Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Perindopril 2mg film-coated Tablets
Perindopril 4mg film-coated Tablets
Perindopril 8mg film-coated Tablets

(perindopril tert-butylamine)

UK/H/1118/01-03/DC

UK licence numbers: PL 15764/0033-0035

Strandhaven Limited

LAY SUMMARY

On 21st February 2008, the MHRA granted Strandhaven Limited Marketing Authorisations (licences) for the medicinal products Perindopril 2mg, 4mg, and 8mg film-coated Tablets (PL 15764/0033-0035, UK/H/1118/01-03/DC). These are prescription-only medicines (POM) that are used to treat high blood pressure (hypertension); heart failure (a condition where the heart is unable to pump enough blood to meet the body's needs); and to reduce the risk of cardiac events in patients with stable coronary artery disease (a condition where the blood supply to the heart is reduced or blocked).

The active ingredient, perindopril, works by widening the blood vessels making it easier for your heart to pump blood through them.

The test products were considered to be generic versions of the reference products Coversyl 2mg, 4mg, and 8mg Tablets (PL 05815/0001, 0002 & 0023, Les Laboratories Servier) based on the data submitted by Strandhaven Limited.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Perindopril 2mg, 4mg, and 8mg film-coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.

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Module 1

Information About Initial Procedure

Product Name	Perindopril 2mg film-coated Tablets Perindopril 4mg film-coated Tablets Perindopril 8mg film-coated Tablets
Type of Application	Generic, Article 10.1
Active Substance	Perindopril tert-butylamine
Form	Film-coated Tablets
Strength	2mg, 4mg, and 8mg
MA Holder	Strandhaven Ltd 600 High Road Seven Kings Ilford Essex IG3 8BS UK
Reference Member State (RMS)	UK
Concerned Member State (CMS)	Cyprus
Procedure Number	UK/H/1118/01-03/DC
Timetable	Day 131 – 18th January 2008

Module 2

Summary of Product Characteristics

Perindopril 2mg film-coated tablets

1 NAME OF THE MEDICINAL PRODUCT

Perindopril 2mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2mg of perindopril tert-butylamine.
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet
White to off-white, circular, biconvex film-coated tablets

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

For oral use.

It is recommended that Perindopril 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 precautions for use”) and blood pressure response.

Hypertension

Perindopril 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 Perindopril; 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 Perindopril (see section 4.4 “Special warnings and precautions for use”).

In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Perindopril should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Perindopril 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 Perindopril, 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 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 Perindopril. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with Perindopril (see section 4.4 “Special warnings and precautions for use”).

Stable coronary artery disease

Perindopril 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 for 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 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 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 medicinal products 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 Perindopril. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of Perindopril may be necessary.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

As with other ACE inhibitors, Perindopril 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 Perindopril 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 perindopril 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 Perindopril 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 perindopril 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 perindopril (see 4.8 Undesirable effects). This may occur at any time during therapy. In such cases, Perindopril 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 (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, Perindopril 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/Anaesthetics

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

Perindopril 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 fetotoxicity 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 fetotoxicity (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 Perindopril 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 EUROPA study, only serious adverse events were collected. Few patients experienced serious adverse events: 16 (0.3%) of the 6122 Coversyl patients and 12 (0.2%) of the 6107 placebo patients. In Coversyl-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 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

Pharmacotherapeutic group: ACE inhibitor, plain

ATC code: C09A A04

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

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

Hypertension

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

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

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

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

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

Discontinuation of treatment does not lead to a rebound effect.

Perindopril reduces left ventricular hypertrophy.

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

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

Heart failure

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

Studies in patients with heart failure have demonstrated:

- decreased left and right ventricular filling pressures,
- reduced total peripheral vascular resistance,
- increased cardiac output and improved cardiac index.

In comparative studies, the first administration of 2 mg of perindopril 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 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, perindopril 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 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 fetal development, resulting in fetal death and congenital effects in rodents and rabbits: renal lesions and an increase in peri- and postnatal mortality have been observed.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Mannitol
Sodium starch glycollate
Sodium carbonate anhydrous
Hypromellose
Macrogol-6000
Siliconised talc
Magnesium stearate

Seal-coating

Hypromellose

Film-coating

Opadry AMB OY-B-28920 white

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25ºC.

Store in the original package.

6.5 Nature and contents of container

Blister of 3 ply Alu-Alu laminated foil and plain aluminium foil
Perindopril 2mg Film-coated Tablets are available in packs of 30 tablets

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Strandhaven Ltd t/a Somex Pharma
600 High Road,
Seven Kings,
Ilford, Essex,
IG3 8BS
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 15764/0033

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/02/2008

10 DATE OF REVISION OF THE TEXT

21/02/2008

Perindopril 4mg film-coated tablets

1 NAME OF THE MEDICINAL PRODUCT

Perindopril 4mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 4mg of perindopril tert-butylamine.
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet
White to off-white, barrel-shaped, biconvex film-coated tablets. One side embossed with central break line and 'PR' and '4' on either side of the break line and central break line on the other side.

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

For oral use.

It is recommended that Perindopril 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 precautions for use") and blood pressure response.

