Public Assessment Report

Mutual Recognition Procedure

Perindopril 2mg Tablets
Perindopril 4mg Tablets
Perindopril 8mg Tablets

UK/H/997/01-03/MR
UK licence no: PL 15922/0078-80

Applicant:Apotex Europe Limited

LAY SUMMARY

The MHRA granted Apotex Europe Limited Marketing Authorisations (licences) for the medicinal products Perindopril 2mg, 4mg and 8mg Tablets on 19th June 2007. These are prescription-only medicines for the treatment of high blood pressure and conditions where heart function is reduced.

These tablets contain the active ingredient perindopril tert-butylamine salt. Perindopril works by widening the blood vessels, thus making it easier for the heart to pump blood through them.

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 Tablets outweigh the risks; hence Marketing Authorisations have been granted.

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Module 1

Product Name	Perindopril 2mg Tablets Perindopril 4mg Tablets Perindopril 8mg Tablets
Type of Application	Generic, Article 10.1
Active Substance	Perindopril Tert-Butylamine Salt
Form	Tablets
Strength	2mg, 4mg and 8mg
MA Holder	Apotex Europe Limited, Rowan House, 41 London Street, Reading, Berkshire, RG1 4PS
Reference Member State (RMS)	UK
CMS	Czech Republic, The Netherlands, Poland (UK/H/997/01/MR); PL 15922/0078 Czech Republic, The Netherlands, Poland and Italy (UK/H/997/02/MR); PL 15922/0079 Czech Republic, The Netherlands, Poland (UK/H/997/03/MR); PL 15922/0080
Procedure Number	UK/H/997/01-03/MR
Timetable	Day 90 – 19th June 2007

Module 2

Summary of Product Characteristics

The UK Summaries of Product Characteristics (SPC) for Perindopril 2mg, 4mg and 8mg Tablets are as follows:

1. NAME OF THE MEDICINAL PRODUCT

Perindopril tert-butylamine 2 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains perindopril tert-butylamine 2 mg (equivalent to 1.669 mg perindopril). Excipient: Lactose anhydrous. Each tablet contains 42.60 mg lactose anhydrous.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White, round, biconvex tablets, engraved "APO" on one side and "PE2" 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 infraction and/or revascularisation.

4.2 Posology and method of administration

It is recommended that Perindopril tert-butylamine Tablets are taken once daily in the morning before a meal. The dose should be individualised according to the patient profile (see 4.4 "Special warnings and special precautions for use") and blood pressure response.

Hypertension

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 tert-butylamine Tablets (see section 4.4 "Special warnings and special precautions for use"). In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Perindopril tert-butylamine Tablets should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Perindopril tert-butylamine Tablets 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 tert-butylamine Tablets generally associated with a non-potassium-sparing diuretic and/or digoxin and/or a beta-blocker, be introduced under close medical supervision with a recommended starting dose of 2 mg taken in the morning. This dose may be increased by increments of 2 mg at intervals of no less than 2 weeks to 4 mg once daily if tolerated. The dose adjustment should be based on the clinical response of the individual patient.

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

Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with Perindopril tert-butylamine Tablets. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with Perindopril tert-butylamine Tablets (see section 4.4 "Special warnings and special precautions for use").

Stable coronary artery disease
Perindopril tert-butylamine Tablets should be introduced at a dose of 4 mg once daily for two weeks, then increased to 8 mg once daily, depending on renal function and provided that the 4 mg dose is well tolerated.

Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 mg one 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
ClCR ≥ 60	4 mg per day
30 < ClCR < 60	2 mg per day
15 < ClCR < 30	2 mg every other day
Haemodialysed patients *	
ClCR < 15	2 mg on the day of dialysis

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

Dosage adjustment in hepatic impairment
No dosage adjustment is necessary in patients with hepatic impairment (see sections 4.4 "Special warnings and special precautions for use" and 5.2 "Pharmacokinetic properties").

Paediatric use
Efficacy and safety of use in children has not been established. Therefore, use in children is not recommended.

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

4.4 Special warnings and precautions for use
Stable coronary artery disease
If an episode of unstable angina pectoris (major or not) occurs during the first month of perindopril treatment, a careful appraisal of the benefit/risk should be performed before treatment continuation.

Hypotension
ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume- depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 "Interaction with other medicaments and other forms of interaction" and 4.8 "Undesirable effects"). In patients with symptomatic heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored (see 4.2 "Posology and method of administration" and 4.8 "Undesirable effects"). Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Perindopril tert-butylamine Tablets. 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 tert-butylamine Tablets 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 tert-butylamine Tablets 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 tert-butylamine Tablets 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 / Anesthetics
Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

4.6 Pregnancy and lactation

Pregnancy
Perindopril tert-butylamine Tablets should not be used during the first trimester of pregnancy.

When a pregnancy is planned or confirmed, the switch to an alternative treatment should be initiated as soon as possible. Controlled studies with ACE inhibitors have not been done in humans, but in a limited number of cases with first trimester exposure there do not appear to have been any malformations consistent with human foetotoxicity as described below.

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

Prolonged ACE inhibitor exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see 5.3 "Preclinical safety data").

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

Lactation
It is not known whether perindopril is excreted into human breast milk. Therefore the use of Perindopril tert-butylamine Tablets 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

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

Hepatobiliary 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 trial
During the randomised period of the EUROPA study, only serious adverse events were controlled. Few patients experienced serious adverse events: 16 (23%) of the 6122 perindopril patients and 10 (0.2%) of the 6017 placebo patients. In perindopril-treated patients, hypotension was observed in 6 patients, angioedema in 3 patients and sudden cardiac arrest in 1 patient. More patients withdrew for cough, hypotension or other intolerance on perindopril than on placebo, 6.0% (n=366) versus 2.1% (n=129) respectively.

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

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis (see 4.4 Special warnings and special precautions for use, Haemodialysis Patients). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: CO9A AO4

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, a multicenter, international, randomised, double-blind, placebo-controlled clinical trial, lasted 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 infraction and/or a previous coronary revascularization. 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 absolutely 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 with placebo.

