SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

COVERSYL 2.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Perindopril arginine.
One film-coated tablet contains 1.6975 mg perindopril corresponding to 2.5 mg perindopril arginine.

Excipient : 36.29 mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, round, convex, film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension:

Treatment of hypertension.

Heart failure:

Treatment of symptomatic heart failure.

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

It is recommended that COVERSYL is taken once daily in the morning before a meal.

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.

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).

Symptomatic heart failure:

It is recommended that COVERSYL, generally associated with a non-potassium-sparing diuretic and/or digoxin and/or a beta-blocker, be introduced under close medical supervision with a recommended starting dose of 2.5 mg taken in the morning. This dose may be increased after 2 weeks to 5 mg once daily if tolerated. The dose adjustment should be based on the clinical response of the individual patient.

In severe heart failure and in other patients considered to be at high risk (patients with impaired renal function and a tendency to have electrolyte disturbances, patients receiving simultaneous treatment with diuretics and/or treatment with vasodilating agents), treatment should be initiated under careful supervision (see section 4.4).

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 COVERSYL. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with COVERSYL (see section 4.4).

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.

Dosage adjustment in renal impairment:

Dosage in patients with renal impairment should be based on creatinine clearance as outlined in table 1 below:

Table 1: dosage adjustment in renal impairment

Creatinine clearance (ml/min)	Recommended dose
$Cl_{CR} \geq 60$	5 mg per day
$30 < Cl_{CR} < 60$	2.5 mg per day
$15 < Cl_{CR} < 30$	2.5 mg every other day
Haemodialysed patients *	
$Cl_{CR} < 15$	2.5 mg on the day of dialysis

* Dialysis clearance of perindoprilat is 70 ml/min.
For patients on haemodialysis, the dose should be taken after dialysis.

Dosage adjustment in hepatic impairment:

No dosage adjustment is necessary in patients with hepatic impairment (see sections 4.4 and 5.2).

Children and adolescents (less than 18 years of age):

Efficacy and safety of use in children and adolescents have not been established. Therefore, use in children and adolescents is not recommended.

4.3 Contraindications

- Hypersensitivity to perindopril, to any of the excipients or to any other ACE inhibitor;
- History of angioedema associated with previous ACE inhibitor therapy;
- Hereditary or idiopathic angioedema*;*
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

Stable coronary artery disease:

If an episode of unstable angina pectoris (major 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 stenosis 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.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis:

Rarely, patients receiving ACE inhibitors during low-density lipoprotein (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.

Anaphylactic reactions during desensitisation:

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In the same patients, these reactions have been avoided when the ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Hepatic failure:

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see section 4.8).

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia:

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. Perindopril 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 perindopril 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 (e.g. sore throat, fever).

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 hyperkalemia 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. Hyperkalemia 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 diuretics, potassium supplements or potassium-containing salt substitutes

The combination of perindopril and potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes 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).

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

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.

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes:

Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with perindopril. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore the combination of perindopril with the above-mentioned drugs is not recommended (see section 4.4). If concomitant use is indicated because of demonstrated hypokalaemia they should be used with caution and with frequent monitoring of serum potassium.

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 risk of lithium toxicity 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).

Non-steroidal anti-inflammatory medicinal products (NSAIDs) including aspirin ≥ 3 g/day:

When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Antihypertensive agents and vasodilators:

Concomitant use of these agents may increase the hypotensive effects of perindopril. Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

Antidiabetic 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.

Tricyclic antidepressants/Antipsychotics/Anesthetics:

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.

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates:

Perindopril may be used concomitantly with acetylsalicylic acid (when used as a thrombolytic), thrombolytics, beta-blockers and/or nitrates.

Gold:

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including perindopril.

4.6 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 antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.
Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetoxicity (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 breast-feeding, 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.

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

The following undesirable effects have been observed during treatment 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).