Hypertension

Perindopril 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 Perindopril; 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 Perindopril (see section 4.4 "Special warnings and precautions for use").

In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Perindopril should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Perindopril 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 Perindopril, 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 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 Perindopril. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with Perindopril (see section 4.4 “Special warnings and precautions for use”).

Stable coronary artery disease

Perindopril 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 for 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 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 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 medicinal products 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 Perindopril. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of Perindopril may be necessary.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

As with other ACE inhibitors, Perindopril 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 Perindopril 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 perindopril 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 Perindopril 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 perindopril 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 perindopril (see 4.8 Undesirable effects). This may occur at any time during therapy. In such cases, Perindopril 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 (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, Perindopril 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/Anaesthetics

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

Perindopril 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 fetotoxicity 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 fetotoxicity (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 Perindopril 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 EUROPA study, only serious adverse events were collected. Few patients experienced serious adverse events: 16 (0.3%) of the 6122 Coversyl patients and 12 (0.2%) of the 6107 placebo patients. In Coversyl-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 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

Pharmacotherapeutic group: ACE inhibitor, plain

ATC code: C09A A04

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

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

Hypertension

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

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

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

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

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

Discontinuation of treatment does not lead to a rebound effect.

Perindopril reduces left ventricular hypertrophy.

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

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

Heart failure

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

Studies in patients with heart failure have demonstrated:

- decreased left and right ventricular filling pressures,
- reduced total peripheral vascular resistance,
- increased cardiac output and improved cardiac index.

In comparative studies, the first administration of 2 mg of perindopril 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 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, perindopril 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 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 fetal development, resulting in fetal death and congenital effects in rodents and rabbits: renal lesions and an increase in peri- and postnatal mortality have been observed.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Mannitol
Sodium starch glycollate
Sodium carbonate anhydrous
Hypromellose
Macrogol-6000
Siliconised talc
Magnesium stearate

Seal-coating

Hypromellose

Film-coating

Opadry AMB OY-B-28920 white

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25ºC.

Store in the original package.

6.5 Nature and contents of container

Blister of 3 ply Alu-Alu laminated foil and plain aluminium foil
Perindopril 4mg Film-coated Tablets are available in packs of 30 tablets

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Strandhaven Ltd t/a Somex Pharma
600 High Road,
Seven Kings,
Ilford, Essex,
IG3 8BS
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 15764/0034

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/02/2008

10 DATE OF REVISION OF THE TEXT

21/02/2008

Perindopril 8mg film-coated tablets

1 NAME OF THE MEDICINAL PRODUCT

Perindopril 8mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 8mg of perindopril tert-butylamine.
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet
White to off-white, barrel-shaped, biconvex film-coated tablets. One side embossed with central break line and 'PR' and '8' on either side of the break line and central break line on the other side.

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

For oral use.

It is recommended that Perindopril 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 precautions for use") and blood pressure response.

Hypertension

Perindopril 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 Perindopril; 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 Perindopril (see section 4.4 "Special warnings and precautions for use").

In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Perindopril should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Perindopril 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 Perindopril, 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 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 Perindopril. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with Perindopril (see section 4.4 “Special warnings and precautions for use”).

Stable coronary artery disease

Perindopril 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 for 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
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$15 < Cl_{CR} < 30$	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 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 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 medicinal products 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 Perindopril. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of Perindopril may be necessary.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

As with other ACE inhibitors, Perindopril 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 Perindopril 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 perindopril 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 Perindopril 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 perindopril 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 perindopril (see 4.8 Undesirable effects). This may occur at any time during therapy. In such cases, Perindopril 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 (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, Perindopril 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/Anaesthetics

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

Perindopril 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 fetotoxicity 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 fetotoxicity (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 Perindopril 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 EUROPA study, only serious adverse events were collected. Few patients experienced serious adverse events: 16 (0.3%) of the 6122 Coversyl patients and 12 (0.2%) of the 6107 placebo patients. In Coversyl-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 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

Pharmacotherapeutic group: ACE inhibitor, plain

ATC code: C09A A04

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

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

Hypertension

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

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

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

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

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

Discontinuation of treatment does not lead to a rebound effect.

Perindopril reduces left ventricular hypertrophy.

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

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

Heart failure

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

Studies in patients with heart failure have demonstrated:

- decreased left and right ventricular filling pressures,
- reduced total peripheral vascular resistance,
- increased cardiac output and improved cardiac index.

In comparative studies, the first administration of 2 mg of perindopril 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 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, perindopril 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 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 fetal development, resulting in fetal death and congenital effects in rodents and rabbits: renal lesions and an increase in peri- and postnatal mortality have been observed.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Mannitol
Sodium starch glycollate
Sodium carbonate anhydrous
Hypromellose
Macrogol-6000
Siliconised talc
Magnesium stearate

Seal-coating

Hypromellose

Film-coating

Opadry AMB OY-B-28920 white

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25ºC.

Store in the original package.

