

ANNEX I

**LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL
PRODUCTS, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION
HOLDERS IN THE MEMBER STATES**

| Member State | Marketing Authorisation Holder | Invented name | Strength | Pharmaceutical form | Route of administration |
|---------------------|---------------------------------------|----------------------|-----------------|----------------------------|--------------------------------|
| Austria | Servier Austria GmbH | COVERSUM | 2 mg | Tablets | Oral use |
| Austria | Servier Austria GmbH | COVERSUM | 4 mg | Tablets | Oral use |
| Belgium | Servier Benelux S.A. | COVERSYL | 2 mg | Tablets | Oral use |
| Belgium | Servier Benelux S.A. | COVERSYL | 4 mg | Tablets | Oral use |
| Denmark | Les Laboratoires Servier | COVERSYL | 2 mg | Tablets | Oral use |
| Denmark | Les Laboratoires Servier | COVERSYL | 4 mg | Tablets | Oral use |
| Finland | Les Laboratoires Servier | COVERSYL | 2 mg | Tablets | Oral use |
| Finland | Les Laboratoires Servier | COVERSYL | 4 mg | Tablets | Oral use |
| France | Les Laboratoires Servier | COVERSYL | 2 mg | Tablets | Oral use |
| France | Les Laboratoires Servier | COVERSYL | 4 mg | Tablets | Oral use |
| Germany | Les Laboratoires Servier | COVERSUM COR | 2 mg | Tablets | Oral use |
| Germany | Les Laboratoires Servier | COVERSUM | 4 mg | Tablets | Oral use |
| Greece | Servier Hellas Pharmaceuticals S.A. | COVERSYL | 2 mg | Tablets | Oral use |
| Greece | Servier Hellas Pharmaceuticals S.A. | COVERSYL | 4 mg | Tablets | Oral use |
| Iceland | Les Laboratoires Servier | COVERSYL | 2 mg | Tablets | Oral use |
| Iceland | Les Laboratoires Servier | COVERSYL | 4 mg | Tablets | Oral use |

| Member State | Marketing Authorisation Holder | Invented name | Strength | Pharmaceutical form | Route of administration |
|-----------------------|--|----------------------|-----------------|----------------------------|--------------------------------|
| Ireland | Les Laboratoires Servier | COVERSYL | 2 mg | Tablets | Oral use |
| Ireland | Les Laboratoires Servier | COVERSYL | 4 mg | Tablets | Oral use |
| Italy | Les Laboratoires Servier | COVERSYL | 4 mg | Tablets | Oral use |
| Luxembourg | Servier Benelux S.A. | COVERSYL | 2 mg | Tablets | Oral use |
| Luxembourg | Servier Benelux S.A. | COVERSYL | 4 mg | Tablets | Oral use |
| Netherlands | Les Laboratoires Servier | COVERSYL | 2 mg | Tablets | Oral use |
| Netherlands | Les Laboratoires Servier | COVERSYL | 4 mg | Tablets | Oral use |
| Norway | Les Laboratoires Servier | COVERSYL | 2 mg | Tablets | Oral use |
| Norway | Les Laboratoires Servier | COVERSYL | 4 mg | Tablets | Oral use |
| Portugal | Servier Portugal - Especialidades Farmacêuticas | COVERSYL | 2 mg | Tablets | Oral use |
| Portugal | Servier Portugal - Especialidades Farmacêuticas | COVERSYL | 4 mg | Tablets | Oral use |
| Spain | Les Laboratoires Servier | COVERSYL | 4 mg | Tablets | Oral use |
| Sweden | Les Laboratoires Servier | COVERSYL | 2 mg | Tablets | Oral use |
| Sweden | Les Laboratoires Servier | COVERSYL | 4 mg | Tablets | Oral use |
| United Kingdom | Les Laboratoires Servier | COVERSYL | 2 mg | Tablets | Oral use |
| United Kingdom | Les Laboratoires Servier | COVERSYL | 4 mg | Tablets | Oral use |

ANNEX II

**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY
OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA**

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF COVERSYL AND ASSOCIATED NAMES (see Annex I)

Coversyl and associated names contain perindopril, a well-known, potent angiotensin converting enzyme inhibitor (ACE-I), marketed in France as Coversyl 2 and 4 mg since 1988, the entire European Union, and world-wide in more than 10 countries including USA and Japan. Perindopril is currently indicated for the treatment of *hypertension* and *symptomatic heart failure*".