5.2 Pharmacokinetic properties

After oral administration, the absorption of perindopril is rapid and the peak concentration complete within I 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 special precautions for use").

5.3 Preclinical safety data

In the chronic oral toxicity studies (rats and monkeys), the target organ is the kidney, with reversible damage.

No mutagenicity has been observed in *in vitro* or *in vivo* studies.

Reproduction toxicology studies (rats, mice, rabbits and monkeys) showed no sign of embryotoxicity or teratogenicity. However, angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects on late foetal development, resulting in foetal death and congenital effects in rodents and rabbits: renal lesions and an increase in peri- and postnatal mortality have been observed.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose anhydrous
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25°C. Store in the original package.

6.5 Nature and contents of container

Blister pack: Aluminium/PVC/PVAC.
Package sizes: 4, 7, 14, 15, 28, 30, 50, 56, 60, 90, 100, 112, 120, 500 tablets.

6.6 Special precautions for disposal

None

7. MARKETING AUTHORISATION HOLDER

Apotex Europe Ltd
Rowan House,
41 London Street
Reading,
Berkshire, RG1 4PS
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PL 15922/0078

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/07/2006

10. DATE OF REVISION OF THE TEXT

24/07/2006

1. NAME OF THE MEDICINAL PRODUCT

Perindopril tert-butylamine 4 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains perindopril tert-butylamine 4 mg (equivalent to 3.338 mg perindopril). Excipient: Lactose anhydrous. Each tablet contains 85.20 mg lactose anhydrous.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White, capsule shaped, biconvex tablets, engraved "APO" on one side and "PE" bisect "4" on the other side. The tablets can be divided into equal halves.

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 infraction and/or revascularisation.

4.2 Posology and method of administration

It is recommended that Perindopril tert-butylamine Tablets are taken once daily in the morning before a meal. The dose should be individualised according to the patient profile (see 4.4 "Special warnings and special precautions for use") and blood pressure response.

Hypertension
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 tert-butylamine Tablets (see section 4.4 "Special warnings and special precautions for use"). In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Perindopril tert-butylamine Tablets should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Perindopril tert-butylamine Tablets 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 tert-butylamine Tablets generally associated with a non-potassium-sparing diuretic and/or digoxin and/or a beta-blocker, be introduced under close medical supervision with a recommended starting dose of 2 mg taken in the morning. This dose may be increased by increments of 2 mg at intervals of no less than 2 weeks to 4 mg once daily if tolerated. The dose adjustment should be based on the clinical response of the individual patient.

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

Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with Perindopril tert-butylamine Tablets. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with Perindopril tert-butylamine Tablets (see section 4.4 "Special warnings and special precautions for use").

Stable coronary artery disease
Perindopril tert-butylamine Tablets should be introduced at a dose of 4 mg once daily for two weeks, then increased to 8 mg once daily, depending on renal function and provided that the 4 mg dose is well tolerated.

Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 mg one 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
ClCR ≥ 60	4 mg per day
30 < ClCR < 60	2 mg per day
15 < ClCR < 30	2 mg every other day
Haemodialysed patients *	
ClCR < 15	2 mg on the day of dialysis

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

Dosage adjustment in hepatic impairment
No dosage adjustment is necessary in patients with hepatic impairment (see sections 4.4 "Special warnings and special precautions for use" and 5.2 "Pharmacokinetic properties").

Paediatric use
Efficacy and safety of use in children has not been established. Therefore, use in children is not recommended.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Stable coronary artery disease
If an episode of unstable angina pectoris (major or not) occurs during the first month of perindopril treatment, a careful appraisal of the benefit/risk should be performed before treatment continuation.

Hypotension
ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume- depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 "Interaction with other medicaments and other forms of interaction" and 4.8 "Undesirable effects"). In patients with symptomatic heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored (see 4.2 "Posology and method of administration" and 4.8 "Undesirable effects"). Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Perindopril tert-butylamine Tablets. 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 tert-butylamine Tablets 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 tert-butylamine Tablets 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 tert-butylamine Tablets 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 / Anesthetics
Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

4.6 Pregnancy and lactation

Pregnancy
Perindopril tert-butylamine Tablets should not be used during the first trimester of pregnancy.

When a pregnancy is planned or confirmed, the switch to an alternative treatment should be initiated as soon as possible. Controlled studies with ACE inhibitors have not been done in humans, but in a limited number of cases with first trimester exposure there do not appear to have been any malformations consistent with human foetotoxicity as described below.

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

Prolonged ACE inhibitor exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see 5.3 "Preclinical safety data").

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

Lactation
It is not known whether perindopril is excreted into human breast milk. Therefore the use of Perindopril tert-butylamine Tablets 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

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

Hepatobiliary 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 trial
During the randomised period of the EUROPA study, only serious adverse events were controlled. Few patients experienced serious adverse events: 16 (23%) of the 6122 perindopril patients and 10 (0.2%) of the 6017 placebo patients. In perindopril-treated patients, hypotension was observed in 6 patients, angioedema in 3 patients and sudden cardiac arrest in 1 patient. More patients withdrew for cough, hypotension or other intolerance on perindopril than on placebo, 6.0% (n=366) versus 2.1% (n=129) respectively.

4.9 Overdose

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

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis (see 4.4 Special warnings and special precautions for use, Haemodialysis Patients). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: CO9A AO4

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, a multicenter, international, randomised, double-blind, placebo-controlled clinical trial, lasted 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 infraction and/or a previous coronary revascularlariation. 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 absolutely 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 with placebo.

5.2 Pharmacokinetic properties

After oral administration, the absorption of perindopril is rapid and the peak concentration complete within I 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 special precautions for use").

5.3 Preclinical safety data

In the chronic oral toxicity studies (rats and monkeys), the target organ is the kidney, with reversible damage.

No mutagenicity has been observed in *in vitro* or *in vivo* studies.