6.5 Nature and contents of container

Blister of 3 ply Alu-Alu laminated foil and plain aluminium foil
Perindopril 8mg Film-coated Tablets are available in packs of 30 tablets

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Strandhaven Ltd t/a Somex Pharma
600 High Road,
Seven Kings,
Ilford, Essex,
IG3 8BS
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 15764/0035

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21/02/2008

10 DATE OF REVISION OF THE TEXT

21/02/2008

Module 3

Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

PERINDOPRIL 2MG, 4MG AND 8MG FILM-COATED TABLETS
(perindopril tert-butylamine)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

The information in this leaflet refers to Perindopril Film-coated Tablets available in 2mg, 4mg and 8mg strengths.

1. WHAT PERINDOPRIL TABLETS ARE AND WHAT THEY ARE USED FOR

Perindopril belongs to a class of medicines called ACE inhibitors. These work by widening the blood vessels making it easier for your heart to pump blood through them.

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

2. BEFORE YOU TAKE PERINDOPRIL TABLETS

Do not take Perindopril Tablets:
- If you are allergic (hypersensitive) to perindopril or any other ACE inhibitor, or to any of the other ingredients in the tablets (see section 6 for a list of ingredients)
- If you have had symptoms such as wheezing, swelling of the face, tongue or throat, intense itching, skin rashes, fainting or dizziness with previous ACE inhibitor treatment or have these symptoms in other circumstances (this is a condition called angioedema)
- If you are pregnant or breast-feeding.
- Perindopril Tablets should not be given to children

If you think any of the above situations applies to you, do not take the tablets. Consult your doctor and take his/her advice.

Take special care with Perindopril Tablets
You should check with your doctor BEFORE taking Perindopril Tablets:
- If you have aortic stenosis (narrowing of the main blood vessel leading from the heart) or hypertrophic cardiomyopathy (cardiac muscle disease) or renal artery stenosis (narrowing of the artery supplying the kidney with blood)
- If you have any other heart or liver or kidney problems, or if you are receiving dialysis
- If you suffer from a collagen disease such as systemic lupus erythematosus of scleroderma
- If you are on a salt restricted diet or use salt substitutes which contain potassium

- If you suffer from diabetes which is not well controlled

You should also inform your doctor or the medical staff that you are taking Perindopril Tablets:

- If you undergo anaesthesia and/or surgery
- If you have suffered from recent diarrhoea or vomiting
- If you are going to have desensitisation treatment to reduce the effects of an allergy to bee or wasp stings
- If you are to undergo LDL apheresis (which is removal of cholesterol from your blood by a machine)

Taking other medicines

In order to avoid possible interactions between different medicines, please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Tell your doctor if you are taking any of the following to be sure that it is safe to take Perindopril at the same time:

- Other medicines for treating high blood pressure including diuretics (water tablets)
- Potassium-sparing diuretics (eg spironolactone, triamterene, or amiloride); potassium supplements and potassium-containing salt substitutes
- Medicines for the treatment of diabetes (insulin) or tablets to lower blood sugar
- Lithium for mania or depression
- Medicines for the treatment of mental disorders such as depression, anxiety, schizophrenia or other psychoses
- Allopurinol used for the treatment of gout
- Immunosuppressants used for the treatment of auto-immune disorders (eg rheumatoid arthritis) or following transplant surgery
- Procainamide, a treatment for irregular heartbeat
- Non-steroidal anti-inflammatory drugs (NSAIDs) for pain relief, including aspirin
- Medicines used for the treatment of low blood pressure, shock or asthma (eg ephedrine, noradrenaline or adrenaline)
- Vasodilators including nitrates (products that make the blood vessels become wider)
- Heparin (used to thin the blood)

Ask your doctor if you are not sure what these medicines are.

Taking Perindopril Tablets with food and drink

It is recommended that you take Perindopril Tablets before a meal. This helps reduce the effect of food on the way in which the medicine works. Drinking alcohol with Perindopril Tablets may make you feel dizzy or light-headed. You should check with your doctor whether drinking is advisable for you.

Pregnancy and breast-feeding

- Pregnancy
  You should not take Perindopril Tablets if you are pregnant, planning to become pregnant or if you suspect you are pregnant.
- Breast-feeding
  You should not take Perindopril Tablets if you are breast-feeding.

Driving and using machines

You may experience dizziness or weariness while taking Perindopril. If this occurs do not drive or use machinery. You should talk to your doctor.

3. HOW TO TAKE PERINDOPRIL TABLETS

Always take Perindopril Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Your doctor will decide on the right starting dose for you and any increase in the dose, depending on your condition, and whether you are taking any other medicines. Do not change your dose unless your doctor tells you to. Perindopril Tablets may be used on their own or with other medicines which lower blood pressure.

How to take your tablets:
Take your tablet(s) with a glass of water in the morning, preferably at the same time each day before a meal.
If you are taking water tablets (diuretics), your doctor may decide to reduce or even discontinue these at the beginning of your treatment with Perindopril Tablets.

The usual doses of Perindopril Tablets are as follows:

High blood pressure
Adults: the usual starting and maintenance dose for treatment is 4 mg once a day. After a month, this can be increased to 8 mg a day (the maximum recommended dose).
Elderly (65 years or over): the usual starting dose is 2 mg once a day. After a month, this can be increased to 4 mg a day and if necessary to 8mg a day.

