symptoms such as wheezing, swelling of the face, tongue or throat, intense itching, skin rash, flushing or dimness), hives
- Psoriasis (a skin condition in which silvery scales develop on the skin), hair loss
- Muscle and/or joint pain
- Abnormal kidney function
- Abnormal liver function tests
- Low blood sodium levels

Very rare (affecting fewer than one person in 10,000):
- Blood abnormalities such as reduced numbers of red or white blood cells, lymph node swelling or enlargement
- Auto-immune disease (e.g., some forms of arthritis)
- Low blood sugar levels
- Nerve disease, which may be associated with pain
- Inflammation of blood vessels
- Inflammation of the pancreas, which causes severe pain in the abdomen and back (pancreatitis)
- Angioedema (swelling in the intestine)
- Inflammation of the liver (hepatitis), jaundice, liver failure
- Swelling, serious skin rash or changes
6. HOW TO STORE <PRODUCT NAME>

Keep out of the reach and sight of children.

Do not use <PRODUCT NAME> after the expiry date which is stated on the blister and the outside packaging after “EXP”. The expiry date refers to the last day of that month.

Do not store above 25°C.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What <PRODUCT NAME> contains:

The active substance is cilazapril. One film-coated tablet contains either 0.5 mg, 1 mg, 2.5 mg, 5 mg of cilazapril as cilazapril monohydrate.

The other ingredients are as follows:

Tablet core:
Lactose, maize starch, hypromellose 3cp, tlc, sodium stearyl fumarate.

Film-coating:
0.5 mg: Opadry pink 06B23718: hypromellose 6cp, tlc, titanium dioxide (E171), Macrogol 400, iron oxide red (E172), iron oxide yellow (E172).
1 mg: Opadry pink 06B23719: hypromellose 6cp, tlc, titanium dioxide (E171), Macrogol 400, iron oxide red (E172), iron oxide yellow(E172).
2.5 mg: Opadry brown 01B26517: hypromellose 5cp, tlc, titanium dioxide (E171), Macrogol 400, iron oxide red (E172).
5 mg: Opadry brown 01B26587: hypromellose 5cp, tlc, titanium dioxide (E171), Macrogol 400, iron oxide red (E172).

What <PRODUCT NAME> looks like and contents of the pack

0.5 mg: Pink, oblong presenting a one sided score, weighing approx 100mg, film coated tablets.
1 mg: Pink, oblong presenting a one sided score, with the mark C1 engraved on one side, weighing approx. 200mg, film-coated tablets.
2.5 mg: Brown, oblong presenting a one sided score, film-coated tablets.
5 mg: Brown, oblong presenting a one sided score, with the mark C5 engraved on one side, weighing approx. 400mg film-coated tablets.

The tablets can be divided into equal halves.

Packaging

- **PRODUCT NAME**: 0.5 mg is available in packs of 30 film-coated tablets (3 blisters x 10 tablets)
- **PRODUCT NAME**: 1 mg is available in packs of 30 film-coated tablets (3 blisters x 10 tablets)
- **PRODUCT NAME**: 2.5 mg is available in packs of 30 film-coated tablets (4 blisters x 7 tablets)
- **PRODUCT NAME**: 5 mg is available in packs of 28 film-coated tablets (4 blisters x 7 tablets)

Marketing authority holder

Symphar Sp. z o.o., ul.
Wloka 1, 00-777
Warsaw,
Poland

Manufacturer

Lasmedicaments, S.A.
Entrada Consiglieri Francesco 608,
Quedra de Banco
2730-065, Baracena,
Bergamo

Symphar Sp. z o.o., ul.
Wloka 1, 00-777
Warsaw,
Poland

This medicinal product is authorised in the member states of the EEA under the following name:

**UK**: Cilazapril 0.5 mg film-coated tablets
Cilazapril 1.0 mg film-coated tablets
Cilazapril 2.5 mg film-coated tablets
Cilazapril 5.0 mg film-coated tablets

**PL**: Symbece., 0.5 mg, tabletki powlekane
Symbece., 1.0 mg, tabletki powlekane
Symbece., 2.5 mg, tabletki powlekane
Symbece., 5.0 mg, tabletki powlekane