Blood and lymphatic system disorders:

Decreases in haemoglobin and haematocrit, thrombocytopenia, leucopenia/neutropenia, and cases of agranulocytosis or pancytopenia, have been reported very rarely. In patients with a congenital deficiency of G-6PDH, very rare cases of haemolytic anaemia have been reported (see section 4.4).

Metabolism and nutrition disorders:

Not known : hypoglycaemia (see sections 4.4 and 4.5).

Psychiatric disorders:

Uncommon: mood or sleep disturbances.

Nervous system disorders:

Common: headache, dizziness, vertigo, paresthaesia.
Very rare: confusion.

Eye disorders:

Common: vision disturbance.

Ear and labyrinth disorders:

Common: tinnitus.

Cardiac disorders:

Very rare: arrhythmia, angina pectoris and myocardial infarction, possibly secondary to excessive hypotension in high-risk patients (see section 4.4).

Vascular disorders:

Common: hypotension and effects related to hypotension.

Very rare: stroke, possibly secondary to excessive hypotension in high-risk patients (see section 4.4).
Not known: vasculitis.

Respiratory, thoracic and mediastinal disorders:

Common: cough, dyspnoea.
Uncommon: bronchospasm.
Very rare: eosinophilic pneumonia, rhinitis.

Gastro-intestinal disorders:

Common: nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea, constipation.
Uncommon: dry mouth.
Very rare: pancreatitis.

Hepato-biliary disorders:

Very rare: hepatitis either cytolytic or cholestatic (see section 4.4).

Skin and subcutaneous tissue disorders:

Common: rash, pruritus.
Uncommon: angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see section 4.4).
Very rare: erythema multiforme.

Musculoskeletal and connective tissue disorders:

Common: muscle cramps.

Renal and urinary disorders:

Uncommon: renal insufficiency.
Very rare: acute renal failure.

Reproductive system and breast disorders:

Uncommon: impotence.

General disorders and administration site conditions:

Common: asthenia.
Uncommon: sweating.

Investigations:

Increases in blood urea and plasma creatinine, hyperkalaemia reversible on discontinuation may occur, especially in the presence of renal insufficiency, severe heart failure and renovascular hypertension. Elevation of liver enzymes and serum bilirubin have been reported rarely.

Clinical trials:

During the randomised period of the EUROPA study, only serious adverse events were collected. Few patients experienced serious adverse events: 16 (0.3%) of the 6122 perindopril patients and 12 (0.2%) of the 6107 placebo patients. In perindopril-treated patients, hypotension was observed in 6 patients, angioedema in 3 patients and sudden cardiac arrest in 1 patient. More patients withdrew for cough, hypotension or other intolerance on perindopril than on placebo, 6.0% (n=366) versus 2.1% (n=129) respectively.

4.9 Overdose

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

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 inhibitor, plain, ATC code: C09A A04

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*.

Hypertension:

Perindopril is active in all grades of hypertension : mild, moderate, severe ; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed.

Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate.

Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged.

The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 87-100 % of peak effects.

The decrease in blood pressure occurs rapidly. In responding patients, normalisation is achieved within a month and persists without the occurrence of tachyphylaxis.

Discontinuation of treatment does not lead to a rebound effect.

Perindopril reduces left ventricular hypertrophy.

In man, perindopril has been confirmed to demonstrate vasodilatory properties. It improves large artery elasticity and decreases the media:lumen ratio of small arteries.

An adjunctive therapy with a thiazide diuretic produces an additive-type of synergy. The combination of an ACE inhibitor and a thiazide also decreases the risk of hypokalaemia induced by the diuretic treatment.

Heart failure:

Perindopril reduces cardiac work by a decrease in pre-load and after-load.

Studies in patients with heart failure have demonstrated:

- decreased left and right ventricular filling pressures,

- reduced total peripheral vascular resistance,
- increased cardiac output and improved cardiac index.

In comparative studies, the first administration of 2.5 mg of perindopril arginine to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo.