Heart failure
Adults, including the elderly: treatment should be started under close medical supervision with 2 mg once a day. After 2 weeks it can be increased to 4 mg once a day if required.

Stable coronary artery disease
Adults: the usual starting dose is 4 mg once daily. After 2 weeks and if 4 mg is well tolerated, this can be increased to 8 mg once daily.
Elderly (65 years or over): the usual starting dose is 2 mg once daily. After one week, this can be increased to 4 mg once daily and after a further week to 8 mg once daily.

Your doctor may give you a blood test to check that your kidneys are working properly before increasing the dose to 8 mg.
Treatment for these conditions is usually life-long.

Perindopril is not suitable for use in children.

If you take more tablets than you should:
If you have taken too many tablets, contact your nearest hospital accident and emergency department or tell your doctor IMMEDIATELY.

If you forget to take your tablets:
It is important to take your medicine every day. However, if you forget to take one or more doses, take another as soon as you remember and then go on as prescribed. Do not take a double dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Perindopril Tablets can cause side effects, although not everybody gets them. Do not be alarmed by the list below, you may not get any of them.

Stop taking your tablets at once and TELL YOUR DOCTOR IMMEDIATELY if you experience any of the following effects of angioedema:
- swelling of the face, lips, mouth, tongue or throat, difficulty in breathing
- dizziness or fainting
- unusually fast or irregular heartbeat

This is an uncommon but serious reaction which can occur with all drugs of this type (ACE inhibitors). It must be treated immediately, usually in hospital

Common (probably affecting up to 1 in 10 people)
- Cough, shortness of breath
- Light-headedness due to low blood pressure (particularly after the first few doses, if the dose is increased or when water tablets are also taken)
- Headache, dizziness, vertigo, tiredness, pins and needles, muscle cramps, visual disturbances (eg blurred vision, eye pain) tinnitus (sensation of noises in the ears)
- Nausea, vomiting, abdominal pain, changes in your sense of taste, feeling of indigestion, diarrhoea, constipation
- Skin rashes, itching

Uncommon (probably affecting less than 1 in 100 people)
- Changes in mood or sleep
- Bronchospasm (tightening of the

chest, wheezing and shortness of breath)
- Dry mouth
- Kidney problems
- Impotence
- Sweating
- Angioedema (see above).

Very rare (probably affecting less than 1 in 10,000 people)
- Confusion
- Irregular heartbeat, angina, heart attack and stroke (these have been reported with ACE inhibitors in association with low blood pressure)
- Eosinophilic pneumonia (a rare type of pneumonia), rhinitis (blocked up or runny nose)
- Pancreatitis (inflammation of the pancreas)
- Hepatitis (inflammation of the liver)
- Erythema multiforme (skin reaction like an allergy)
- Kidney failure

Changes in the blood: your doctor may decide to carry out blood tests at intervals to monitor this.

If you experience any of the above symptoms and they persist or become troublesome, you should tell your doctor.
If you notice any other effects not mentioned in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE PERINDOPRIL TABLETS

Store below 25°C.
Store in the original package
Keep out of the reach and sight of children.

Do not use Perindopril Tablets after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Perindopril Tablets contain:

- The active substance is perindopril tert-butylamine. Each tablet contains 2, 4 or 8mg of perindopril tert-butylamine.
- The other ingredients are mannitol, sodium starch glycollate, sodium carbonate anhydrous, hypromellose, macrogol-6000, siliconised talc and magnesium stearate
- The tablet coating contains hypromellose and Opadry white

What Perindopril Tablets look like and contents of the pack
The 2mg tablets are circular, white to off-white, plain on both sides
The 4mg tablets are barrel-shaped, white to off-white, with a break line on both sides and 'PR' and '4' on one side.
The 8mg tablets are barrel-shaped, white to off-white, with a break line on both sides and 'PR' and '8' on one side.

The tablets are packed in blister strips and are available in cartons containing 30 tablets.

This medicinal product is authorised in the Member States of the EEA under the following names:
Perindopril 2mg Film-coated Tablets, Perindopril 4mg Film-coated Tablets and Perindopril 8mg Film-coated Tablets.

Marketing Authorisation Holder:
Strandhaven Ltd trading as Somex Pharma, Seven Kings, Ilford, Essex, IG3 8BS, UK