This leaflet was last approved in: [DD/MM/YYYY]
Module 4
Labelling

### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**CARTON BOX**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;PRODUCT NAME&gt; 0.5 mg, film-coated tablets</td>
</tr>
<tr>
<td>&lt;PRODUCT NAME&gt; 1 mg, film-coated tablets</td>
</tr>
<tr>
<td>&lt;PRODUCT NAME&gt; 2.5 mg, film-coated tablets</td>
</tr>
<tr>
<td>&lt;PRODUCT NAME&gt; 5 mg, film-coated tablets</td>
</tr>
</tbody>
</table>

Cilazapril

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One film-coated tablet contains 0.5 mg of Cilazapril (as cilazapril monohydrate).</td>
</tr>
<tr>
<td>One film-coated tablet contains 1.0 mg of Cilazapril (as cilazapril monohydrate).</td>
</tr>
<tr>
<td>One film-coated tablet contains 2.5 mg of Cilazapril (as cilazapril monohydrate).</td>
</tr>
<tr>
<td>One film-coated tablet contains 5.0 mg of Cilazapril (as cilazapril monohydrate).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contains lactose monohydrate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet</td>
</tr>
<tr>
<td>0.5 mg: 30 film-coated tablets</td>
</tr>
<tr>
<td>1 mg: 30 film-coated tablets</td>
</tr>
<tr>
<td>2.5 mg: 28 film-coated tablets</td>
</tr>
<tr>
<td>5 mg: 28 film-coated tablets</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>For oral use.</td>
</tr>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the reach and sight of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
</tr>
</thead>
</table>
8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Not applicable

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SymPhar Sp. z o.o.
ul. Wlońska 1
00-777 Warsaw
Poland

12. MARKETING AUTHORISATION NUMBER(S)

<To be completed Nationally>

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

<To be completed nationally>
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
Alu-Alu foil blisters strips

1. NAME OF THE MEDICINAL PRODUCT

<PRODUCT NAME>, 0.5 mg, film-coated tablets
<PRODUCT NAME>, 1 mg, film-coated tablets
<PRODUCT NAME>, 2.5 mg, film-coated tablets
<PRODUCT NAME>, 5 mg, film-coated tablets

Cilazapril

2. NAME OF THE MARKETING AUTHORISATION HOLDER

SymPhar Sp. z o.o.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot:

5. OTHER

Logo SymPhar Sp. z o.o.
Module 5

Scientific discussion during initial procedure

EXECUTIVE SUMMARY

Problem statement
Hypertension is a chronic disorder and a major risk factor for cardiovascular morbidity and mortality. The treatment of hypertension is complex with various classes of drugs available with variable benefits. These include diuretics, calcium channel blockers, beta-blockers, ACE inhibitors and angiotensin receptor blockers. In this application, authorisation is sought for a generic form of Cilazapril, an ACE inhibitor for the following indications:

- Hypertension
- Congestive heart failure

About the product
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. It is effective in all degrees of essential hypertension as well as in renal hypertension. In patients with chronic heart failure, 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.

The current formulation under discussion, Cilazapril tablets (0.5, 1.0, 2.5 and 5mg) are a generic preparation manufactured by Lusomedicamenta SA. These are immediate release formulations seeking authorisation in UK as RMS and PL as CMS under Art 10 (generics).

General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

QUALITY ASPECTS

Drug substance

The chemical-pharmaceutical documentation and Expert Report in relation to cilazapril monohydrate are generally of sufficient quality in view of the present European regulatory requirements.

The applicant refers to a European Drug Master File. This EDMF has been already assessed in the UK and there are no outstanding issues.
The control tests and specifications for drug substance product are adequately drawn up. Stability studies have been performed with the drug substance. A retest period of 24 months is justified.

**Drug Product**

**Other Ingredients**
The tablet core has the following other ingredients

*Tablet core*
Lactose monohydrate
Maize starch
Hypermellose 3cp
Talc
Sodium stearyl fumarate

0.5mg Tablet

*Film -Coating*
0.5 mg: Opadry pink 03B23719: hypromellose 6cp, talc, titanium dioxide (E171), Macrogol 400, iron oxide red (E172), iron oxide yellow (E172).

1mg Tablet

*Film -Coating*
Opadry pink 03B23719: hypromellose 6cp, talc, titanium dioxide (E171), Macrogol 400, iron oxide red (E172), iron oxide yellow (E172).

2.5mg Tablet

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

5mg Tablet

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

The development of the product has been described, the choice of excipients is justified and their functions explained. Data and discussion of the optimisation of the manufacturing process and operating conditions are adequately described.

The description of the products was the same for strengths of 0.5 and 1mg (Pink, oblong presenting a one sided score film coated tablets), and for the strengths 2.5 and 5mg (brown, oblong presenting a one sided score film coated tablets) and this might have caused a mistake by the patient/applicant and or health professionals. To overcome this issue the applicant has
included an engraving in the 1mg ("C1") and in the 5 mg ("C5") tablets to distinguish one strength from the other.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed and batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. The proposed shelf-life of 36 months with storage conditions ‘Do not store above 25°C’ for the drug product is considered acceptable based on new stability data.

The proposed shelf-life of 36 months with storage conditions ‘Do not store above 25°C’ for the drug product is considered acceptable based on new stability data.

**NON CLINICAL ASPECTS**
Specific non-clinical studies have not been performed, which is acceptable for this application for a generic product.
CLINICAL ASPECTS
These are generic applications claiming essential similarity to an established product already on the market in a number of EU member states. Therefore the pharmacokinetics, the pharmacodynamics, efficacy and safety are well established for the active. A summary of these are presented below. Whether these are extendable to the current formulation will depend on the satisfactory demonstration of bioequivalence.

Pharmacokinetics

Absorption
Cilazapril is efficiently absorbed and rapidly converted to the active form, cilazaprilat. Peak plasma concentrations and time to peak concentrations following oral administration of 0.05 to 5mg cilazapril are summarised below;

<table>
<thead>
<tr>
<th>Oral Dose (mg)</th>
<th>Cilazapril</th>
<th>Cilazaprilat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>$t_{\text{max}}$ (h)</td>
</tr>
<tr>
<td>0.5</td>
<td>17.0</td>
<td>1.1</td>
</tr>
<tr>
<td>1.0</td>
<td>33.9</td>
<td>1.1</td>
</tr>
<tr>
<td>2.5</td>
<td>62.7</td>
<td>1.1</td>
</tr>
<tr>
<td>5.0</td>
<td>182.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

The bioavailability of cilazaprilat from oral cilazapril approximates 60% based on urinary recovery data. Maximum plasma concentrations are reached within two hours after administration and are directly related to dosage. Ingestion of food immediately prior to cilazapril administration delays and reduces the absorption (average peak concentration reduced by 29% and delays the peak by an hour and reduces bioavailability of the metabolite cilazaprilat by 14%) which, however, is therapeutically not considered relevant as they have little influence on plasma ACE inhibition.

Metabolism/Elimination
Cilazaprilat is eliminated unchanged by the kidneys, with an effective half-life of nine hours after once-daily dosing with cilazapril. The half lives after intravenous administrations suggest saturable binding of Cilazaprilat to ACE (half lives for periods of 1-4 hours and 1-7 days are 0.90 and 46.2 hours respectively). Early elimination phase corresponds to clearance of free drug. After oral administration of 0.5, 1, 2.5 and 5 mg Cilazapril, the terminal elimination half-lives for the metabolite are 48.9, 39.8, 38.5 and 35.8 hours respectively.

Pharmacodynamics
Cilazapril is a specific, long-acting 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.

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 remains unchanged.
The anti-hypertensive effect of cilazapril is maintained during long-term therapy. In patients with chronic heart failure, the renin-angiotensin-aldosterone and sympathetic nervous systems are generally activated. By suppressing the RAA 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 showing an improvement in quality of life. The haemodynamic and clinical effects occur promptly and persist.

**Clinical studies**
The applicant has provided the requisite Biostudy in support of this application based on essential similarity. The study compared Cilazapril 2.5mg tablets with the reference product Vascase 5mg Tablets Roche Products Ltd. This study was a randomised, open label, two-period, two-treatment, cross-over study in 24 healthy volunteers. The design was appropriate for a biostudy.

Table 1. Pharmacokinetic parameters for Cilazapril (parent compound)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC(_{0-12}) ng/ml/h</th>
<th>AUC(_{0-\infty}) ng/ml/h</th>
<th>C(_{\text{max}}) ng/ml</th>
<th>t(_{\text{max}}) h</th>
<th>T(_{1/2}) h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>87.6± 40.0</td>
<td>90.3± 39.2</td>
<td>52.29± 22.01</td>
<td>0.99±0.28</td>
<td>1.11±0.52</td>
</tr>
<tr>
<td>Reference</td>
<td>87.4± 45.7</td>
<td>91.1±44.6</td>
<td>51.82±23.14</td>
<td>0.92±0.23</td>
<td>1.10±0.52</td>
</tr>
<tr>
<td>*Ratio (90% CI) (Geo mean data)</td>
<td>1.0272</td>
<td>1.0126</td>
<td>1.0203</td>
<td>91.03 – 115.89</td>
<td>90.88 – 112.83</td>
</tr>
<tr>
<td>CV (%)</td>
<td>24.71</td>
<td>22.08</td>
<td>15.75</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(\text{AUC}_{0-\infty}\) area under the plasma concentration-time curve from time zero to infinity
\(\text{AUC}_{0-t}\) area under the plasma concentration-time curve from time zero to \(t\) hours
\(C_{\text{max}}\) maximum plasma concentration
\(t_{\text{max}}\) time for maximum concentration
\(T_{1/2}\) half-life

*ln-transformed values

Table 2. Pharmacokinetic parameters for Cilazaprilat (active metabolite)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC(_{0-144}) ng/ml/h</th>
<th>AUC(_{0-\infty}) ng/ml/h</th>
<th>C(_{\text{max}}) ng/ml</th>
<th>t(_{\text{max}}) h</th>
<th>T(_{1/2}) h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>422.1± 115.5</td>
<td>478.5 ± 143.9</td>
<td>53.40 ±17.90</td>
<td>1.95 ±0.31</td>
<td>44.76 ±21.30</td>
</tr>
<tr>
<td>Reference</td>
<td>442.9 ±125.2</td>
<td>496.7 ±136.2</td>
<td>52.37 ±18.45</td>
<td>1.99± 0.46</td>
<td>41.96 ±12.53</td>
</tr>
<tr>
<td>*Ratio (90% CI) (Geo mean data)</td>
<td>0.9532</td>
<td>0.9562</td>
<td>1.0207</td>
<td>88.01—103.22</td>
<td>87.39 – 104.62</td>
</tr>
<tr>
<td>CV (%)</td>
<td>16.18</td>
<td>18.30</td>
<td>19.54</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>
Symphar, Cilaprazil 0.5mg, 1mg, 2.5mg and 5mg Tablets

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{AUC}_{0-\infty}$</td>
<td>area under the plasma concentration-time curve from time zero to infinity</td>
</tr>
<tr>
<td>$\text{AUC}_{0-t}$</td>
<td>area under the plasma concentration-time curve from time zero to $t$ hours</td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>maximum plasma concentration</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>time for maximum concentration</td>
</tr>
<tr>
<td>$T_{1/2}$</td>
<td>half-life</td>
</tr>
</tbody>
</table>

The study was considered to have demonstrated the bioequivalence of the test against the reference product.

**Clinical efficacy**

No new efficacy data have been submitted and none are required for this application.

**Clinical safety**

No new safety data have been submitted and none are required for this application.

**Pharmacovigilance system**

The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

**Product Literature**

Satisfactory Summary of Product Characteristics, Patient Information Leaflet and labelling has been provided.

**BENEFIT RISK ASSESSMENT**

There are no major public health concerns raised in this assessment and a marketing authorisation may be granted.
Module 6

Steps taken after procedure

There have been no non-confidential changes to the marketing authorisations.