Reproduction toxicology studies (rats, mice, rabbits and monkeys) showed no sign of embryotoxicity or teratogenicity. However, angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects on late foetal development, resulting in foetal death and congenital effects in rodents and rabbits: renal lesions and an increase in peri- and postnatal mortality have been observed.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose anhydrous
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25°C. Store in the original package.

6.5 Nature and contents of container

Blister pack: Aluminium/PVC/PVAC.
Package sizes: 4, 7, 14, 15, 28, 30, 50, 56, 60, 90, 100, 112, 120, 500 tablets.

6.6 Special precautions for disposal

None

7. MARKETING AUTHORISATION HOLDER

Apotex Europe Ltd
Rowan House,
41 London Street
Reading,
Berkshire, RG1 4PS
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PL 15922/0079

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24/07/2006

10. DATE OF REVISION OF THE TEXT
24/07/2006

1. NAME OF THE MEDICINAL PRODUCT
Perindopril tert-butylamine 8 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains perindopril tert-butylamine 8 mg (equivalent to 6.676 mg perindopril). Excipient: Lactose anhydrous. Each tablet contains 170.40 mg lactose anhydrous.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablet.

White, capsule shaped, biconvex tablets, engraved "APO" on one side and "PE" bisect "8" on the other side. The tablets can be divided into equal halves.

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 infraction and/or revascularisation.

4.2 Posology and method of administration

It is recommended that Perindopril tert-butylamine Tablets are taken once daily in the morning before a meal. The dose should be individualised according to the patient profile (see 4.4 "Special warnings and special precautions for use") and blood pressure response.

Hypertension
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 tert-butylamine Tablets (see section 4.4 "Special warnings and special precautions for use"). In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Perindopril tert-butylamine Tablets should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Perindopril tert-butylamine Tablets 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 tert-butylamine Tablets generally associated with a non-potassium-sparing diuretic and/or digoxin and/or a beta-blocker, be introduced under close medical supervision with a recommended starting dose of 2 mg taken in the morning. This dose may be increased by increments of 2 mg at intervals of no less than 2 weeks to 4 mg once daily if tolerated. The dose adjustment should be based on the clinical response of the individual patient.

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

Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with Perindopril tert-butylamine Tablets. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with Perindopril tert-butylamine Tablets (see section 4.4 "Special warnings and special precautions for use").

Stable coronary artery disease
Perindopril tert-butylamine Tablets should be introduced at a dose of 4 mg once daily for two weeks, then increased to 8 mg once daily, depending on renal function and provided that the 4 mg dose is well tolerated.

Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 mg one 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

ClCR ≥ 60	4 mg per day
30 < ClCR < 60	2 mg per day
15 < ClCR < 30	2 mg every other day

Haemodialysed patients *
ClCR < 15 2 mg on the day of dialysis

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

Dosage adjustment in hepatic impairment
No dosage adjustment is necessary in patients with hepatic impairment (see sections 4.4 "Special warnings and special precautions for use" and 5.2 "Pharmacokinetic properties").

Paediatric use
Efficacy and safety of use in children has not been established. Therefore, use in children is not recommended.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Stable coronary artery disease
If an episode of unstable angina pectoris (major or not) occurs during the first month of perindopril treatment, a careful appraisal of the benefit/risk should be performed before treatment continuation.

Hypotension
ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume- depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 "Interaction with other medicaments and other forms of interaction" and 4.8 "Undesirable effects"). In patients with symptomatic heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored (see 4.2 "Posology and method of administration" and 4.8 "Undesirable effects"). Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Perindopril tert-butylamine Tablets. 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 tert-butylamine Tablets 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 tert-butylamine Tablets 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 tert-butylamine Tablets 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 / Anesthetics
Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

4.6 Pregnancy and lactation

Pregnancy
Perindopril tert-butylamine Tablets should not be used during the first trimester of pregnancy.

When a pregnancy is planned or confirmed, the switch to an alternative treatment should be initiated as soon as possible. Controlled studies with ACE inhibitors have not been done in humans, but in a limited number of cases with first trimester exposure there do not appear to have been any malformations consistent with human foetotoxicity as described below.

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

Prolonged ACE inhibitor exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see 5.3 "Preclinical safety data").

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

Lactation
It is not known whether perindopril is excreted into human breast milk. Therefore the use of Perindopril tert-butylamine Tablets 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

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

Hepatobiliary 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 trial
During the randomised period of the EUROPA study, only serious adverse events were controlled. Few patients experienced serious adverse events: 16 (23%) of the 6122 perindopril patients and 10 (0.2%) of the 6017 placebo patients. In perindopril-treated patients, hypotension was observed in 6 patients, angioedema in 3 patients and sudden cardiac arrest in 1 patient. More patients withdrew for cough, hypotension or other intolerance on perindopril than on placebo, 6.0% (n=366) versus 2.1% (n=129) respectively.

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

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis (see 4.4 Special warnings and special precautions for use, Haemodialysis Patients). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
ATC code: CO9A AO4

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, a multicenter, international, randomised, double-blind, placebo-controlled clinical trial, lasted 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 infraction and/or a previous coronary revascularization. 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 absolutely 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 with placebo.

5.2 Pharmacokinetic properties

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

After repeated administration, no accumulation of perindopril is observed.

Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure. Dosage adjustment in renal insufficiency is desirable depending on the degree of impairment (creatinine clearance).

Dialysis clearance of perindoprilat is equal to 70 ml/min.

Perindopril kinetics are modified in patients with cirrhosis: hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required (see also sections 4.2 "Posology and method of administration" and 4.4 "Special warnings and special precautions for use").

5.3 Preclinical safety data

In the chronic oral toxicity studies (rats and monkeys), the target organ is the kidney, with reversible damage.

No mutagenicity has been observed in *in vitro* or *in vivo* studies.

Reproduction toxicology studies (rats, mice, rabbits and monkeys) showed no sign of embryotoxicity or teratogenicity. However, angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects on late foetal development, resulting in foetal death and congenital effects in rodents and rabbits: renal lesions and an increase in peri- and postnatal mortality have been observed.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose anhydrous
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25°C. Store in the original package.

6.5 Nature and contents of container

Blister pack: Aluminium/PVC/PVAC.
Package sizes: 4, 7, 14, 15, 28, 30, 50, 56, 60, 90, 100, 112, 120, 500 tablets.

6.6 Special precautions for disposal

None

7. MARKETING AUTHORISATION HOLDER

Apotex Europe Ltd
Rowan House,
41 London Street
Reading,
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United Kingdom

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Module 3
Patient Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

PERINDOPRIL 2 mg TABLETS
PERINDOPRIL 4 mg TABLETS
PERINDOPRIL 8 mg 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 gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT PERINDOPRIL TERT-BUTYLAMINE TABLETS ARE AND WHAT THEY ARE USED FOR

Perindopril belongs to a group of medicines called ACE inhibitors. These work by widening the blood vessels. This makes it easier for your heart to pump blood through the body.

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

2. BEFORE YOU TAKE PERINDOPRIL TERT-BUTYLAMINE TABLETS

Do not take Perindopril tert-butylamine Tablets
- if you are allergic (hypersensitive) to perindopril or any of the other ingredients of Perindopril tert-butylamine Tablets (see Further Information, section 6).
- if you have had symptoms such as wheezing, swelling of the face, tongue or throat, intense itching, skin rash, fainting or feeling dizzy.
  If you have had these symptoms when you have taken an ACE inhibitor in the past or at any other time, this may be angioedema. If so, do not take Perindopril tert-butylamine Tablets.
- if you are pregnant or breast-feeding.

If any of the above applies to you, talk to your doctor and do not take Perindopril tert-butylamine Tablets.

Take special care with Perindopril tert-butylamine Tablets

Talk to your doctor before taking Perindopril tert-butylamine Tablets if:
- you have narrowing of the heart valves (aortic or mitral stenosis) or heart muscle disease (hypertrophic cardiomyopathy) or narrowing of the artery supplying the kidney with blood (renal artery stenosis)
- you have any other heart or liver or kidney problems, or if you are having dialysis
- you have diabetes which is not well controlled
- you have been told to limit the salt in your diet or to use a salt-substitute containing potassium
- you have a collagen disease such as systemic lupus erythematosus or scleroderma.

Tell the doctor or pharmacist that you are taking Perindopril tert-butylamine Tablets if:
- you are about to have an operation or a general anaesthetic
- you have recently had diarrhoea or vomitted
- you are going to have treatment to reduce the effects of an allergy to bee or wasp stings
- you are going to have cholesterol removed from your blood by a machine (LDL apheresis).

Tell the doctor if any of the situations above have happened to you in the past.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. In particular, talk to your doctor before taking Perindopril tert-butylamine Tablets if you are taking:
- medicines for high blood pressure including water tablets (diuretics)
- water tablets (diuretics) which affect potassium, such as spironolactone, triamterene or amiloride
- medicines to increase your level of potassium
- heparin (for thinning the blood) can also affect potassium levels in your blood
- medicines for diabetes (insulin or tablets)
- lithium (for mania or depression)
- medicines for mental illness such as depression, anxiety, schizophrenia or other psychosis
- allopurinol for gout
- medicines to treat auto-immune disorders (such as rheumatoid arthritis) or given after transplant surgery. These are called immunosupressants.
- procainamide (for irregular heartbeat)
- non-steroidal anti-inflammatory drugs (NSAIDs such as ibuprofen, diclofenac), including aspirin for pain
- medicines for low blood pressure, shock or asthma (including ephedrine, noradrenaline or adrenaline)
- medicines that make the blood vessels wider (vasodilators, such as nitrates)

Ask your doctor if you are not sure what these medicines are. Tell the doctor if you have taken any of the medicines listed above in the past, but have now stopped.

Taking Perindopril tert-butylamine Tablets with food and drink

Drinking alcohol with Perindopril tert-butylamine Tablets may make you feel dizzy. Check with your doctor whether you can drink alcohol when taking this medicine.

Take your Perindopril tert-butylamine Tablets in the morning before a meal.

Pregnancy and breast-feeding

You should not take Perindopril tert-butylamine Tablets if you:
- are pregnant, planning to become pregnant or if you think you may be pregnant
- are breast-feeding.

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

Driving and using machines

You may feel dizzy or tired when taking Perindopril tert-butylamine Tablets. If this happens, do not drive or use machines. You must talk to your doctor about this.

Important information about some of the ingredients of Perindopril tert-butylamine Tablets

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

Information on special patient groups

Perindopril tert-butylamine Tablets should not be given to children.

3. HOW TO TAKE PERINDOPRIL TERT-BUTYLAMINE TABLETS

Your doctor will decide on the amount of perindopril you should start to take. This may be increased depending on your condition and other medicines you are taking. Always take Perindopril tert-butylamine Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. Do not change the amount of medicine you take unless your doctor tells you. Perindopril may be used on its own, or with other medicines which lower blood pressure.
- Take Perindopril tert-butylamine Tablets by mouth only.
- Take them in the morning, before a meal.
- It is best to take your tablet(s) with a glass of water at the same time each day.

The usual dose is:

High blood pressure:
- 4 mg each day
- after a month, this may be raised to 8 mg each day.

8 mg each day is the highest amount normally used.

In *older people with high blood pressure the daily amounts are usually:*
- 2 mg each day
- after a month, this may be raised to 4 mg each day.

8 mg each day is the highest amount used.

If you are *taking water tablets* (diuretics):
- your doctor may stop them 2 to 3 days before you start taking Perindopril tert-butylamine Tablets. This is to prevent a fall in your blood pressure.
- if needed, you can start taking water tablets again after you have started Perindopril tert-butylamine Tablets.
- if it is not possible to stop your water tablets, then you can take 2 mg of perindopril as well.

Your doctor or pharmacist will tell you exactly what you should do.