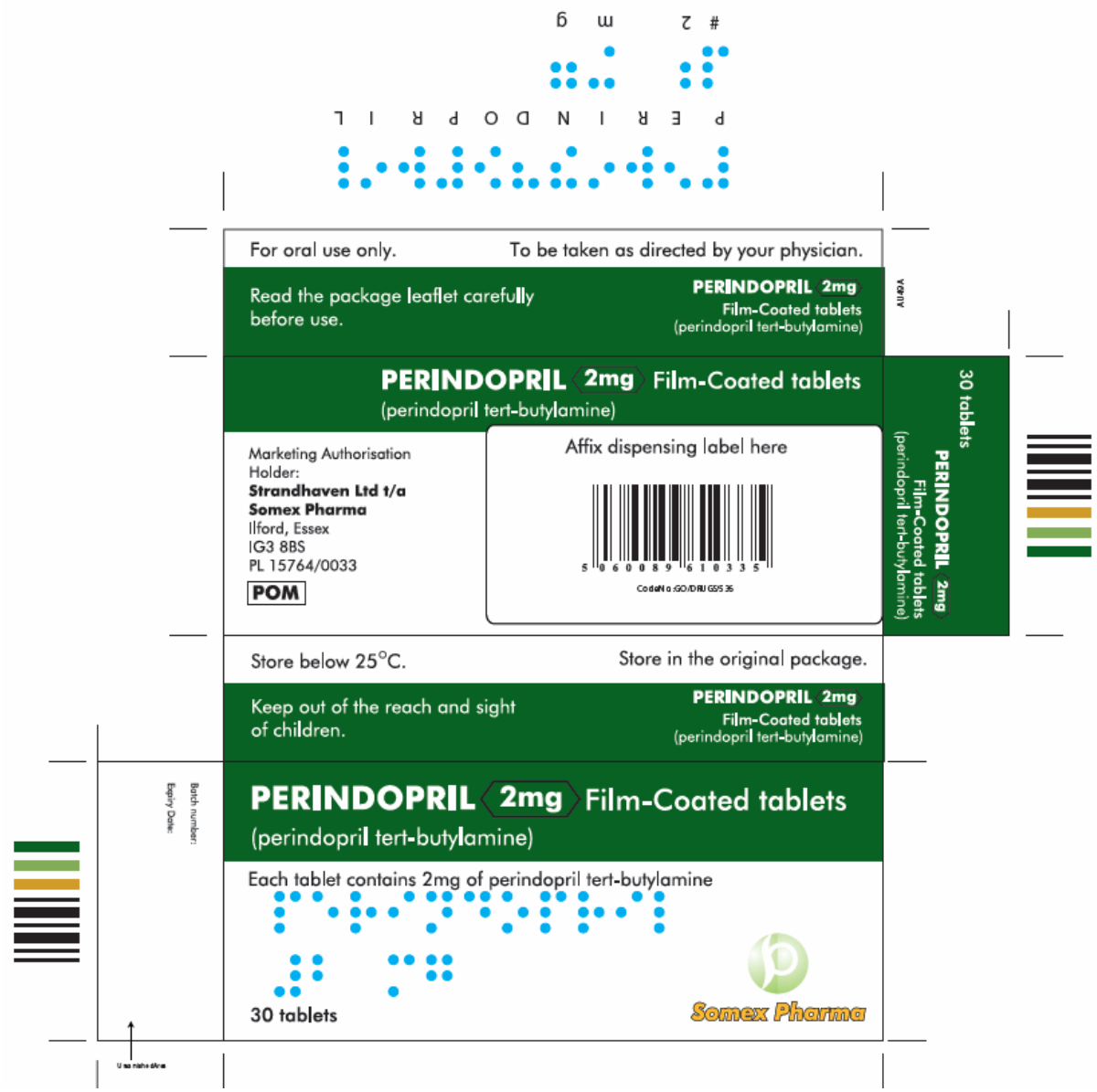
Manufacturer:
Strandhaven Ltd trading as Somex Pharma, Seven Kings, Ilford, Essex, IG3 8RA, UK

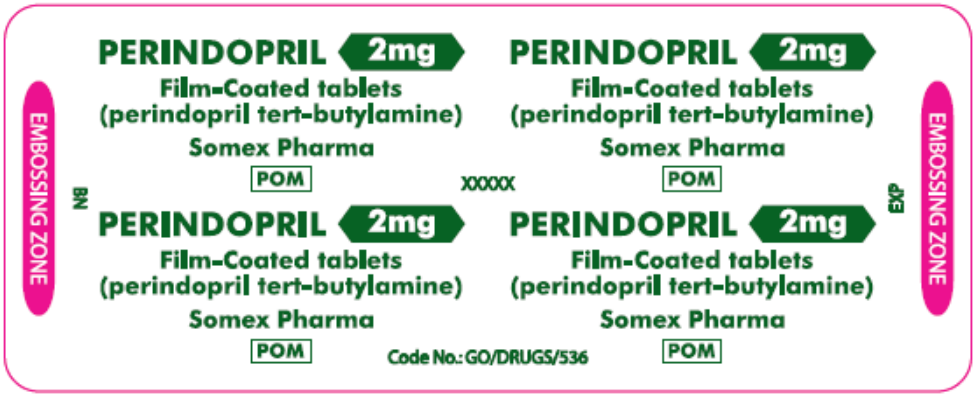
This leaflet was last approved in Jan 2008.

Module 4

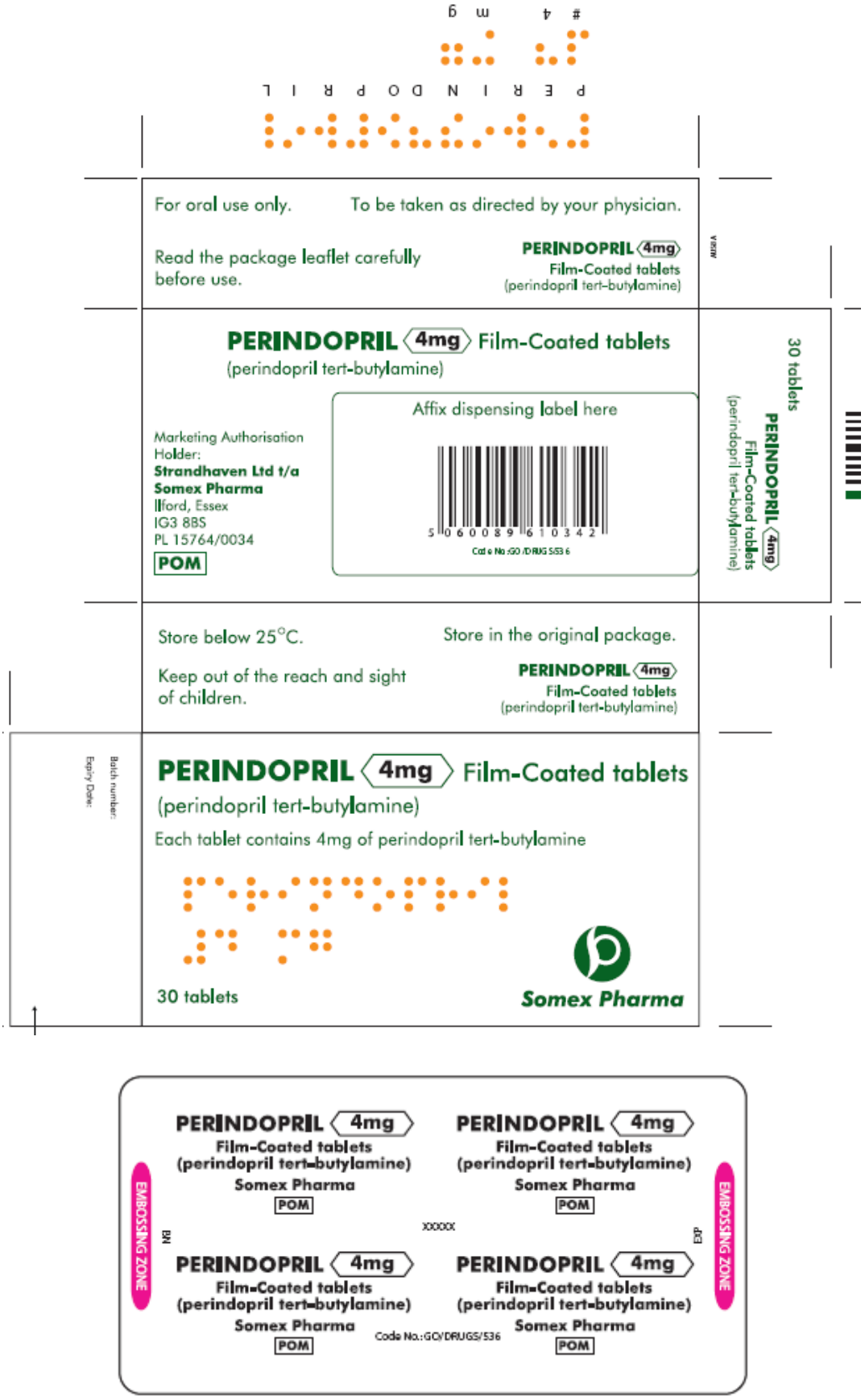
Labelling

Perindopril 2mg film-coated Tablets (PL 15764/0033)

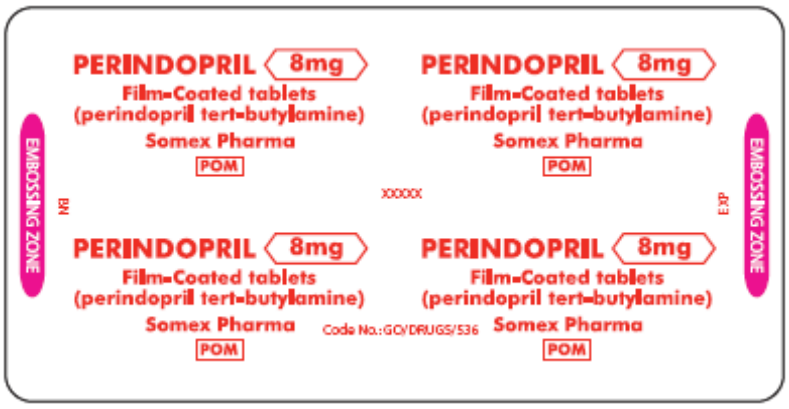




Perindopril 4mg film-coated Tablets (PL 15764/0034)



Perindopril 8mg film-coated Tablets (PL 15764/0035)



Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Strandhaven Limited Marketing Authorisations for the medicinal products Perindopril 2mg, 4mg, and 8mg film-coated Tablets (PL 15764/0033-0035, UK/H/1118/01-03/DC). The products are prescription-only medicines.