Background information on the type II variation through the MRP

In the initial type II variation dossier submitted by MRP (FR/H/246/01-02/001), the applicant claimed the following indication:

"Stable coronary artery disease: Reduction of risk of cardiovascular events in patients with stable coronary artery disease".

This wording was based on a significant relative risk reduction (RRR) of 20% (95% CI [9.4; 28.6] p=0.0003) in the primary combined endpoint of cardiovascular mortality, non-fatal myocardial infarction (MI) or cardiac arrest with successful resuscitation observed in the EUROPA study. A beneficial effect of perindopril was observed for all individual subcomponents of the primary combined endpoint, although only the risk reduction in "non-fatal MI" reached statistical significance.

In the Final Assessment report (dated on 14.02.2005), the indication proposed by the RMS was restricted to **"Reduction of risk of recurrent MI in patients with a history of MI"** considering that the risk reduction was only demonstrated on the "non fatal MI" component of the primary endpoint and that the effect of perindopril was only clearly established in patients with previous MI. The applicant subsequently sent on 23.02.2005 a Position Paper to all MS stating that the indication proposed by the RMS was not acceptable, and that a broader indication reflecting the study population should be approved, namely:

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

This indication was endorsed by several CMS. At the end of the MRP procedure there was a discrepancy between CMS regarding the wording of the indication that adequately reflects the EUROPA data. An official referral for arbitration was notified by the Netherlands to the CHMP on 17.03.2005. The following LoQ was adopted by the CHMP in April 2005:

- 1.- The Applicant should justify the proposed indication based on the results of the EUROPA trial and relevant published literature on other ACE-Is in terms of patients to be included and goals of therapy. The Applicant should focus in particular on the patients with a history of revascularisation but without history of MI, as this population is heterogeneous in terms of severity of lesions, revascularisation technique and concomitant treatments. Results in this population are less convincing and further differentiation of risk may be needed before this patient group can be included in the wording of the indication.
- 2.- The second issue addresses the question whether the beneficial effect may extend beyond a mere reduction of MI to a reduction of cardiac events. Consistency was noted between the various components of the primary endpoint although significance was only reached for prevention of MI. A significant effect was noted on the occurrence of heart failure. This needs point further discussion.

Evaluation of Clinical Efficacy

The indication under review is based on the results of the EUROPA study, a trial designed to evaluate the ability of Perindopril to reduce the risk of the combined endpoint of cardiovascular death, non-fatal acute MI and cardiac arrest with successful resuscitation in patients with stable coronary heart disease, without evidence of heart failure. The results showed that treatment with perindopril once daily resulted in a significant absolute reduction in the primary endpoint. This benefit was statistically significant for non-fatal MI, one of the components of the combined endpoint. A non-statistically significant favourable trend was observed in the other two components.

As it was expected that the subgroup of patients with a history of revascularisation but with no history of MI was heterogeneous in terms of severity of lesions, revascularisation technique and concomitant treatments, the Applicant was asked to address this issue in order to justify the inclusion of this specific group of patients in the proposed indication.

The Company has provided data showing that this population is not so heterogeneous but quite similar to the whole population included in EUROPE study, at least in terms of revascularisation techniques and concomitant treatments. The higher percentage of patients who had at least 70% narrowing of one or more major arteries (82.4% vs. 60.5%) would reflect serious coronary lesions in the group of patients with a history of revascularisation and with no history of MI.

The Applicant was also requested to justify the indication based on the results of relevant published literature on other ACE-Is in terms of patients to be included and goals of therapy. Difficulties in making comparisons among the different trials are recognised as they include a different population and use different endpoints. Nevertheless the Applicant has tried to address the results of two studies (PEACE and HOPE) where patients with stable CAD and normal fraction ejection were included. The results of the HOPE and PEACE trials seem to support the beneficial effect of perindopril observed in the EUROPA study for patients with medium to high risk of cardiac events. Patients with a history of revascularisation would be included in these groups of patients.

