

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Coversyl 4 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 4 mg of Perindopril tert-butylamine salt.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, rod-shaped tablets, scored on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Essential Hypertension: in the treatment of essential hypertension as monotherapy or combined with thiazide type diuretics.
- Congestive heart failure: in the treatment of congestive heart failure as adjunctive therapy with non-potassium sparing diuretics and, where appropriate digitalis. Treatment with Coversyl should always be initiated under medical supervision (for severe heart failure, it should be initiated in hospital).

4.2 Posology and method of administration

Oral Administration

Adults

Essential hypertension: The usual initial dosage is 4 mg given as a single dose in the morning which may be increased after one month of treatment to 8 mg if necessary. The long-term maintenance regimen is a single daily dose.

In the case of previous diuretic treatment, the diuretic should be discontinued for at least 3 days before commencing Perindopril and reinstated subsequently if necessary. If the diuretic therapy cannot be discontinued, the initial dose of Perindopril should be 2 mg.

Congestive heart failure: The treatment should be initiated under close medical supervision with a recommended starting dose of 2 mg as a single dose in the morning which in most cases, in the absence of symptomatic hypotension can be increased to 4 mg daily.

In severe heart failure, treatment should be initiated in hospital.

Elderly: The usual initial dose of 2 mg once daily may be increased after one month of treatment to 4 mg if necessary.

Patients with Renal Insufficiency: The following dosages are recommended in patients with renal insufficiency.

<i>Creatinine Clearance</i>	<i>Recommended Dose</i>
30 –60 ml /min	2 mg /day
15 – 30 ml / min	2 mg every other day
< 15 ml / min	2 mg on the day of dialysis

Children: Safety and efficacy of Perindopril have not been established and therefore its use is not recommended in this age-group.

4.3 Contraindications

- Aortic stenosis, outflow tract obstruction, bilateral renal artery stenosis.
- Hypersensitivity to any of the ingredients.
- Pregnancy.
- History of angioneurotic oedema relating to previous treatment with an ACE inhibitor.

4.4 Special warnings and precautions for use

- Increase in blood urea nitrogen and plasma creatinine levels have occasionally been seen, usually with co-prescription of diuretics. This may necessitate reduction in dosage of both treatments.
- Symptomatic hypotension may occur particularly in patients with salt and/or volume depletion usually as a result of previous diuretic therapy. Any electrolyte or fluid imbalance should be corrected preferably before initial dose of the product. Careful medical supervision is necessary for a period after dosing.
- In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with ACE inhibitors. Such patients should be kept under close medical supervision. If such hypotension becomes symptomatic, a reduction of dose or discontinuation of Coversyl may become necessary.
 - Administration of 2mg of Coversyl to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure.
- The pharmacological action of Perindopril may prevent the normal body response to induction of hypotension during anaesthesia or shock. Such depression of blood pressure should be corrected by a volume expansion preferably with normal saline.
- Angioneurotic oedema has been reported rarely with ACE inhibitors including Coversyl. In some cases symptoms have been observed up to 2 years after initiation of treatment. Such reactions should be regarded as an indication to discontinue therapy immediately and the patient closely monitored.
 - Where swelling is confined to the face, lips and mouth, the condition will usually resolve without further treatment, although antihistamines may be useful in relieving symptoms. These patients should be followed carefully until the swelling has resolved. However, where there is involvement of the tongue, glottis or larynx, likely to cause airways obstruction, appropriate therapy such as subcutaneous adrenaline (0.5 ml 1: 1000) should be administered promptly when indicated.
 - Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (*see also "Contra-indications"*).
 - Other hypersensitivity reactions have been reported.
- Coversyl should be used with caution in those known to be hypersensitive to other ACE inhibitors.
- Coversyl combines particularly well with a non-potassium sparing diuretic. As Coversyl decreases aldosterone production and therefore may tend to increase serum potassium, combination with a potassium-sparing diuretic or potassium supplements is not recommended.

- Coversyl may be used in patients with renovascular hypertension while awaiting corrective surgery or if this type of surgery is not possible. Treatment however must be cautiously begun in order to prevent an abrupt drop in blood pressure and/or functional and possibly acute renal failure. Renal function must be closely monitored in these patients.
- Patients haemodialysed using highflux polyacrylonitrile (“AN69”) membranes are highly likely to experience anaphylactoid reactions if they are treated with ACE inhibitors. This combination should therefore be avoided, either by use of alternative antihypertensive drugs or alternative membranes for haemodialysis.

4.5 Interaction with other medicinal products and other forms of interaction

Other antihypertensive agents, eg. β -adrenoceptor blockers, methyldopa, diuretics and calcium antagonists may supplement the hypotensive effects of Perindopril. Ganglionic and adrenergic blocking drugs should only be combined with Perindopril under careful supervision.

Concomitant propranolol may reduce the bioavailability of Perindopril but this does not appear to be clinically significant.

- Concomitant therapy with lithium may increase the serum lithium concentrations.
- Concomitant administration of ACE-inhibitors and anti-diabetic medicines (insulin, oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with the risk of hypoglycaemia. This phenomenon may be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

4.6 Pregnancy and lactation

Use in Pregnancy: Animal experiments have shown maternal and foetal toxicity at the highest doses in rats and rabbits but not in monkeys. Neither embryotoxicity nor teratogenicity was observed.

Oligohydramnios, neonatal hypotension and anuria have been reported following use of ACE inhibitors in the 2nd and 3rd trimester of pregnancy.

Pregnancy should be excluded before starting Coversyl treatment. Women treated with an ACE inhibitor should change treatment on becoming aware of pregnancy, according to their doctor’s advice.

Breast Feeding Mothers: It is not known if perindopril is excreted in breast milk. Coversyl should not be used during lactation.

4.7 Effects on ability to drive and use machines

As a result of different reactions in individual cases, the ability to drive vehicles or to operate machinery may be impaired.

4.8 Undesirable effects

Side effects are infrequent and may include headache, dizziness, mood / sleep disturbances, fatigue, cough, gastrointestinal disturbances, localised skin rashes and disturbances of taste. Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely with ACE inhibitors including Coversyl (*see special warnings*).

4.9 Overdose

To date, no case of overdosage has been reported. Signs and symptoms expected in case of overdosage would be related to hypotension and should be relieved by intravenous infusion of isotonic saline solution. Gastric lavage should be considered.

Perindopril is dialysable (70 ml/min).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Perindopril is an inhibitor of the enzyme which converts angiotensin I into angiotensin II (ACE inhibitor).

The converting enzyme or kininase is an exopeptidase which converts angiotensin I into vasoconstrictive angiotensin II and degrades vasodilatory bradykinin into an inactive heptapeptide. Perindopril acts through its active metabolite, perindoprilat, the other metabolites being inactive.

Systemic Hypertension:

Efficacy is sustained throughout the 24 hour cycle. Maximum antihypertensive effect is reached 4 to 6 hours after a single perindopril dose.

The decrease in blood pressure is rapidly achieved; in responding patients, normalisation is achieved within 1 month and is sustained.

Discontinuation of treatment does not lead to a rebound effect.

In man, perindopril has been confirmed to demonstrate vasodilatory properties, to restore elastic properties of the arterial blood vessels and to decrease left ventricular hypertrophy.

5.2 Pharmacokinetic properties

Perindopril is rapidly absorbed and de-esterified to the diacid perindoprilate, an angiotensin converting enzyme inhibitor, which reaches peak plasma levels at 3-4 hours. With repeated dosing a steady state is achieved within 4 days. Elimination is via the kidney.

5.3 Preclinical safety data

No findings in the preclinical testing which could be of relevance for the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Lactose
Hydrophobic colloidal silica
Magnesium stearate

6.2 Incompatibilities

None known.

6.3 Shelf Life

The shelf life expiry date for this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC/Aluminium blister strip of 30 tablets packaged in carton box.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special instructions.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

PRIMECROWN Ltd
28 Sarum Complex
Uxbridge
Middlesex UB8 2RZ
England

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1071/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 November 2002