These are abridged applications for Perindopril 2mg, 4mg, and 8mg film-coated Tablets, three strengths of perindopril, submitted under Article 10.1 of 2001/83 EC, as amended, claiming to be generic medicinal products of Coversyl 2mg, 4mg and 8mg Tablets (PL 05815/0001, 0002, and 0023, Les Laboratories Servier) respectively. The reference products have been authorised in at least one EU member state for more than 10 years, so the period of data exclusivity has expired.

The active ingredient is perindopril, present as perindopril tert-butylamine. 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 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 is active in all grades of hypertension, and is also used to treat heart failure where it reduces cardiac work by a decrease in pre-load and after-load. Perindopril is also used to reduce the risk of cardiac events in patients with stable coronary artery disease.

No new preclinical studies were conducted, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

The application depends upon the bioequivalence study presented by the applicant comparing the test product, Perindopril 8mg film-coated Tablets, to the reference product Coversyl 8mg Tablets (Les Laboratories Servier).

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Perindopril 2mg film-coated Tablets Perindopril 4mg film-coated Tablets Perindopril 8mg film-coated Tablets
Name(s) of the active substance(s) (INN)	Perindopril erbumine
Pharmacotherapeutic classification (ATC code)	ACE inhibitor (C09A A04)
Pharmaceutical form and strength(s)	2mg, 4mg, and 8mg film-coated tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/1118/01-03/DC
Reference Member State	United Kingdom
Member States concerned	Cyprus
Marketing Authorisation Number(s)	PL 15764/0033-0035
Name and address of the authorisation holder	Strandhaven Ltd 600 High Road Seven Kings Ilford Essex IG3 8BS UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

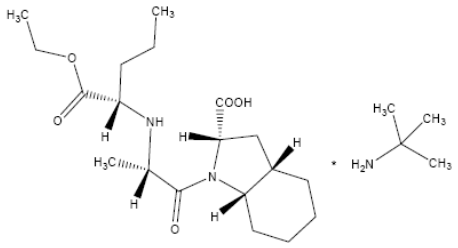
ACTIVE SUBSTANCE

Perindopril tert-butylamine

Nomenclature:

INN:	Perindopril Erbumine monohydrate
Chemical name:	2-Methylpropan-2-amine (2S,3aS,7aS)-1-[(2S)-2-[[(1S)-1 (ethoxycarbonyl)butyl]amino]propanoyl]octahydro-1H-indole-2-carboxylate monohydrate

Structure:



Molecular formula:	$C_{23}H_{43}N_3O_5 . H_2O$
Molecular weight:	459.6
CAS No:	690267-97-1
Physical form:	White or almost-white crystalline powder
Solubility:	Freely soluble in alcohol, sparingly soluble in methylene chloride

The active substance, Perindopril tert-butylamine, is the subject of a European Pharmacopeia (EP) monograph.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin, and therefore comply with the TSE requirements.

An appropriate active substance specification has been provided. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for primary and working reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. It is packed into double polythene bags as the primary container, secured with fasteners. These bags are then placed into secondary triple laminated high barrier bags, which are hermetically sealed. These are packed inside fibre drums. Specifications and Certificates of Analysis have been provided for the packaging materials used. The polythene bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been generated for active substance stored in the proposed packaging. These data demonstrate the stability of the active substance and support a retest period of 2 years when stored between 2°C and 8°C in the proposed packaging.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely mannitol, sodium starch glycollate, sodium carbonate anhydrous, hypromellose macrogol 6000, siliconised talc, and magnesium stearate making up the tablet core; hypromellose making up the seal-coating; and Opadry AMB OY-B-28920 white making up the film-coating. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monograph, with the exception of siliconised talc and Opadry AMB OY-B-28920 which comply with suitable in-house specifications. The components of Opadry AMB OY-B-28920 (polyvinyl alcohol, titanium dioxide, talc, soya lecithin, and xantham gum) are all stated as complying with the European Pharmacopoeia, apart from soya lecithin which complies with the National Formulary. Satisfactory Certificates of Analysis have been provided for all excipients.

The only excipient used that contains material of animal or human origin is magnesium stearate. A Certificate of Suitability has been provided by the supplier of magnesium stearate stating that the magnesium stearate they provide meets the criteria described in the current version of the monograph ‘Products with risk of transmitting agents of animal spongiform encephalopathies’.

There were no novel excipients used.

A 10 % overage for film-coating materials is included to compensate for manufacturing losses. This is acceptable.

Dissolution and impurity profiles

There is an absence of comparative impurity and in vitro dissolution data with information from only the 8 mg UK innovator product. However, given the known, rapid, dissolution of the drug substance and its degradation profile this information is acceptable for the UK.

Pharmaceutical development

Details of the pharmaceutical development of the drug products have been supplied and are satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are satisfactory.

Finished product specification

The finished product specifications are satisfactory, and provide an assurance of the quality and consistency of the finished products. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The tablets are packed in blisters of 3 ply Aluminium- Aluminium laminated foil and plain aluminium foil, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The product is packaged in cartons of pack size 30. Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 24 months has been set, which is satisfactory. Storage conditions are 'Store below 25°C' and 'Store in the original package'.

Bioequivalence Study

A bioequivalence study was presented comparing the test product, Perindopril 8mg film-coated Tablets, to the reference product, Coversyl 8mg Tablets (Les Laboratories Servier).

An evaluation of the bioequivalence study is found in the Clinical Aspects section.

Expert Report

A satisfactory expert report is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

Product Information

The approved SmPCs, leaflet, and labelling are satisfactory.

Conclusion

The test products are pharmaceutically equivalent to the reference products which have been licensed in at least one EU member state for over 10 years. The drug products correspond to the current EU definition of a generic medicinal product because they comply with the criteria of having the same qualitative and quantitative composition in terms of the active substance and pharmaceutical form. On this basis, and considering the bioequivalence data provided, the applicant's claim that Perindopril 8mg film-coated Tablets is a generic medicinal product of Coversyl 8mg Tablets appears justified.

As the test products, Perindopril 2mg, 4mg, and 8mg film-coated Tablets, meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 8mg strength were extrapolated to the 2mg and 4mg strength tablets.

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. It is recommended that Marketing Authorisations are granted.

III.2 PRE-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable for these applications for generic products. The non-clinical overview provides a reasonable review of the known pharmacological and toxicological properties of perindopril tert-butylamine.

III.3 CLINICAL ASPECTS

The clinical pharmacology of perindopril tert-butylamine is well known.

Pharmacokinetics

The applicant has submitted a single bioequivalence study. This was a randomised, open label, two treatment, two period, two sequence, single dose, crossover, oral bioavailability study in healthy subjects. A single 8mg tablet of test product (Perindopril 8mg film-coated tablets) and the reference product (Coversyl 8mg tablets) were administered under fasting condition to 32 subjects. 30 subjects completed both periods of the study, and pharmacokinetic and statistical evaluation was done on 28 subjects.

Blood samples were collected before and up to 144 hours post-drug administration. Plasma levels of perindopril and its metabolite perindoprilat were measured by a validated Liquid chromatography/mass spectrometry method. The results were as follows:

Geometric mean, ratio and 90% confidence intervals of In-transformed parameters for perindopril

Parameters	Least square mean		T/R	90% Confidence Interval for In-transformed data
	Test (T)	Reference (R)		
C_{max} (ng/mL)	101.304	112.057	90.404	82.60 – 98.95
AUC_{0-t} (h.ng/mL)	128.153	123.424	103.831	98.02 – 109.98
AUC_{0-inf} (h.ng/mL)	134.726	130.358	103.351	98.11 – 108.87

Geometric mean, ratio and 90% confidence intervals of In-transformed parameters for perindoprilat

Parameters	Least square mean		T/R	90% Confidence Interval for In-transformed data
	Test (T)	Reference (R)		
C_{max} (ng/mL)	11.333	10.104	112.165	103.84 – 121.16
AUC_{0-t} (h.ng/mL)	250.250	232.305	107.725	103.54 – 112.08
AUC_{0-inf} (h.ng/mL)	282.198	263.263	107.193	102.22 – 112.41

The sample size, sampling period and pharmacokinetic parameters chosen were appropriate. Based on the above data, the bioequivalence of the test product with the reference product has been shown.

As Perindopril 2mg, 4mg, and 8mg film-coated tablets meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 8mg strength were extrapolated to the 2mg and 4mg strength products.

Pharmacodynamics

No new data have been submitted. The pharmacodynamics of perindopril tert-butylamine are well-known.

Clinical efficacy

No new data have been submitted and none are required. Efficacy is reviewed in the clinical overview. The efficacy of perindopril tert-butylamine is well-established from its extensive use in clinical practice.

Clinical safety

No new data have been submitted and none are required for applications of this type. Safety is reviewed in the clinical overview. The safety profile of perindopril tert-butylamine is well-known.

EXPERT REPORT

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

CONCLUSIONS

All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and demonstrates the bioequivalence of the test (Perindopril 8mg film-coated tablets) and reference (Coversyl 8mg tablets) products within general acceptance limits. The results and conclusions of the bioequivalence study on the 8mg strength were extrapolated to the 2mg and 4mg strength products.

Sufficient clinical information has been submitted to support these applications. Marketing Authorisations may be granted on medical grounds.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Perindopril 2mg, 4mg, and 8mg film-coated tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Perindopril 8mg film-coated tablets, and the reference product Coversyl 8mg tablets (PL 05815/0023, Les Laboratoires Servier).

As Perindopril 2mg, 4mg, and 8mg film-coated tablets were deemed to meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 8mg strength were extrapolated to the 2mg and 4mg tablet strengths, and no separate bioequivalence studies were necessary.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study, and the valid extrapolation of its results and conclusions, support the claim that the applicant's products and their respective reference products are interchangeable. Extensive clinical experience with perindopril tert-butylamine is considered to have demonstrated the therapeutic value of the active substance. The risk benefit is, therefore, considered to be positive.

Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

There have been no variation applications submitted after approval of the initial procedure.

Date submitted	Application type	Scope	Outcome