The Applicant was also requested to justify the beneficial effect of Perindopril beyond a mere reduction of MI. Although a statistically significant benefit was not shown for two of the three components of the composite endpoint due to the smaller number of occurrences, a positive tendency in favour of perindopril was observed. Consistency for secondary variables was also observed and even a significant effect was shown on the occurrence of heart failure in the overall population.

The CHMP believes that the lack of a statistically significant difference for two of the three components of the composite endpoint in the EUROPA study is not a reason to restrict the indication to a single component, given that a positive and fully consistent trend for these two components is observed. As further consistency is shown for the secondary variables, it is reasonable to extend the indication from “reduction of MI” to “reduction of cardiac events”, a term that includes patients with a history of MI and/or a history of revascularisation. This wording would be in line with the general CHMP policy regarding products using composite endpoints for evaluation of efficacy.

In the light of the above the CHMP concludes that the proposed indication for Coversyl “*Stable coronary artery disease: Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation*” is adequately supported by the information provided.

Overall conclusion on benefit/risk

At its meeting of 25-28 July 2005, the CHMP considered the data on efficacy presented by the MAHs and concluded that it had been shown that Coversyl and associated names was effective in the *reduction of risk of cardiac events in patients with stable coronary artery disease with a history of myocardial infarction and/or revascularisation*.

The CHMP recommended the granting of the type II variation to extend the indication.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS

Whereas,

- the CHMP considered the referral made under article 6.12 of Commission Regulation (EC) No 1084/2003, for Coversyl and associated names (see Annex I),
- The MAH has implemented the text proposed by the CHMP in the SPC:
 - It is proposed to add the following indication in section 4.1:
“Stable coronary artery disease: Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation.”
 - The posology in Section 4.2 has been updated as follows:
Stable coronary artery disease:
COVERSYL should be introduced at a dose of 4 mg once daily for two weeks, then increased to 8 mg once daily, depending on renal function and provided that the 4 mg dose is well tolerated.
Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 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.
 - A warning has been introduced in Section 4.4:
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.
 - The following description of the observed side-effects has been added in Section 4.8:
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.
 - Section 5.1 has been updated to include the results of the EUROPA trial as follows:
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 perindopril 8 mg (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 perindopril 8 mg 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.

- no untoward safety findings related to the extension of the indication have been identified.
- the CHMP, as a consequence, considered the benefit/risk balance for the above-mentioned extension of indication to be favourable,

The CHMP has recommended the granting of the variation of the Marketing Authorisations for which the Summary of Product Characteristics is set out in Annex III for Coversyl and related names (see Annex I).

ANNEX III
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<COVERSYL and associated names (see Annex I)>, <strength>, tablets

<[See Annex I - to be completed nationally]>

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<COVERSYL and associated names> 2 mg:

2 mg perindopril tert-butylamine salt, equivalent to 1.669 mg perindopril

Each tablet contains:

2 mg perindopril tert-butylamine salt, equivalent to 1.669 mg perindopril

<[To be completed nationally]>

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

<[To be completed nationally]>

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 and associated names> is taken once daily in the morning before a meal.

The dose should be individualised according to the patient profile (see 4.4 “Special warnings and special precautions for use”) and blood pressure response.

Hypertension:

< COVERSYL and associated names> may be used in monotherapy or in combination with other classes of antihypertensive therapy.

The recommended starting dose is 4 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 mg is recommended in such patients and the initiation of treatment should take place under medical supervision.

The dose may be increased to 8 mg once daily after one month of treatment. Symptomatic hypotension may occur following initiation of therapy with <COVERSYL and associated names>; 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 and associated names> (see section 4.4 “Special warnings and special precautions for use”).

In hypertensive patients in whom the diuretic cannot be discontinued, therapy with <COVERSYL and associated names> should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of <COVERSYL and associated names> 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 mg which may be progressively increased to 4 mg after one month then to 8 mg if necessary depending on renal function (see table below).

Symptomatic heart failure:

It is recommended that <COVERSYL and associated names>, 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 mg taken in the morning. This dose may be increased by increments of 2 mg at intervals of no less than 2 weeks to 4 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 4.4 “Special warnings and special precautions for use”).