The doctor may *start you with 2 mg perindopril if:*
- your blood pressure is very high
- you have not enough water in your body (dehydrated)
- you have a low level of salt in your blood
- you have a heart problem which means that it has difficulty in pumping blood through the body (cardiac decompensation)
- you have high blood pressure due to the blood vessels in the kidneys being blocked (constriction of the arteries).

Heart failure:
- 2 mg each day to start
- after 2 weeks, this may be raised to 4 mg each day.

Stable coronary artery disease:
- the usual starting dose is 4 mg once daily
- after two weeks, this may be raised to 8 mg each day.

In *older people with stable coronary artery disease* the daily amounts are usually:
- 2 mg each day
- after one week, this may be raised to 4 mg each day
- and after a further week to 8 mg each day which is the highest amount used.

If you take more Perindopril tert-butylamine Tablets than you should, talk to a doctor or pharmacist straight away.

The following effects may happen:
Low blood pressure, shock, kidney problems, fast breathing, fast heartbeat, uneven heartbeat (palpitations), slow heartbeat, feeling dizzy or anxious, cough.

If you forget to take Perindopril tert-butylamine Tablets
It is important to take your medicine every day. If you forget to take your tablets, take another as soon as you remember. Then take the normal amount the next day. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Perindopril tert-butylamine Tablets
Do not stop taking Perindopril tert-butylamine Tablets without talking to your doctor. Medicines for high blood pressure or heart failure will normally have to be taken for the rest of your life. If you stop taking Perindopril tert-butylamine Tablets your condition may get worse.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Perindopril tert-butylamine Tablets can cause side effects, although not everybody gets them.

If any of the following effects happen, **stop taking your tablets and tell your doctor immediately**:
- swelling of the face, lips, mouth, tongue or throat
- difficulty in breathing
- feeling dizzy or faint
- very fast or uneven heartbeat.

This is a very rare but serious reaction called angioedema, which can happen with all medicines of this type (ACE inhibitors). You must get treatment immediately, usually in hospital.

Common (affecting less than 1 person in 10):
- cough, shortness of breath
- feeling faint due to low blood pressure (especially when you start Perindopril tert-butylamine Tablets, or when the amount is increased, or when you also take water tablets)
- headache, feeling dizzy or tired, feeling dizzy with a spinning sensation (vertigo), pins and -needles, muscle cramps, blurred vision, eye pain, sensation of noises in the ears (tinnitus)
- feeling or being sick, stomach pain or indigestion, changes in your sense of taste, diarrhoea, -constipation
- skin rash, itching.

Uncommon (affecting less than 1 person in 100):
- changes in mood or sleep
- tight feeling in the chest, wheezing and short of breath (bronchospasm)
- dry mouth
- kidney problems
- unable to get an erection
- sweating
- wheezing, swelling of the face, tongue or throat, intense itching, skin rash, fainting or feeling dizzy (angioedema).

Very rare (affecting less than 1 person in 10,000):
- feeling confused
- uneven heartbeat, chest pain that happens in heart disease (angina), heart attack and stroke (these have happened with ACE inhibitors in people with low blood pressure)
- chest infection (eosinophilic pneumonia), blocked up or runny nose (rhinitis)
- inflamed pancreas (pancreatitis)
- inflamed liver (hepatitis)
- skin reaction like an allergy (erythema multiforme)
- changes in the blood. Your doctor may carry out blood tests to check for this.

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

5. HOW TO STORE PERINDOPRIL TERT-BUTYLAMINE TABLETS

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

Use-by date
Do not use Perindopril tert-butylamine Tablets after the expiry date which is stated on the packet after EXP. 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 tert-butylamine Tablets contain
- The active substance is perindopril tert-butylamine.
- The other ingredients are lactose anhydrous and magnesium stearate.

What Perindopril tert-butylamine Tablets look like and contents of the pack
Perindopril tert-butylamine 2 mg Tablets are white, round tablets, engraved "APO" on one side and "PE2" on the other.

Perindopril tert-butylamine 4 mg Tablets are white, capsule shaped tablets, engraved "APO" on one side and "PE" bisect "4" on the other. The tablets can be divided into equal halves.

Perindopril tert-butylamine 8 mg Tablets are white, capsule shaped tablets, engraved "APO" on one side and "PE" bisect "8" on the other. The tablets can be divided into equal halves.

Each strength of Perindopril tert-butylamine Tablets is available in cartons of 4, 7, 14, 15, 28, 30, 50, 56, 60, 90, 100, 112, 120, 500 tablets.

Not all pack sizes may be available.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Apotex Europe Limited,
Rowan House, 41 London Street, Reading, Berkshire, RG1 4PS, United Kingdom