Patients with stable coronary artery disease:

The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years.
Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to 8 mg perindopril tert-butylamine (equivalent to 10 mg perindopril arginine) (n=6110) or placebo (n=6108).
The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure. Overall, 90% of the patients had a previous myocardial infarction and/or a previous coronary revascularisation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers.
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.

5.2 Pharmacokinetic properties

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.

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.

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.

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 fetal development, resulting in fetal death and congenital effects in rodents and rabbits: renal lesions and an increase in peri- and postnatal mortality have been observed.

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
Hypromellose
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

Medicines no longer required should not be disposed of via the waste water or the municipal sewage system. Return them to a pharmacy or ask your pharmacist how to dispose of them in accordance with the national regulations. These measures will help to protect the environment.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

<[To be completed nationally]>

LABELLING AND PACKAGE LEAFLET

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

{CARTON}

1. NAME OF THE MEDICINAL PRODUCT

COVERSYL 2.5 mg film-coated tablets
Perindopril arginine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One film-coated tablet contains 1.6975 mg perindopril corresponding to 2.5 mg perindopril arginine.

3. LIST OF EXCIPIENTS

Contains lactose: See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets, 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)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Keep the container tightly closed in order to protect from moisture.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

<[To be completed nationally]>
COVERSYL 2.5 mg

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CONTAINER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

COVERSYL 2.5 mg film-coated tablets
Perindopril arginine
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 film-coated tablets
10 film-coated tablets
14 film-coated tablets
20 film-coated tablets
30 film-coated tablets
50 film-coated tablets

6. OTHER

Abbreviations for days of the week

MON
TUE
WED
THU
FRI
SAT
SUN

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

COVERSYL 2.5 mg film-coated tablets
perindopril arginine

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 serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT COVERSYL IS AND WHAT IT IS USED FOR

COVERSYL is an angiotensin converting enzyme (ACE) inhibitor. These work by widening the blood vessels, which makes it easier for your heart to pump blood through them.

COVERSYL is used:
- to treat ***high blood pressure*** (hypertension),
- to treat ***heart failure*** (a condition where the heart is unable to pump enough blood to meet the body's needs),
- to reduce the risk of cardiac events, such as heart attack, in patients with ***stable coronary artery disease*** (a condition where the blood supply to the heart is reduced or blocked) and who have already had a heart attack and/or an operation to improve the blood supply to the heart by widening the vessels that supply it.

2. BEFORE YOU TAKE COVERSYL

Do not take COVERSYL

- if you are allergic (hypersensitive) to perindopril, to any other ACE inhibitor or to any of the other ingredients of COVERSYL,
- If you are more than 3 months pregnant. (It is also better to avoid COVERSYL in early pregnancy – see pregnancy section.)
- if you have experienced symptoms such as wheezing, swelling of the face, tongue or throat, intense itching or severe skin rashes with previous ACE inhibitor treatment or if you or a member of your family have had these symptoms in any other circumstances (a condition called angioedema).

Take special care with COVERSYL

If any of the following apply to you please talk to your doctor before taking COVERSYL:
- if you have aortic stenosis (narrowing of the main blood vessel leading from the heart) or hypertrophic cardiomyopathy (heart muscle disease) or renal artery stenosis (narrowing of the artery supplying the kidney with blood),
- if you have any other heart problems,
- if you have liver problems,
- if you have kidney problems or if you are receiving dialysis,
- if you suffer from a collagen vascular disease (disease of the connective tissue) such as systemic lupus erythematosus or scleroderma,
- if you have diabetes,
- if you are on a salt restricted diet or use salt substitutes which contain potassium,
- if you are to undergo anaesthesia and/or major surgery,
- if you are to undergo LDL apheresis (which is removal of cholesterol from your blood by a machine),
- if you are going to have desensitisation treatment to reduce the effects of an allergy to bee or wasp stings,
- if you have recently suffered from diarrhoea or vomiting, or are dehydrated,
- if you have been told by your doctor that you have an intolerance to some sugars,
- You must tell your doctor if you think you are (or might become) pregnant. COVERSYL is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

COVERSYL is not recommended for use in children and adolescents.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Treatment with COVERSYL can be affected by other medicines. These include:
- other medicines for high blood pressure, including diuretics (medicines which increase the amount of urine produced by the kidneys),
- potassium-sparing diuretics (spironolactone, triamterene, amiloride), potassium supplements or potassium-containing salt substitutes,
- lithium for mania or depression,
- non-steroidal anti-inflammatory drugs (e.g. ibuprofen) for pain relief or high dose aspirin,
- medicines to treat diabetes (such as insulin or metformin),
- medicines to treat mental disorders such as depression, anxiety, schizophrenia etc (e.g. tricyclic antidepressants, antipsychotics),
- immunosuppressants (medicines which reduce the defence mechanism of the body) used for the treatment of auto-immune disorders or following transplant surgery (e.g. ciclosporin),
- allopurinol (for the treatment of gout),
- procainamide (for the treatment of an irregular heart beat),
- vasodilators including nitrates (products that make the blood vessels become wider),
- heparin (medicines used to thin blood),
- medicines used for the treatment of low blood pressure, shock or asthma (e.g. ephedrine, noradrenaline or adrenaline).

Taking COVERSYL with food and drink

It is preferable to take COVERSYL before a meal.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Pregnancy
You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking COVERSYL before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of COVERSYL. COVERSYL is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breastfeeding

Tell your doctor if you are breast-feeding or about to start breast-feeding. COVERSYL is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Driving and using machines

COVERSYL usually does not affect alertness but dizziness or weakness due to low blood pressure may occur in certain patients. If you are affected in this way, your ability to drive or to operate machinery may be impaired.

Important information about some of the ingredients of COVERSYL

COVERSYL contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE COVERSYL

Always take COVERSYL exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
Swallow your tablet with a glass of water, preferably at the same time each day, in the morning, before a meal. Your doctor will decide on the correct dose for you.

The usual dosages are as follows:
High blood pressure: the usual starting and maintenance dose is 5 mg once daily. After one month, this can be increased to 10 mg once a day if required. 10 mg a day is the maximum recommended dose for high blood pressure.
If you are 65 or older, the usual starting dose is 2.5 mg once a day. After a month this can be increased to5 mg once a day and then if necessary to 10 mg once daily.

Heart failure: the usual starting dose is 2.5 mg once daily. After two weeks, this can be increased to 5 mg once a day, which is the maximum recommended dose for heart failure.

Stable coronary artery disease**:** the usual starting dose is 5 mg once daily. After two weeks, this can be increased to 10 mg once daily, which is the maximum recommended dose in this indication.
If you are 65 or older, the usual starting dose is 2.5 mg once a day. After a week this can be increased to 5 mg once a day and after a further week to 10 mg once daily.

If you take more COVERSYL than you should

If you take too many tablets, contact your nearest accident and emergency department or tell your doctor immediately. The most likely effect in case of overdose is low blood pressure which can make you feel dizzy or faint. If this happens, lying down with the legs raised can help.

If you forget to take COVERSYL

It is important to take your medicine every day as regular treatment works better. However, if you forget to take a dose of COVERSYL, take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

If you stop taking COVERSYL

As the treatment with COVERSYL is usually life-long, you should discuss with your doctor before stopping this medicinal product.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, COVERSYL can cause side effects, although not everybody gets them.
If you experience any of the following, stop taking the medicinal product at once and tell your doctor immediately:

- swelling of the face, lips, mouth, tongue or throat, difficulty in breathing,
- severe dizziness or fainting,
- unusual fast or irregular heart beat.

In decreasing order of frequency, side effects can include:

- Common (occur in fewer than 1 in 10 users but in more than 1 in 100 users): headache, dizziness, vertigo, pins and needles, vision disturbances, tinnitus (sensation of noises in the ears), light-headedness due to low blood pressure, cough, shortness of breath, gastro-intestinal disorders (nausea, vomiting, abdominal pain, taste disturbances, dyspepsia or difficulty of digestion, diarrhoea, constipation), allergic reactions (such as skin rashes, itching), muscle cramps, feeling of tiredness,
- Uncommon (occur in fewer than 1 in 100 users but in more than 1 in 1000 users): mood swings, sleep disturbances, bronchospasm (tightening of the chest, wheezing and shortness of breath), dry mouth, angioedema (symptoms such as wheezing, swelling of the face, tongue or throat, intense itching or severe skin rashes), kidney problems, impotence, sweating,
- Very rare (occur in fewer than 1 in 10,000 users): confusion, cardiovascular disorders (irregular heart beat, angina, heart attack and stroke), eosinophilic pneumonia (a rare type of pneumonia), rhinitis (blocked up or runny nose), erythema multiforme, disorders of the blood, pancreas or liver.
- In case of diabetic patients, hypoglycaemia (very low blood sugar level) can occur.
- Vasculitis (inflammation of blood vessels) has been reported.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE COVERSYL

Keep out of the reach and sight of children.

Do not use COVERSYL after the expiry date which is stated on the carton and bottle. The expiry date refers to the last day of that month.
Keep the bottle tightly closed in order to protect from moisture.

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 COVERSYL 2.5 mg contains

- The active substance is perindopril arginine. One film-coated tablet contains 1.6975 mg perindopril (corresponding to 2.5 mg perindopril arginine).
- The other ingredients in the tablet core are: lactose monohydrate, magnesium stearate, maltodextrin, hydrophobic colloidal silica, sodium starch glycolate (type A), and in the tablet film-coating: glycerol, hypromellose, macrogol 6000, magnesium stearate, titanium dioxide.

What COVERSYL 2.5 mg looks like and contents of the pack

COVERSYL 2.5 mg tablets are white, round, convex, film coated tablets.
The tablets are available in 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.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

<[To be completed nationally]>

For RMS (France):
Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex– France

Manufacturer

Les Laboratoires Servier Industrie
905 route de Saran
45520 Gidy - France

and

Servier (Ireland) Industries Ltd
Gorey Road
Arklow - Co. Wicklow – Ireland

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria	COVERSUM-ARGININ 2.5 mg-Filmtabletten
Belgium	COVERSYL 2.5 mg
Cyprus	COVERSYL 2.5 mg
Czech Republic	Perindopril arginine 2.5 mg Servier
Denmark	COVERSYL NOVUM 2,5 mg
Finland	COVERSYL NOVUM 2,5 mg
France	COVERSYL 2,5 mg
Germany	COVERSUM Arginin 2.5 mg
Greece	COVERSYL 2,5 mg
Hungary	ARMIX Arginin 2,5 mg
Iceland	COVERSYL NOVUM 2,5 mg
Ireland	COVERSYL Arginine 2.5 mg film-coated tablets
Italy	COVERSYL 2.5 mg
Latvia	PRESTARIUM 2.5 mg
Lithuania	PRESTARIUM 2.5 mg
Luxembourg	COVERSYL 2.5 mg
Malta	COVERSYL 2.5 mg
Netherlands	COVERSYL arg 2,5 mg
Norway	PERINDOPRILARGININ SERVIER 2,5 mg
Poland	PRESTARIUM 2.5 mg
Portugal	COVERSYL 2.5 mg
Slovakia	PRESTARIUM A 2.5 mg
Slovenia	BIOPREXANIL 2.5 mg
Spain	COVERSYL 2.5 mg
Sweden	COVERSYL NOVUM 2,5 mg
United Kingdom	COVERSYL Arginine 2.5 mg

This leaflet was last approved in {MM/YYYY}.

<[To be completed nationally]>