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 and associated names>. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with <COVERSYL and associated names> (see section 4.4 “Special warnings and special precautions for use”).

Stable coronary artery disease:

<COVERSYL and associated names> should be introduced at a dose of 4 mg once daily for two weeks, then increased to 8 mg once daily, depending on renal function and provided that the 4 mg dose is well tolerated.

Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 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 |
|-------------------------------|-----------------------------|
| $Cl_{CR} \geq 60$ | 4 mg per day |
| $30 < Cl_{CR} < 60$ | 2 mg per day |
| $15 < Cl_{CR} < 30$ | 2 mg every other day |
| Haemodialysed patients * | |
| $Cl_{CR} < 15$ | 2 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 “Special warnings and special precautions for use” and 5.2 “Pharmacokinetic properties”)

Paediatric use:

Efficacy and safety of use in children has not been established. Therefore, use in children 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 4.6 “Pregnancy and lactation”).

4.4 Special warnings and special 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 “Interaction with other medicaments and other forms of interaction” and 4.8 “Undesirable effects”). 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 4.2 “Posology and method of administration” and 4.8 “Undesirable effects”). 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 normal saline. 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 and associated names>. 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 and associated names> may be necessary.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy:

As with other ACE inhibitors, < COVERSYL and associated names> 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 4.2 “Posology and method of administration”) 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 4.8 “Undesirable effects”).

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 and associated names> 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 and associated names> 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 and associated names> 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 and associated names> 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 and associated names> (see 4.8 Undesirable effects). This may occur at any time during therapy. In such cases, <COVERSYL and associated names> 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.

Angiotensin converting enzyme 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 4.3 Contraindications).

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 4.8 Undesirable effects).

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.

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 and associated names> 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. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, uncontrolled diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended.

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 4.5 Interaction with other medicinal products and other forms of interaction, Antidiabetics.)

Lithium:

The combination of lithium and perindopril is generally not recommended (see 4.5 Interaction with other medicinal products and other forms of interaction).

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 4.5 Interaction with other medicinal products and other forms of interaction).

Pregnancy and lactation:

(See section 4.3 “Contraindications” and section 4.6 “Pregnancy and lactation”).

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 drugs (NSAIDs) including aspirin ≥ 3 g/day:

The administration of a non-steroidal anti-inflammatory drugs may reduce the antihypertensive effect of ACE inhibitors. Additionally, NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium and may result in a deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function such as those who are elderly or dehydrated.

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.

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.

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.

4.6 Pregnancy and lactation

Pregnancy:

<COVERSYL and associated names> should not be used during the first trimester of pregnancy. When a pregnancy is planned or confirmed, the switch to an alternative treatment should be initiated as soon as possible. Controlled studies with ACE inhibitors have not been done in humans, but in a

limited number of cases with first trimester exposure there do not appear to have been any malformations consistent with human foetotoxicity as described below.
Perindopril is contraindicated during the second and third trimesters of pregnancy.
Prolonged ACE inhibitor exposure 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 5.3 “Preclinical safety data”)
Should exposure to perindopril have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Lactation:

It is not known whether perindopril is excreted into human breast milk. Therefore the use of <COVERSYL and associated names> is not recommended in women who are breast-feeding.

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

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), including isolated reports.

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

Cardio-vascular disorders:

Common: hypotension and effects related to hypotension

Very rare: arrhythmia, angina pectoris, myocardial infarction and stroke, possibly secondary to excessive hypotension in high-risk patients (see 4.4 Special warnings and special precautions for use).

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 Special warnings and special precautions for use)

Skin and subcutaneous tissue disorders:

Common: rash, pruritus

Uncommon: angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see 4.4 Special warnings and special precautions for use).

Very rare: erythema multiforme

Musculoskeletal, connective tissue and bone 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:

Common: asthenia

Uncommon: sweating

Blood and the 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 Special warnings and special precautions for use).

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 normal saline 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 4.4 Special warnings and special precautions for use, Haemodialysis Patients.) 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

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:

<COVERSYL and associated names> 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 mg of <COVERSYL and associated names> 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 perindopril 8 mg (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 perindopril 8 mg 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 complete within 1 hour. Bioavailability is 65 to 70 %.