Manufacturer
Katwijk Farma BV,
Archimedesweg 2, 2333 CN Leiden, The Netherlands

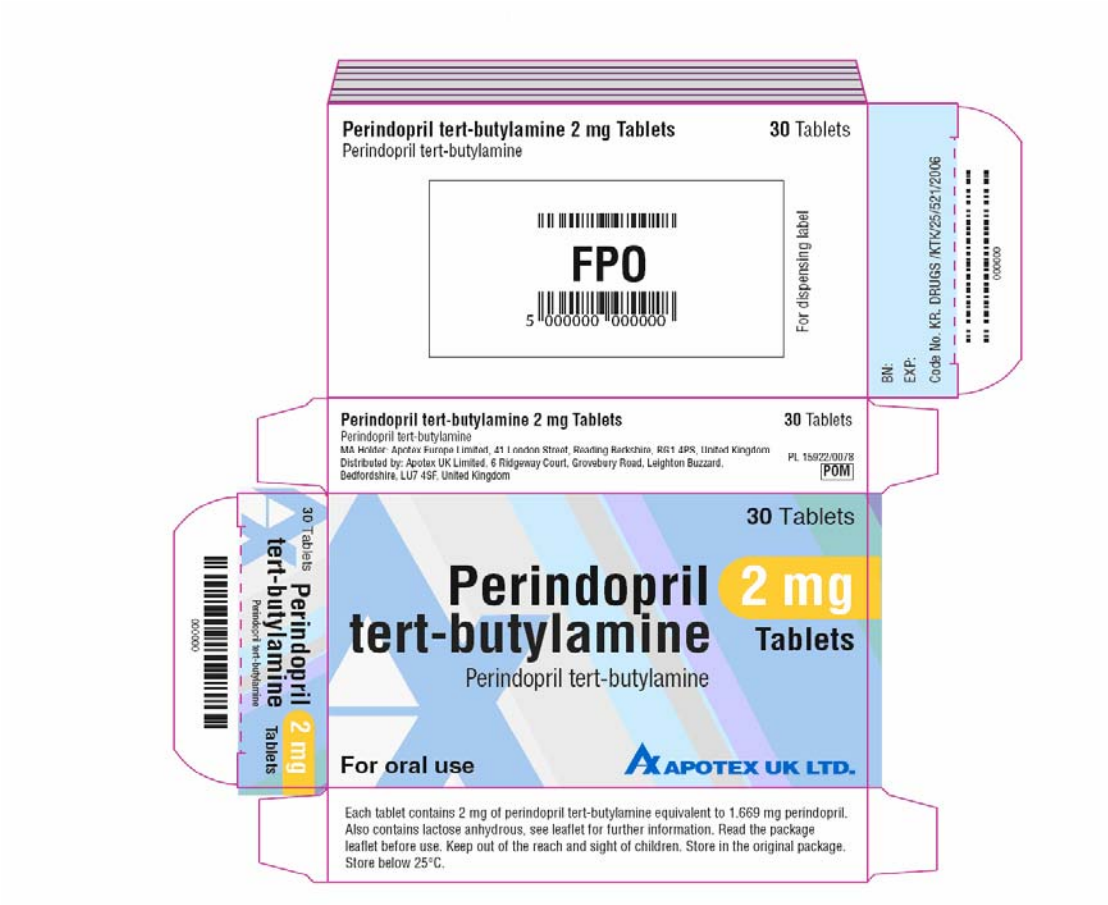
Distributor
Distributed by: Apotex UK Ltd, 6 Ridgeway Court, Grovebury Road, Leighton Buzzard, Bedfordshire, LU7 4SF, United Kingdom

This leaflet was last approved in

APOTEX UK LTD.

Module 4
Labelling

Perindopril tert-butylamine 2mg Tablets
Carton



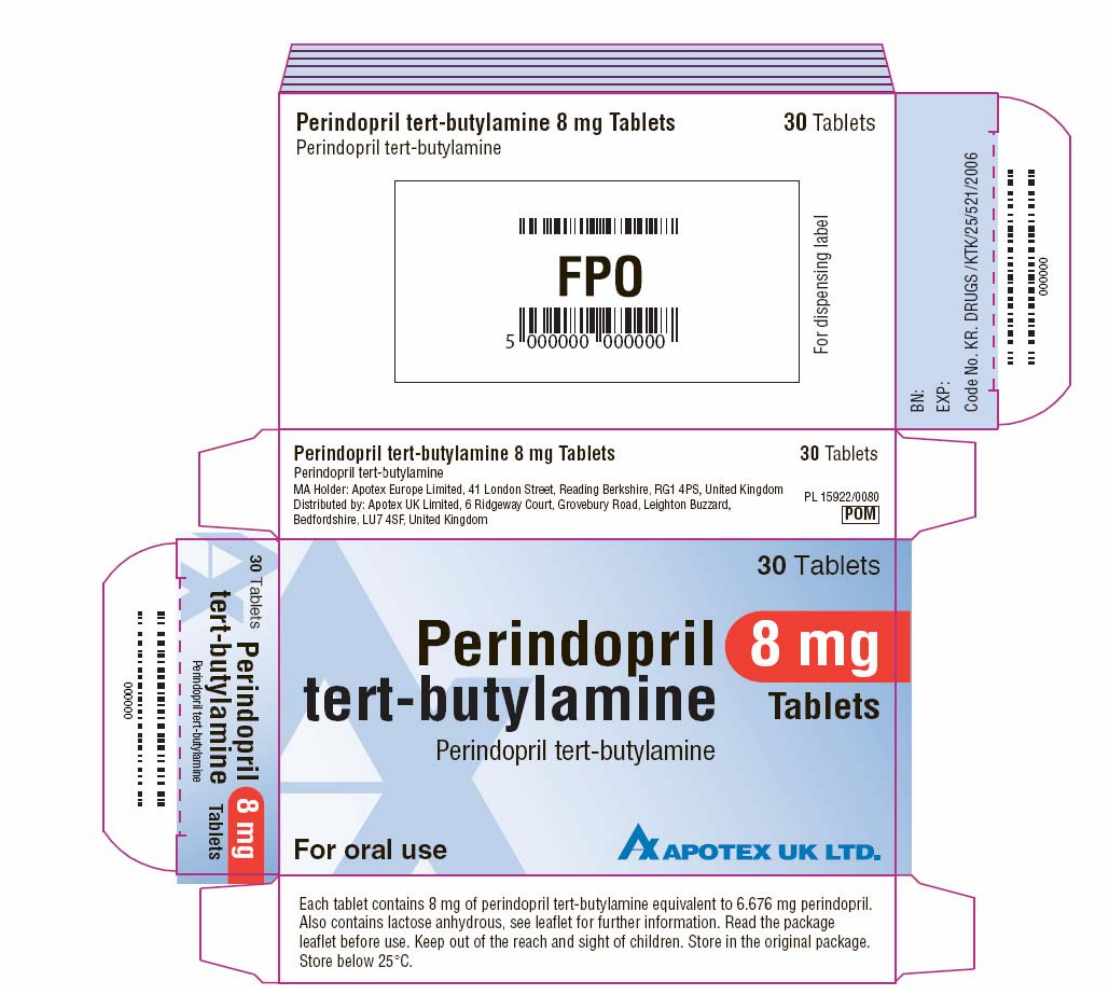
Blister Foil

Perindopril tert-butylamine 4mg Tablets
Carton

Blister foil

Perindopril tert-butylamine 8mg Tablets

Carton



Blister foil

Module 5

Scientific discussion during initial procedure

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Perindopril 2mg, 4mg and 8mg Tablets in the treatment of hypertension, heart failure and risk reduction of cardiac events in patients with a history of myocardial infarction and/or revascularisation, could be approved. A national marketing authorisation was granted on 24th July 2006.

These applications were submitted under Article 10.1 of Directive 2001/83 EC (as amended), for Perinodopril 2 mg Tablets, Perinodopril 4 mg Tablets and Perinodopril 8 mg Tablets and have been shown to be generic medicinal products of the originator products. The originator products are Coversyl 2mg, 4mg and 8mg Tablets (Marketing Authorisation Holder: Les Laboratoires Servier, France), which was first granted a licence in France in June 1988.

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.

Perindopril is an angiotensin-converting enzyme (ACE) inhibitor, used in the treatment of hypertension and heart failure. 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 side effects (e.g. cough).

Perindopril is a prodrug which, following oral absorption, is hydrolysed to its active metabolite, perindoprilat. The other metabolites show no inhibition of ACE activity *in vitro*.

No new preclinical studies were conducted, which is acceptable given that the applications were based on essential similarity to 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 GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

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.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Perindopril 2mg, 4mg and 8mg Tablets
Name(s) of the active substance(s) (INN)	Perindopril Tert-Butylamine Salt
Pharmacotherapeutic classification (ATC code)	ACE inhibitors, plain (C09A A04)
Pharmaceutical form and strength(s)	2mg, 4mg and 8mg Tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/997/01-03/MR
Reference Member State	United Kingdom
Member States concerned	Czech Republic, The Netherlands, Poland (UK/H/997/01/MR) Czech Republic, The Netherlands, Poland and Italy (UK/H/997/02/MR) Czech Republic, The Netherlands, Poland (UK/H/997/03/MR)
Marketing Authorisation Number(s)	PL 15922/0078-80
Name and address of the authorisation holder	Apotex Europe Limited, Rowan House, 41 London Street, Reading, Berkshire, RG1 4PS

III SCIENTIFIC OVERVIEW AND DISCUSSION

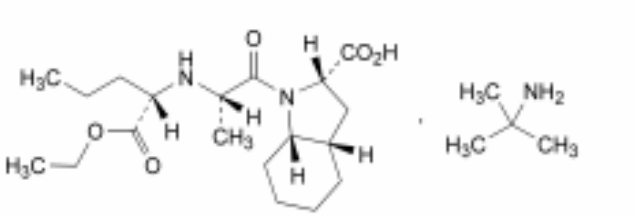
III.1 QUALITY ASPECTS

S. Active substance

INN name: Perindopril Tert-butylamine Salt

Chemical name: (2)-2-[(1S)-1 carbethoxbutylamino]-1-oxopropyl-(2S,3aS,7aS)-perhydroindole-2-carboxylic acid,t-butlamine salt.

Structural formula



Molecular formula: $C_{23}H_{43}N_3O_5$
Molecular weight: 441.6

General Properties

Characteristics: White or almost white, crystalline powder, slightly hygroscopic. Solubility: freely soluble in water (pH 1.2 to 8.0) and in alcohol, sparingly soluble in methylene chloride.

Polymorphism and potential isomerism:
This information has been satisfactorily discussed and analytical results have been provided. Perindopril contains five chiral carbons. The potential impurities are listed in the transparency statement of the Ph. Eur. monograph and are well controlled by the analytical method.

The drug substance is described in a monograph of the European Pharmacopoeia and the application is supported by a drug master file (DMF) provided by the drug substance manufacturer. The DMF has been assessed and is satisfactory.

The drug substance specification is in-line with the requirements of the Ph. Eur. Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug.

P. Medicinal Product

Other Ingredients

Other ingredients consist of pharmaceutical excipients namely lactose anhydrous and magnesium stearate.

Satisfactory certificates of analysis have been provided for both ingredients showing compliance with their respective EP monograph.

Both the excipients used contain material derived from animal or human origin. The applicant has provided a declaration that milk used in the production of lactose

anhydrous is sourced from healthy animals under the same conditions as that for human consumption and a satisfactory TSE certificate of suitability has been provided for the supplier of magnesium stearate.

Pharmaceutical development
The objectives of the development programme were to develop a formula and a manufacturing process for Perindopril Tablets, to produce tablets with the following characteristics:
1) similar appearance to the brand product (colour, size and shape)
2) comparable dissolution profile to the brand
3) bioequivalent to the brand
4) meet all physical and chemical specifications for the dosage form in general and for this product in particular

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated on nine pilot-scale batches with satisfactory results and process validation protocol for the proposed commercial scale-up batches have been provided and are acceptable.

Finished Product Specification
The finished product specifications proposed are acceptable. 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 working standards used.

Container-Closure System
Perindopril tablets are blister packed employing an aluminium/PVC cold formable foil and an aluminium PVC/PVAC blister foilin pack sizes of 4, 7, 14, 15, 28, 30, 50, 56, 60, 90, 100, 112, 120, 500 tablets. Specifications and a certificate of analysis have been provided. The materials supplier has provided a statement of compliance to EEC directives as confirmation that the packaging is suitable for contact with foodstuffs.

Stability of the product
Stability studies have been performed on the nine pilot-scale batches (three batches of each strength). All batches are packaged in the proposed commercial packaging. Stability testing is performed according to the relevant ICH guidelines.
Based on the results of the stability studies, the applicant has proposed a shelf life of 2 years, with storage conditions of “Store in original package” and “Store below 25°C”. These are acceptable.

SPC, PIL, Labels
The SPC, PIL and Labels are pharmaceutically acceptable. 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.

Conclusion
The grant of marketing authorisations is recommended.

III.2 PRE-CLINICAL ASPECTS
The applicant's expert provides a sufficiently comprehensive overview of the pharmacology and toxicology of perindopril. No new preclinical toxicology data were submitted, which is acceptable given the nature of these applications.

III.3 CLINICAL ASPECTS

BACKGROUND
ATC Code: CO9A A04, ACE inhibitors, plain

The innovator product Coversyl tablets is marketed throughout Europe by Servier Laboratories.

There is no evidence of a direct relationship between plasma concentrations of perindopril/perindoprilat and haemodynamic response, at therapeutic doses. The dose response to perindopril does appear to be linear over the range of 2-8mg daily in hypertensive patients.

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 infraction and/or revascularisation.

Assessor's comments
This is consistent with the SPC of the reference product.

DOSE & DOSE SCHEDULE
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 special precautions for use") and blood pressure response.

Hypertension
Perindopril may be used in monotherapy or in combination with other classes of antihyper–tensive 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 special 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 adjus ted 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 special precautions for use").

Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with 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 special 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 the next week, before increasing the dose up to 8 mg one 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
$Cl_{CR} = 60$	4 mg per day
$30 < Cl_{CR} < 60$	2 mg per day
$15 < Cl_{CR} < 30$	2 mg every other day
Haemodialysed patients *	
$Cl_{CR} < 15$	2 mg on the day of dialysis

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

Dosage adjustment in hepatic impairment
No dosage adjustment is necessary in patients with hepatic impairment (see sections 4.4 "Special warnings and special precautions for use" and 5.2 "Pharmacokinetic properties")

Paediatric use
Efficacy and safety of use in children has not been established. Therefore, use in children is not recommended.

Assessor's comments
This is consistent with the SPC of the reference product.

TOXICOLOGY
Perindopril has been in clinical use for many years. The applicant has provided a non-clinical overview written by Dr Peter Honerjager, M.D, PhD, Professor of Pharmacology and Toxicology who is a CEO of an independent pharmaceutical consultant company.

CLINICAL PHARMACOLOGY
The clinical pharmacology of perindopril is well known. The drug has been in clinical use for many years.

Bioequivalence study
A single-dose bioeqvivalence study was conducted comparing 8mg tablet (Apotex) with the brand leader Coversyl 8 mg tablet. The study was randomised, comparative and two-way crossover design. Healthy male subjects (18–55 years of age) were recruited in this study. The study was conducted according to GCP guidelines and according to the Health Canada Food and Drug Regulations.
The subjects received a single 8mg tablets of either the test or the reference product, on two separate occasions, following an overnight fast. The sampling period was 120 hours. There was a washout period of 3 weeks between each treatment.

Perindopril and perindoprilat were measured by means of a HPLC/MS/MS method using analytical ranges of 0.501–100.1 ng/ml for perindopril and 0.500-25.000 ng/ml for perindoprilat.

Summary pharmackokinetic data for perindopril : mean* (%CV)

Parameter	Apotex Perindopril 8 mg	Coversyl 8 mg	Relative mean** (%)	90% Confidence interval
C_{max} (ng/ml)	75.5 (25)	73.0 (26)	103.8	97.4 – 110.6
AUC_{0-t} (ng.hr/ml)	89.3 (24)	87.2 (22)	102.1	98.2 – 106.2
$AUC_{0-\infty}$ (ng.hr/ml)	91.1 (24)	87.9 (22)	104.4	101.8 – 107.0
T_{max} (hr)	0.66 (26)	0.66 (21)	113.2	

* for raw data. For T_{max} these are medians

** based on least square means (geometric means for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$; T_{max} was calculated by a non-parametric method.

Summary pharmackokinetic data for perindoprilat : mean* (%CV)

Parameter	Apotex Perindopril 8 mg	Coversyl 8 mg	Relative mean** (%)	90% Confidence interval
C_{max} (ng/ml)	12.02 (48)	10.54 (46)	113.4	108.2 – 118.9
AUC_{0-t} (ng.hr/ml)	190.1 (31)	184.1 (31)	103.7	100.7 – 106.9
$AUC_{0-\infty}$ (ng.hr/ml)	230.0 (31)	225.7 (31)	102.4	99.4 – 105.4
T_{max} (hr)	4.02 (32)	5.00 (36)	99.4	

* for raw data. For T_{max} these are medians

** based on least square means (geometric means for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$; T_{max} was calculated by a non-parametric method.

Assessor's comments on bioequivalence

The kinetic data show bioequivalence both for the parent compound as well as for the metabolite. As kinetics of Perindopril is considered linear, a single bioequivalence study with the highest dose is acceptable.

EFFICACY

The clinical efficacy of perindopril is known. This has been clinically used for many years in treatment of hypertension and heart failure.

SAFETY

The safety profile of perindopril is well known through its extensive use in clinical practice.

EXPERT REPORT

A suitably qualified person wrote the clinical overview. The report has adequately addressed the issue of efficacy and safety and has discussed the bioequivalence study.

SUMMARY OF PRODUCT CHARACTERISTICS

The SPCs are in line with those of the reference products and are satisfactory.

PATIENT INFORMATION LEAFLET

The PIL is satisfactory.

LABELLING
Medically satisfactory.

DISCUSSION
Essential similarity of the proposed formulation with the reference product has been shown. Bioequivalence of the 8mg tablet is accepted. As the kinetics of perindopril are considered linear, a single BE study is acceptable.

The clinical safety and efficacy of perindopril is well established as it has been used extensively in clinical practice.

The SPCs are in line with those for the reference products and are satisfactory. The PIL and labelling are medically satisfactory.

CONCLUSIONS
The grant of marketing authorisations is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Perindopril 2 mg, 4 mg and 8 mg 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 8 mg Tablets and the reference product Coversyl® 8 mg Tablets (Servier Laboratories Ltd). As these products meet the criteria as 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 can be extrapolated to the 2 mg and 4 mg strength tablets.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with perindopril erbumine is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome