1. NAME OF THE MEDICINAL PRODUCT
Coversyl 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Perindopril arginine.
One film-coated tablet contains 6.790 mg perindopril corresponding to 10 mg perindopril arginine.
Excipient with known effect: 145.16 mg lactose monohydrate.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet.
Green, round, biconvex, film-coated tablet engraved with \( \heartsuit \) on one face and \( \equiv \) on the other face.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Hypertension
Treatment of hypertension.

Stable coronary artery disease
Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation.

4.2 Posology and method of administration
Posology
The dose should be individualised according to the patient profile (see section 4.4) and blood pressure response.

Hypertension
Coversyl may be used in monotherapy or in combination with other classes of antihypertensive therapy (see sections 4.3, 4.4, 4.5 and 5.1).
The recommended starting dose is 5 mg given once daily in the morning.
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 drop in blood pressure following the initial dose. A starting dose of 2.5 mg is recommended in such patients and the initiation of treatment should take place under medical supervision.
The dose may be increased to 10 mg once daily after one month of treatment.
Symptomatic hypotension may occur following initiation of therapy with Coversyl; this is more likely in patients who are being treated concurrently with diuretics. Caution is therefore recommended 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 Coversyl (see section 4.4).

In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Coversyl should be initiated with a 2.5 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Coversyl should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.

In elderly patients treatment should be initiated at a dose of 2.5 mg which may be progressively increased to 5 mg after one month then to 10 mg if necessary depending on renal function (see table below).

Stable coronary artery disease
Coversyl should be introduced at a dose of 5 mg once daily for two weeks, then increased to 10 mg once daily, depending on renal function and provided that the 5 mg dose is well tolerated.

Elderly patients should receive 2.5 mg once daily for one week, then 5 mg once daily the next week, before increasing the dose up to 10 mg once daily depending on renal function (see Table 1 “Dosage adjustment in renal impairment”). The dose should be increased only if the previous lower dose is well tolerated.

Special population
Patients with renal impairment
Dosage in patients with renal impairment should be
or not) occurs during the first month of perindopril treatment, a careful appraisal of the benefit/risk should be performed before treatment continuation.

Hypotension
ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). In patients with symptomatic 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 (see sections 4.2 and 4.8). 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 congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Coversyl. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of Coversyl may be necessary.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy
As with other ACE inhibitors, Coversyl should be given with caution to patients with mitral valve ste-
nosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Renal impairment
In cases of renal impairment (creatinine clearance <60 ml/min) the initial perindopril dosage should be adjusted according to the patient’s creatinine clearance (see section 4.2) and then as a function of the patient’s response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients (see section 4.8).

In patients with symptomatic 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 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 Coversyl therapy.

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 Coversyl 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 Coversyl may be required.

Haemodialysis patients
Anaphylactoid reactions have been reported in patients dialysed with high flux membranes, 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.

Kidney transplantation
There is no experience regarding the administration of Coversyl in patients with a recent kidney transplantation.

Hypersensitivity/Angioedema
Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including Coversyl (see section 4.8). This may occur at any time during therapy. In such cases, Coversyl should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, 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.

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.
Race
ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients. As with other ACE inhibitors, perindopril may be less effective in lowering blood pressure in black people 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, Coversyl may block angiotensin II formation secondary to compensatory renin release. The treatment should be discontinued one day prior to the surgery. 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 perindopril. Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (>70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal arrhythmias. If concomitant use of the above-mentioned agents is deemed appropriate, they should...
be used with caution and with frequent monitoring of serum potassium (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 perindopril is generally not recommended (see section 4.5).

**Potassium-sparing drugs, potassium supplements or potassium-containing salt substitutes**
The combination of perindopril and potassium-sparing drugs, potassium supplements or potassium-containing salt substitutes is generally not recommended (see section 4.5).

**Dual blockade of the renin-angiotensin-aldosterone system (RAAS)**
There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

**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).

**Excipients**
Due to the presence of lactose, patients with rare hereditary problems of galactose intolerance, glucose-galactose malabsorption, or the Lapp lactase deficiency should not take this medicinal product.

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

**Drugs inducing hyperkalaemia**
Some drugs or therapeutic classes may increase the occurrence of hyperkalaemia: aliskiren, potassium salts, potassium-sparing diuretics, ACE inhibitors, angiotensin-II receptor antagonists, NSAIDs, heparins, immunosuppressant agents such as ciclosporin or tacrolimus, trimethoprim. The combination of these drugs increases the risk of hyperkalaemia.

**Concomitant use contra-indicated (see section 4.3)**
Aliskiren
In diabetic or impaired renal patients, risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increase.

**Concomitant use not recommended (see section 4.4)**
Aliskiren
In patients other than diabetic or impaired renal patients, risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increase.

**Concomitant therapy with ACE inhibitor and angiotensin-receptor blocker**
It has been reported in the literature that in patients with established atherosclerotic disease, heart failure, or with diabetes with end organ damage, concomitant therapy with ACE inhibitor and
angiotensin-receptor blocker is associated with a higher frequency of hypotension, syncope, hyperkalaemia, and worsening renal function (including acute renal failure) as compared to use of a single renin-angiotensin-aldosterone system agent. Dual blockade (e.g., by combining an ACE-inhibitor with an angiotensin II receptor antagonist) should be limited to individually defined cases with close monitoring of renal function, potassium levels, and blood pressure.

**Baclofen**
Increased antihypertensive effect. Monitor blood pressure and adapt antihypertensive dosage if necessary.

**Non-potassium-sparing diuretics**
Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating therapy with low and progressive doses of perindopril.

In arterial hypertension, when prior diuretic therapy can have caused salt/volume depletion, either the diuretic must be discontinued before initiating the ACE inhibitor, in which case a non-potassium-sparing diuretic can be thereafter reintroduced or the ACE inhibitor must be initiated with a low dosage and progressively increased.

In diuretic-treated congestive heart failure, the ACE inhibitor should be initiated at a very low dosage, possibly after reducing the dosage of the associated non-potassium-sparing diuretic.

In all cases, renal function (creatinine levels) must be monitored during the first few weeks of ACE inhibitor therapy.

**Potassium-sparing diuretics (e.g., triamterene, amiloride,...), potassium salts**
Hyperkalaemia (potentially lethal), especially in conjunction with renal impairment (additive hyperkalaemia effects).

The combination of perindopril with the above-mentioned drugs is not recommended (see section 4.4). If concomitant use is nonetheless indicated, they should be used with caution and with frequent monitoring of serum potassium. For use of spironolactone in heart failure, see below.

**Lithium**
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Use of perindopril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

**Concomitant use which requires special care**
Antidiabetic agents (insulins, oral hypoglycaemic agents)
Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (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.

**Potassium-sparing diuretics (eplerenone, spironolactone)**
With eplerenone or spironolactone at doses between 12.5mg to 50mg by day and with low doses of ACE inhibitors:

In the treatment of class II-IV heart failure (NYHA) with an ejection fraction <40%, and previously treated with ACE inhibitors and loop diuretics, risk of hyperkalaemia, potentially lethal, especially in case of non-observance of the prescription recommendations on this combination.

Before initiating the combination, check the absence of hyperkalaemia and renal impairment.

A close monitoring of the kalaemia and creatinemia is recommended in the first month of the treatment once a week at the beginning and, monthly thereafter.
4.6 Fertility, pregnancy and lactation

Pregnancy
The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4).
The use of ACE inhibitors is contra-indicated during the 2nd and 3rd trimester of pregnancy (see sections 4.3 and 4.4).

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

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see also sections 4.3 and 4.4).

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

Fertility
There was no effect on reproductive performance or fertility.

4.7 Effects on ability to drive and use machines
Coversyl has no direct influence on the ability to drive and use machines but individual reactions
related to low blood pressure may occur in some patients, particularly at the start of treatment or in combination with another antihypertensive medication.

As a result the ability to drive or operate machinery may be impaired.

4.8 Undesirable effects

a. Summary of safety profile

The safety profile of perindopril is consistent with the safety profile of ACE inhibitors:

The most frequent adverse events reported in clinical trials and observed with perindopril are: dizziness, headache, paraesthesia, vertigo, visual disturbances, tinnitus, hypotension, cough, dyspnoea, abdominal pain, constipation, diarrhoea, dysgeusia, dyspepsia, nausea, vomiting, prurit, rash, muscle cramps, and asthenia.

b. Tabulated list of adverse reactions

The following undesirable effects have been observed during clinical trials and/or post-marketing use with perindopril and ranked under the following frequency:

Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare (<1/10000); not known (cannot be estimated from the available data).

### MedDRA System Organ Class

<table>
<thead>
<tr>
<th>Undesirable Effects</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and the lymphatic System Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>Uncommon*</td>
</tr>
<tr>
<td>Agranulocytosis or pancytopenia</td>
<td>Very rare</td>
</tr>
<tr>
<td>Haemoglobin decreased and haematocrit decreased</td>
<td>Very rare</td>
</tr>
<tr>
<td>Leucopenia/neutropenia</td>
<td>Very rare</td>
</tr>
<tr>
<td>Haemolytic anaemia in patients with a congenital deficiency of G-6PDH (see section 4.4)</td>
<td>Very rare</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Very rare</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Hypoglycaemia (see sections 4.4 and 4.5)</td>
<td>Uncommon*</td>
</tr>
<tr>
<td>Hyperkalaemia, reversible on discontinuation (see section 4.4)</td>
<td>Uncommon*</td>
</tr>
<tr>
<td>Hyponatraemia</td>
<td>Uncommon*</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Mood disturbances</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Nervous System disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>Common</td>
</tr>
<tr>
<td>Headache</td>
<td>Common</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>Common</td>
</tr>
<tr>
<td>Vertigo</td>
<td>Common</td>
</tr>
<tr>
<td>Somnolence</td>
<td>Uncommon*</td>
</tr>
<tr>
<td>Syncope</td>
<td>Very rare</td>
</tr>
<tr>
<td>Confusion</td>
<td></td>
</tr>
<tr>
<td><strong>Eye Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Visual disturbances</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Ear and labyrinth disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Tinnitus</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>Uncommon*</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Very rare</td>
</tr>
<tr>
<td>Angina pectoris (see section 4.4)</td>
<td>Very rare</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction, possibly secondary to excessive hypotension in high risk patients (see section 4.4)</td>
<td>Very rare</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Hypotension (and effects related to hypotension)</td>
<td>Common</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Uncommon*</td>
</tr>
<tr>
<td>Stroke possibly secondary to excessive hypotension in high risk patients (see section 4.4)</td>
<td>Very rare</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>Common</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>Common</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Eosinophilic pneumonia</td>
<td>Very rare</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>Very rare</td>
</tr>
<tr>
<td><strong>Gastro-intestinal Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Common</td>
</tr>
<tr>
<td>Constipation</td>
<td>Common</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Common</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>Common</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>Common</td>
</tr>
<tr>
<td>Nausea</td>
<td>Common</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Common</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Common</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Hepato-biliary Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Hepatitis either cytolytic or cholestatic (see section 4.4)</td>
<td>Very rare</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Prurit</td>
<td>Common</td>
</tr>
<tr>
<td>Rash</td>
<td>Common</td>
</tr>
<tr>
<td>Urticaria (see section 4.4)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx (see section 4.4)</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Photosensitivity reactions</td>
<td>Uncommon*</td>
</tr>
<tr>
<td>Pemphigoid</td>
<td>Uncommon*</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Erythema multiforme</td>
<td>Very rare</td>
</tr>
</tbody>
</table>
The recommended treatment of overdosage is intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis (see section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: ACE inhibitors, plain, ATC code: C09A A04

Mechanism of action
Perindopril is an inhibitor of the enzyme that converts angiotensin I into angiotensin II (Angiotensin Converting Enzyme ACE). The converting enzyme, or kinase, is an exopeptidase that allows conversion of angiotensin I into the vasoconstrictor angiotensin II as well as causing the degradation of the vasodilator bradykinin into an inactive heptapeptide. Inhibition of ACE results in a reduction of angiotensin II in the plasma, which leads to increased plasma renin activity (by inhibition of the negative feedback of renin release) and reduced secretion of aldosterone. Since ACE inactivates bradykinin, inhibition of ACE also results in an increased activity of circulating and local kallikrein-kinin systems (and thus also activation of the prostaglandin system). It is possible that this mechanism contributes to the blood pressure-lowering action of ACE inhibitors and is partially responsible for certain of their side effects (e.g. cough).

Perindopril acts through its active metabolite, perindoprilat. The other metabolites show no inhibition of ACE activity in vitro.

Clinical efficacy and safety
Hypertension
Perindopril is active in all grades of hypertension:
The main efficacy criterion was the composite of cardiovascular mortality, non fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with 8 mg perindopril tert-butylamine (equivalent to 10 mg perindopril arginine) once daily resulted in a significant absolute reduction in the primary endpoint of 1.9% (relative risk reduction of 20%, 95%CI [9.4; 28.6] – p<0.001).

In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2.2% corresponding to a RRR of 22.4% (95%CI [12.0; 31.6] – p<0.001) in the primary endpoint was observed by comparison to placebo.

Paediatric use
The safety and efficacy of perindopril in children and adolescents aged below 18 years have not been established.

In an open, non-comparative clinical study in 62 hypertensive children aged from 2 to 15 years with a glomerular filtration rate >30 ml/min/1.73 m², patients received perindopril with an average dose of 0.07 mg/kg. The dose was individualised according to the patient profile and blood pressure response up to a maximum dose of 0.135 mg/kg/day. 59 patients completed the period of three months, and 36 patients completed the extension period of the study, i.e. were followed at least 24 months (mean study duration: 44 months).

Systolic and diastolic blood pressure remained stable from the inclusion to the last assessment in patients previously treated by other antihypertensive treatments, and decreased in naïve patients. More than 75% of children had systolic and diastolic blood pressure below the 95th percentile at their last assessment.

The safety was consistent with the known safety profile of perindopril.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) clinical trial data:
Two large randomised, controlled trials (ONTARGET (ONGoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of combination...
of an ACE-inhibitor with an angiotensin II receptor blocker.
ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.
These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed.
Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.
ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.
ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

5.2 Pharmacokinetic properties

Absorption
After oral administration, the absorption of perindopril is rapid and the peak concentration is achieved within 1 hour. The plasma half-life of perindopril is equal to 1 hour.
Perindopril is a prodrug. Twenty seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.
As ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril arginine should be administered orally in a single daily dose in the morning before a meal.
It has been demonstrated a linear relationship between the dose of perindopril and its plasma exposure.

Distribution
The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Protein binding of perindoprilat to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration-dependent.

Elimination
Perindoprilat is eliminated in the urine and the terminal half-life of the unbound fraction is approximately 17 hours, resulting in steady-state within 4 days.

Special population
Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure. Dosage adjustment in renal insufficiency is desirable depending on the degree of impairment (creatinine clearance).
Dialysis clearance of perindoprilat is equal to 70 ml/min.
Perindopril kinetics are modified in patients with cirrhosis: hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required (see sections 4.2 and 4.4).

5.3 Preclinical safety data
In the chronic oral toxicity studies (rats and monkeys), the target organ is the kidney, with reversible damage.
No mutagenicity has been observed in in vitro or in vivo studies.
Reproduction toxicology studies (rats, mice, rabbits and monkeys) showed no sign of embryotoxicity or teratogenicity. However, angiotensin converting
enzyme inhibitors, as a class, have been shown to induce adverse effects on late foetal development, resulting in foetal death and congenital effects in rodents and rabbits: renal lesions and an increase in peri- and postnatal mortality have been observed. Fertility was not impaired either in male or in female rats.

No carcinogenicity has been observed in long term studies in rats and mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Lactose monohydrate
Magnesium stearate
Maltodextrin
Hydrophobic colloidal silica
Sodium starch glycolate (type A)

Film-coating:
Glycerol
Hypermellose
Copper chlorophyllin
Macrogol 6000
Magnesium stearate
Titanium dioxide

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container
White polypropylene tablet container equipped with a polyethylene flow reducer and a white opaque stopper containing a dessicant gel.

Box of 5, 10, 14, 20, 30, 50, 60 (60 or 2 containers of 30), 90 (90 or 3 containers of 30), 100 (100 or 2 containers 50), 120 (120 or 4 containers of 30) or 500 tablets (500 or 10 containers of 50).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements for disposal.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

LES LABORATOIRES SERVIER
50, rue Carnot
92284 Suresnes Cedex
France

For any updates please refer to www.servier.com. As the SmPC may vary from country to country please also refer to SERVIER’s local agents and/or distributors.