About 20 % of the total quantity of perindopril absorbed is converted into perindoprilat, the active metabolite. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The plasma half-life of perindopril is equal to 1 hour. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.

As ingestion of food decreases conversion to perindoprilat, hence bioavailability, <COVERSYL and associated names> should be administered orally in a single daily dose in the morning before a meal. The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Protein binding is slight (binding of perindoprilat to angiotensin converting enzyme is less than 30 %), but is concentration-dependent.

Perindoprilat is eliminated in the urine and the half-life of the unbound fraction is approximately 3 to 5 hours. Dissociation of perindoprilat bound to angiotensin converting enzyme leads to an “effective” elimination half-life of 25 hours, resulting in steady-state within 4 days.

After repeated administration, no accumulation of perindopril is observed.

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 also sections 4.2 “Posology and method of administration” and 4.4 “Special warnings and special precautions for use”).

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<[To be completed nationally]>

6.2 Incompatibilities

<[To be completed nationally]>

6.3 Shelf life

<[To be completed nationally]>

6.4 Special precautions for storage

<[To be completed nationally]>

6.5 Nature and contents of container

<[To be completed nationally]>

6.6 Instructions for use and handling < and disposal>

<[To be completed nationally]>

7. MARKETING AUTHORISATION HOLDER

<[See Annex I- to be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

<COVERSYL and associated names (see Annex I)>, <strength>, tablets

<[See Annex I - to be completed nationally]>

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<COVERSYL and associated names> 4 mg:

4 mg perindopril tert-butylamine salt, equivalent to 3.338 mg perindopril

Each tablet contains:

4 mg perindopril tert-butylamine salt, equivalent to 3.338 mg perindopril

<[To be completed nationally]>

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

<[To be completed nationally]>

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 and associated names> is taken once daily in the morning before a meal.

The dose should be individualised according to the patient profile (see 4.4 “Special warnings and special precautions for use”) and blood pressure response.

Hypertension:

< COVERSYL and associated names> may be used in monotherapy or in combination with other classes of antihypertensive therapy.

The recommended starting dose is 4 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 mg is recommended in such patients and the initiation of treatment should take place under medical supervision.

The dose may be increased to 8 mg once daily after one month of treatment. Symptomatic hypotension may occur following initiation of therapy with <COVERSYL and associated names>; 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 and associated names> (see section 4.4 “Special warnings and special precautions for use”).

In hypertensive patients in whom the diuretic cannot be discontinued, therapy with <COVERSYL and associated names> should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of <COVERSYL and associated names> 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 mg which may be progressively increased to 4 mg after one month then to 8 mg if necessary depending on renal function (see table below).

Symptomatic heart failure:

It is recommended that <COVERSYL and associated names>, 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 mg taken in the morning. This dose may be increased by increments of 2 mg at intervals of no less than 2 weeks to 4 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 4.4 “Special warnings and special precautions for use”).

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 and associated names>. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with <COVERSYL and associated names> (see section 4.4 “Special warnings and special precautions for use”).

Stable coronary artery disease:

<COVERSYL and associated names> should be introduced at a dose of 4 mg once daily for two weeks, then increased to 8 mg once daily, depending on renal function and provided that the 4 mg dose is well tolerated.

Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 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 |
|-------------------------------|-----------------------------|
| $Cl_{CR} \geq 60$ | 4 mg per day |
| $30 < Cl_{CR} < 60$ | 2 mg per day |
| $15 < Cl_{CR} < 30$ | 2 mg every other day |
| Haemodialysed patients * | |
| $Cl_{CR} < 15$ | 2 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 “Special warnings and special precautions for use” and 5.2 “Pharmacokinetic properties”)

Paediatric use:

Efficacy and safety of use in children has not been established. Therefore, use in children 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 4.6 “Pregnancy and lactation”).

4.4 Special warnings and special 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 “Interaction with other medicaments and other forms of interaction” and 4.8 “Undesirable effects”). 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 4.2 “Posology and method of administration” and 4.8 “Undesirable effects”). 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 normal saline. 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 and associated names>. 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 and associated names> may be necessary.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy:

As with other ACE inhibitors, < COVERSYL and associated names> 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 4.2 “Posology and method of administration”) 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 4.8 “Undesirable effects”).

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 and associated names> 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 and associated names> 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 and associated names> 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 and associated names> 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 and associated names> (see 4.8 Undesirable effects). This may occur at any time during therapy. In such cases, <COVERSYL and associated names> 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.

Angiotensin converting enzyme 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 4.3 Contraindications).

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 4.8 Undesirable effects).

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.

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 and associated names> 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. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, uncontrolled diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended.

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 4.5 Interaction with other medicinal products and other forms of interaction, Antidiabetics.)

Lithium:

The combination of lithium and perindopril is generally not recommended (see 4.5 Interaction with other medicinal products and other forms of interaction).

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 4.5 Interaction with other medicinal products and other forms of interaction).

Pregnancy and lactation:

(See section 4.3 “Contraindications” and section 4.6 “Pregnancy and lactation”).

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 drugs (NSAIDs) including aspirin ≥ 3 g/day:

The administration of a non-steroidal anti-inflammatory drug may reduce the antihypertensive effect of ACE inhibitors. Additionally, NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium and may result in a deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function such as those who are elderly or dehydrated.

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.

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.

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.

4.6 Pregnancy and lactation

Pregnancy:

<COVERSYL and associated names> should not be used during the first trimester of pregnancy. When a pregnancy is planned or confirmed, the switch to an alternative treatment should be initiated as soon as possible. Controlled studies with ACE inhibitors have not been done in humans, but in a

limited number of cases with first trimester exposure there do not appear to have been any malformations consistent with human foetotoxicity as described below.

Perindopril is contraindicated during the second and third trimesters of pregnancy.

Prolonged ACE inhibitor exposure 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 5.3 “Preclinical safety data”)

Should exposure to perindopril have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Lactation:

It is not known whether perindopril is excreted into human breast milk. Therefore the use of <COVERSYL and associated names> is not recommended in women who are breast-feeding.

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

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), including isolated reports.

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

Cardio-vascular disorders:

Common: hypotension and effects related to hypotension

Very rare: arrhythmia, angina pectoris, myocardial infarction and stroke, possibly secondary to excessive hypotension in high-risk patients (see 4.4 Special warnings and special precautions for use).

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 Special warnings and special precautions for use)

Skin and subcutaneous tissue disorders:

Common: rash, pruritus

Uncommon: angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see 4.4 Special warnings and special precautions for use).

Very rare: erythema multiforme

Musculoskeletal, connective tissue and bone 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:

Common: asthenia

Uncommon: sweating

Blood and the 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 Special warnings and special precautions for use).

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 normal saline 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 4.4 Special warnings and special precautions for use, Haemodialysis Patients.) 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

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:

<COVERSYL and associated names> 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 mg of <COVERSYL and associated names> 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 perindopril 8 mg (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 perindopril 8 mg 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 complete within 1 hour. Bioavailability is 65 to 70 %.

About 20 % of the total quantity of perindopril absorbed is converted into perindoprilat, the active metabolite. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The plasma half-life of perindopril is equal to 1 hour. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.

As ingestion of food decreases conversion to perindoprilat, hence bioavailability, <COVERSYL and associated names> should be administered orally in a single daily dose in the morning before a meal. The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Protein binding is slight (binding of perindoprilat to angiotensin converting enzyme is less than 30 %), but is concentration-dependent.

Perindoprilat is eliminated in the urine and the half-life of the unbound fraction is approximately 3 to 5 hours. Dissociation of perindoprilat bound to angiotensin converting enzyme leads to an “effective” elimination half-life of 25 hours, resulting in steady-state within 4 days.

After repeated administration, no accumulation of perindopril is observed.

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 also sections 4.2 “Posology and method of administration” and 4.4 “Special warnings and special precautions for use”).

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<[To be completed nationally]>

6.2 Incompatibilities

<[To be completed nationally]>

6.3 Shelf life

<[To be completed nationally]>

6.4 Special precautions for storage

<[To be completed nationally]>

6.6 Nature and contents of container

<[To be completed nationally]>

6.6 Instructions for use and handling < and disposal>

<[To be completed nationally]>

7. MARKETING AUTHORISATION HOLDER

<[See Annex I- to be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT