# ANNEX I

# LIST OF THE INVENTED NAMES OF THE MEDICINAL PRODUCTS, MARKETING AUTHORISATION HOLDERS, STRENGTHS, PHARMACEUTICAL FORMS, ROUTE OF ADMINISTRATION, PACKAGING AND PACKAGE SIZE

 

| Member State | Marketing Authorisation Holder Address | Marketing Authorisation Holder Tel and Fax | Invented name | Strength | Pharmaceutical form | Route of administration | Packaging | Package sizes |
|---|---|---|---|---|---|---|---|---|
| Austria | Servier Austria GmbH<br>Mariahilfer Strasse N°20/5<br>1070 Wien - Austria | Tel: 43 1 524 39 99<br>Fax: 43 1 524 39 99 | COVERSUM 2 mg | 2 mg | Tablets | Oral use | PVC/aluminium blister strip in carton box | 30 tablets |
| | | | COVERSUM 4 mg | 4 mg | Tablets | Oral use | | 30 tablets |
| Belgium | Servier Benelux S.A.<br>Bvd International, 57<br>1070 Bruxelles - Belgium | Tel: 32 2 529 43 11<br>Fax: 32 2 529 43 15 | COVERSYL 2 mg | 2 mg | Tablets | Oral use | NOT MARKETED | |
| | | | COVERSYL 4 mg | 4 mg | Tablets | Oral use | PVC/aluminium blister strip in carton box | 30 tablets & 30 tablets (unit dose) (*Only packages of 30 tablets are marketed*) |
| Denmark | Les Laboratoires Servier<br>22, rue Garnier<br>92200 Neuilly-sur-Seine<br>France | Tel: 33 1 55 72 60 00<br>Fax: 33 1 55 72 60 11 | COVERSYL | 2 mg | Tablets | Oral use | PVC/aluminium blister strip in carton box | 30 tablets |
| | | | COVERSYL | 4 mg | Tablets | Oral use | | 30 & 90 tablets |
| Finland | Les Laboratoires Servier<br>22, rue Garnier<br>92200 Neuilly-sur-Seine<br>France | Tel: 33 1 55 72 60 00<br>Fax: 33 1 55 72 60 11 | COVERSYL 2 mg | 2 mg | Tablets | Oral use | NOT MARKETED, blister 30 & 90 | |
| | | | COVERSYL 4 mg | 4 mg | Tablets | Oral use | PVC/aluminium blister strip in carton box | 30 & 90 tablets |
| | | | ACERTIL 2 mg | 2 mg | Tablets | Oral use | NOT MARKETED, blister 30 & 90 | |
| | | | ACERTIL 4 mg | 4 mg | Tablets | Oral use | NOT MARKETED, blister 30 & 90 | |
| France | Les Laboratoires Servier<br>22, rue Garnier<br>92200 Neuilly-sur-Seine<br>France | Tel: 33 1 55 72 60 00<br>Fax: 33 1 55 72 60 11 | COVERSYL 2 mg | 2 mg | Tablets | Oral use | PVC/aluminium blister strip in carton box | 30 tablets & 100 tablets (unit dose) |
| | | | COVERSYL 4 mg | 4 mg | Tablets | Oral use | | 30 tablets & 100 tablets (unit dose) |
| | | | ELECTAN 2 mg | 2 mg | Tablets | Oral use | NOT MARKETED | |
| | | | ELECTAN 4 mg | 4 mg | Tablets | Oral use | NOT MARKETED | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | PROCAPTAN 2 mg | 2 mg | Tablets | Oral use | NOT MARKETED | |
| | | | PROCAPTAN 2 mg | 4 mg | Tablets | Oral use | NOT MARKETED | |
| Germany | Les Laboratoires Servier<br>22, rue Garnier<br>92200 Neuilly-sur-Seine<br>France | Tel: 33 1 55 72 60 00<br>Fax: 33 1 55 72 60 11 | COVERSUM COR 2 mg | 2 mg | Tablets | Oral use | PVC/aluminium blister strip in carton box | 30, 50 & 100 tablets |
| | | | COVERSUM 4 mg | 4 mg | Tablets | Oral use | | 30, 50 & 100 tablets |
| | | | COVERAX COR 2 mg | 2 mg | Tablets | Oral use | NOT MARKETED | |
| | | | COVERAX 4 mg | 4 mg | Tablets | Oral use | NOT MARKETED | |
| Greece | Servier Hellas<br>Pharmaceuticals S.A.<br>181 Syngrou Ave.<br>171 21 N. Smyrni - Greece | Tel.: 30 210 93 91 000<br>Fax: 30 210 93 91 001 | COVERSYL | 2 mg | Tablets | Oral use | PVC/aluminium blister strip in carton box | 30 tablets |
| | | | COVERSYL | 4 mg | Tablets | Oral use | | 30 tablets |
| Ireland | Les Laboratoires Servier<br>22, rue Garnier<br>92200 Neuilly-sur-Seine<br>France | Tel: 33 1 55 72 60 00<br>Fax: 33 1 55 72 60 11 | COVERSYL tablets 2 mg | 2 mg | Tablets | Oral use | NOT MARKETED | |
| | | | COVERSYL tablets 4 mg | 4 mg | Tablets | Oral use | PVC/aluminium blister strip in carton box | 30 tablets |
| | | | Perindopril 2 mg tablets | 2 mg | Tablets | Oral use | NOT MARKETED | |
| | | | Perindopril 4 mg tablets | 4 mg | Tablets | Oral use | NOT MARKETED | |
| | | | Perindopril Servier 2 mg tablets | 2 mg | Tablets | Oral use | NOT MARKETED | |
| | | | Perindopril Servier 4 mg tablets | 4 mg | Tablets | Oral use | NOT MARKETED | |
| Italy | Les Laboratoires Servier<br>22, rue Garnier<br>92200 Neuilly-sur-Seine<br>France | Tel: 33 1 55 72 60 00<br>Fax: 33 1 55 72 60 11 | COVERSYL | 4 mg | Tablets | Oral use | PVC/aluminium blister strip in carton box | 14 tablets |
| Luxembourg | Servier Benelux S.A.<br>Bvd International, 57 | Tel: 32 2 529 43 11<br>Fax: 32 2 529 43 15 | COVERSYL 2 mg | 2 mg | Tablets | Oral use | NOT MARKETED | |

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|---|---|---|---|---|---|---|---|---|
| | 1070 Bruxelles - Belgium | | COVERSYL 4 mg | 4 mg | Tablets | Oral use | PVC/aluminium blister strip in carton box | 30 tablets |
| Netherlands | Les Laboratoires Servier<br>22, rue Garnier<br>92200 Neuilly-sur-Seine<br>France | Tel: 33 1 55 72 60 00<br>Fax: 33 1 55 72 60 11 | COVERSYL 2 mg | 2 mg | Tablets | Oral use | PVC/aluminium blister strip in carton box | 14 & 50 tablets |
| | | | COVERSYL 4 mg | 4 mg | Tablets | Oral use | | 30 & 50 tablets |
| Portugal | Servier Portugal - Especialidades Farmacêuticas, Lda<br>Av. Antonio Augusto Aguiar, 128 – 1069-133 Lisboa<br>Portugal | Tel.: +35 1 21 3122000<br>Fax: +35 1 21 3122090 | COVERSYL | 2 mg | Tablets | Oral use | NOT MARKETED | |
| | | | COVERSYL | 4 mg | Tablets | Oral use | PVC/aluminium blister strip in carton box | 14, 30, 60 tablets |
| Spain | Les Laboratoires Servier<br>22, rue Garnier<br>92200 Neuilly-sur-Seine –<br>France | Tel: 33 1 55 72 60 00<br>Fax: 33 1 55 72 60 11 | COVERSYL 4 mg | 4 mg | Tablets | Oral use | PVC/aluminium blister strip in carton box | 30 & 500 tablets |
| Sweden | Les Laboratoires Servier<br>22, rue Garnier<br>92200 Neuilly-sur-Seine<br>France | Tel: 33 1 55 72 60 00<br>Fax: 33 1 55 72 60 11 | COVERSYL | 2 mg | Tablets | Oral use | NOT MARKETED, PVC/aluminium blister strip in carton box 30 tablets | |
| | | | COVERSYL | 4 mg | Tablets | Oral use | NOT MARKETED, PVC/aluminium blister strip in carton box 30 & 90 tablets | |
| United-Kingdom | Les Laboratoires Servier<br>22, rue Garnier<br>92200 Neuilly-sur-Seine<br>France | Tel: 33 1 55 72 60 00<br>Fax: 33 1 55 72 60 11 | COVERSYL 2 mg | 2 mg | Tablets | Oral use | PVC/aluminium blister strip in carton box | 7, 14 ,28, 30, 56, 112 tablets |
| | | | COVERSYL 4 mg | 4 mg | Tablets | Oral use | | |
| | | | Perindopril tablets 2mg | 2 mg | Tablet | Oral use | | |
| | | | Perindopril tablets 4mg | 4 mg | Tablet | Oral use | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Iceland | Les Laboratoires Servier<br>22, rue Garnier<br>92200 Neuilly-sur-Seine<br>France | Tel: 33 1 55 72 60 00<br>Fax: 33 1 55 72 60 11 | COVERSYL | 2 mg | Tablets | Oral use | PVC/aluminium blister strip in carton box | 30 tablets |
| | | | COVERSYL | 4 mg | Tablets | Oral use | | 30 & 90 tablets |
| Norway | Les Laboratoires Servier<br>22, rue Garnier<br>92200 Neuilly-sur-Seine<br>France | Tel: 33 1 55 72 60 00<br>Fax: 33 1 55 72 60 11 | COVERSYL<br>2 mg | 2 mg | Tablets | Oral use | NOT MARKETED YET -30 tablets (blister) | |
| | | | COVERSYL<br>4 mg | 4 mg | Tablets | Oral use | NOT MARKETED YET -30 & 90 tablets (blister) | |

**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**

- Quality issues

No significant issues relating to Quality were identified.
The pharmaceutical particulars of the SPC were harmonised, except the sections, which need to be introduced nationally by the Member States when implementing the harmonised SPC (section 6).

- Efficacy issues

The divergences that previously existed across the SPCs of EU Member States included:

Section 4.1 Therapeutic indications

The MAH was requested to propose and scientifically justify a common EU wide approach as there were divergencies between national approvals regarding the wording and therefore the precise meaning of the indication in the Member States:

- Hypertension (essential hypertension, arterial hypertension, hypertension, hypertension with more or less details regarding the type of hypertension. One MS has also the following precision: treatment of essential hypertension as monotherapy or combined with thiazides type diuretics.)
- Heart failure (heart failure, congestive heart failure, mild to moderate congestive heart failure, congestive heart failure as adjunctive/in combination with diuretics and/or digitalis, left ventricular heart insufficiency. In one MS a difference between congestive heart failure and severe heart failure has been made.)

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of COVERSYL, the following was considered to be the most suitable harmonised Section 4.1 indications text:

*"Hypertension*

*Treatment of hypertension*

*Heart Failure*

*Treatment of symptomatic heart failure"*

Section 4.2 Posology and method of administration

The 1 mg strength is available in 3 Member States in the following indication: severe heart failure, in elderly patients with diuretic treatment and severe heart insufficiency. In these Member States, the initial dose is 1mg/day.
The 4 mg starting dose has been approved in 14 of the 17 Member States. The one-month duration of titration (strictly one month or 3 to 4 weeks) has been approved in 14 of the 17 Member States. Only 2 Member States have longer duration of titration (6 to 8 weeks) and 1 Member States has no proposal. However, considering usual clinical practice, the duration of titration should be not be limited to a spcific interval e.g. 4 weeks.

Patients already treated with diuretics, as well as patients with renovascular hypertension or elderly, have been identified as being associated with a higher hypotensive risk related to ACE inhibitors use. They may thus require a lower perindopril starting-dose of 2 mg as proposed in most of the SPCs.

 

As the 2 mg starting dose was shown to be well tolerated with respect to blood pressure reduction, the heart failure treatment should be started with the 2 mg dose, whatever the conditions.
Regarding time of administration, the morning dose regimen reduces blood pressure over 24 hours whereas this control is not achieved with the evening dose (no significant fall in blood pressure in the interval between 18 and 24 hours after the dose). Since food and time affect absorption of perindoprilat, the tablets may be administered orally in a single daily dose in the morning before meals.

In patients with renal impairment dose adjustment should be based on creatinine clearance values but these are not identical in all Member States as well as the recommended dose.
Overall, it is considered that there is no clinical experience concerning the effects of perindopril on renal haemodynamics and tubular function in cyclosporine-treated hypertensive renal allograft recipients.
Based on the provided data, the SPC should state that no dosage adjustment is necessary in patients with hepatic impairment. However, as for the other ACE inhibitors, a cross-reference to sections 4.4. "Special warnings and special precautions for use" and 5.2 "Pharmacokinetic properties" should be added, detailing results of the studies performed in these patients.
In elderly, dosage adjustment should be done according to blood pressure response and to renal function. Efficacy and safety of use in children has not been established. Therefore, use in children is not recommended.

After an assessment of the documentation provided by the MAH to substantiate scientifically the divergent information across member states and justify a proposed common wording, especially with regard to the recommended starting dose in hypertension, and the recommendations on dosage in renal impairment and paediatric use, and following an evaluation of the current EU-wide clinical practices relating to the use of COVERSYL, the wording considered to be the most suitable harmonised text for Section 4.2 Posology was agreed with the MAH (see Annex III).

- Safety issues

The divergencies that previously existed across the SPCs of EU Member States included:

Section 4.3 Contraindications

Different contra-indications have been approved in the EU Member States. Currently, the following contra-indications have been included in the SPCs in some but not all Member States:
- hypersensitivity to perindopril or to any other ACE inhibitor;
- history of angioneurotic oedema;
- oedema related to previous treatment with an ACE inhibitor;
- hereditary idiopathic angioneurotic oedema;
- bilateral renal artery stenosis or single functioning kidney;
- children;
- pregnancy, lactation.

Some of them are commonly mentioned in most SPCs like the following:
- Hypersensitivity to perindopril or to any other ACE inhibitor,
- History of angioedema related to previous treatment with an ACE inhibitor,
- Second and third trimesters of pregnancy (see 4.6"Pregnancy and lactation"), lactation.

The below listed contra-indications are less frequently mentioned, only in a few SPCs:
- Hypersensitivity to any component of COVERSYL,
- Hereditary idiopathic angioedema,
- Bilateral renal artery stenosis or single functioning kidney,
- Status post-renal transplantation,
- Severe renal function disorders,
- Dialysis,
- Aortic or mitral valve stenosis or hypertrophic cardiomyopathy
- Primary hyperaldosteronism,

- Primary liver disease or liver failure,
- Untreated, decompensated congestive heart failure,
- Hyperkaliemia,
- Children,
- Combination with potassium sparing diuretics, potassium salts, lithium.

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of COVERSYL, the following was considered to be the most suitable harmonised Section 4.3 Contraindications text:

- *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").*

Section 4.4. Special warnings and precautions for use

After assessment of the documentation provided by the MAH to substantiate scientifically the divergent information across member states and justify a proposed common wording and following an evaluation of the current EU-wide clinical practices relating to the use of COVERSYL, the most suitable harmonised Section 4.4 Special Warnings and Precautions for Use text was approved (See Annex III).

All other sections of the SPC were harmonised as a result of the referral procedure (except see below; Administrative Issues).

- Administrative issues

Other sections of the SPC which were not harmonised and which need to be introduced nationally by the Member States when implementing the harmonised SPC are the following: MAH, MA number, date of first authorisation/renewal of authorisation, Date of revision of the text.

**Benefit/Risk considerations**

Based on the documentation submitted by the MAH and the scientific discussion within the Committee, the CPMP considered that the benefit/risk ratio of COVERSYL is favourable for use relating to treatment of hypertension and symptomatic heart failure.

**GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS**

Whereas,

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics,
- the Summary of Products Characteristic proposed by the Marketing Authorisation Holders has been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CPMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics is set out in Annex III of the Opinion. The major divergences identified at the start of the referral have been resolved.

## ANNEX III

## SUMMARY OF PRODUCT CHARACTERISTICS

**NOTE:**
**THIS SPC IS THE ONE THAT WAS ANNEXED TO THE COMMISSION DECISION CONCERNING THIS REFERRAL; THE TEXT WAS VALID AT THAT TIME.**

**IT IS NOT SUBSEQUENTLY MAINTAINED OR UPDATED BY THE EMEA, AND THEREFORE MAY NOT NECESSARILY REPRESENT THE CURRENT TEXT.**

 

## 1. NAME OF THE MEDICINAL PRODUCT

*<COVERSYL and associated names (see annex I)>, <strength>,* tablets
*[To be implemented nationally]*

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<COVERSYL and associated names> 2 mg:
2 mg perindopril tert-butylamine salt, equivalent to 1.669 mg perindopril

<COVERSYL and associated names)> 4 mg:
4 mg perindopril tert-butylamine salt, equivalent to 3.338 mg perindopril

Each tablet contains:
2 mg perindopril tert-butylamine salt, equivalent to 1.669 mg perindopril
4 mg perindopril tert-butylamine salt, equivalent to 3.338 mg perindopril
*[To be implemented nationally]*

For excipients, see Section 6.1.

## 3. PHARMACEUTICAL FORM

Tablets.
*[To be implemented nationally]*

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Hypertension

Treatment of hypertension

Heart Failure

Treatment of symptomatic heart failure

### 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”).

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

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 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 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 ACEinhibitor 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 inhibitor***s*** 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 (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*s* 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.

### 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.

### 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 implemented nationally]>*

### 6.2 Incompatibilities

*<[To be implemented nationally]>*

### 6.3 Shelf life

*<[To be implemented nationally]>*

### 6.4 Special precautions for storage

*<[To be implemented nationally]>*

### 6.5 Nature and contents of container

*<[To be implemented nationally]>*

### 6.6 Instructions for use and handling

*<[To be implemented nationally]>*

## 7. MARKETING AUTHORISATION HOLDER

*<[See Annex 1 - to be implemented nationally]>*

## 8. MARKETING AUTHORISATION NUMBER

*<[To be implemented nationally]>*

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

*<[To be implemented nationally]>*

## 10. DATE OF (PARTIAL) REVISION OF THE TEXT

 