Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Perindopril 2mg and 4mg Tablets

UK/H/0965/001-2/DC
UK licence no: PL 04416/0758-9

UK/H/0966/001-2/DC
UK licence no: PL 04416/0761-2

UK/H/0967/001-2/DC
UK licence no: PL 04416/0764-5

Sandoz Ltd

LAY SUMMARY

On 14 March 2008, the MHRA granted Sandoz Ltd Marketing Authorisations (licences) for the medicinal products Perindopril 2mg Tablets (PL 04416/0758, PL 04416/0761 and PL 04416/0764) and Perindopril 4mg Tablets (PL 04416/0759, PL 04416/0762 and PL 04416/0765). These are prescription only medicines for the treatment of high blood pressure and heart failure and for the reduction in the risk of heart related problems.

Perindopril works by widening the blood vessels which makes it easier for your 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 and 4mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.

TABLE OF CONTENTS

Module 1: Information About Initial Procedure Page 4

Module 2: Summary of Product Characteristics Page 6

Module 3: Patient Information Leaflet Page 96

Module 4: Labelling Page 98

Module 5: Scientific Discussion During Initial Procedure Page 104

I Introduction
II About the Product
III Scientific Overview and Discussion
IV Overall Conclusion and Benefit-Risk Assessment

Module 6: Steps Taken After Initial Procedure - Summary Page 113

Module 1

Information About Initial Procedure

Product Name	Perindopril 2mg Tablets
Type of Application	Article 10.1, Generic Application
Active Substance	Perindopril tert-butylamine
Form	Tablet
Strength	2mg
MA Holder	Sandoz Ltd 37 Woolmer Way Bordon Hampshire GU35 9QE
Reference Member State	United Kingdom
Concerned Member States	PL 04416/0758 UK/H/0965/01/DC Belgium, Czech Republic, Denmark, Finland, France, Netherlands, Poland, Portugal, Slovenia and Slovakia. PL 04416/0761 UK/H/0966/01/DC Czech Republic, Germany, Hungary and Slovakia. PL 04416/0764 UK/H/0967/01/DC Denmark, Finland, France, Hungary, Ireland and Poland.
Procedure Number	UK/H/0965-7/01/DC
Timetable	Day 210 – 22 January 2008

Product Name	Perindopril 4mg Tablets
Type of Application	Article 10.1, Generic Application
Active Substance	Perindopril tert-butylamine
Form	Tablet
Strength	4mg
MA Holder	Sandoz Ltd 37 Woolmer Way Bordon Hampshire GU35 9QE
Reference Member State	United Kingdom
Concerned Member States	PL 04416/0759 UK/H/0965/02/DC Belgium, Czech Republic, Denmark, Finland, France, Italy, Netherlands, Poland, Portugal, Slovenia and Slovakia. PL 04416/0762 UK/H/0966/02/DC Czech Republic, Germany, Hungary, Lithuania, Latvia and Slovakia. PL 04416/0765 UK/H/0967/02/DC Germany, Denmark, Finland, France, Hungary, Ireland, Italy, Lithuania, Luxembourg, Latvia and Poland.
Procedure Number	UK/H/0965-7/02/DC
Timetable	Day 210 – 22 January 2008

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Perindopril 2 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains, 2 mg perindopril tert-butylamine, equivalent to 1.669 mg perindopril.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, round, biconvex tablet debossed with 2 on one side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Hypertension:

  Treatment of hypertension

- Heart failure:

  Treatment of symptomatic heart failure

- Stable coronary artery disease:

  Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation

4.2 Posology and method of administration

It is recommended that Perindopril tert-butylamine is taken once daily in the morning before a meal with sufficient amount of fluid (e.g. water).

The dose should be individualised according to the patient profile (see 4.4) and blood pressure response.

Hypertension:

Perindopril tert-butylamine 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 tert-butylamine; 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 (see section 4.4).

In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Perindopril tert-butylamine should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Perindopril tert-butylamine 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, generally associated with a nonpotassium-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).

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. Blood pressure, renal function and serum

potassium should be monitored closely, both before and during treatment with Perindopril tert-butylamine (see section 4.4).

Stable coronary artery disease:

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

Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 mg once daily depending on renal function (see Table 1 "Dosage adjustment in renal impairment"). The dose should be increased only if the previous lower dose is well tolerated.

Dosage adjustment in renal impairment:

Dosage in patients with renal impairment should be based on creatinine clearance as outlined in table 1 below:

Table 1: dosage adjustment in renal impairment

creatinine clearance (ml/min)	***recommended dose***
$Cl_{CR} \geq 60$	4 mg per day
$30 < Cl_{CR} < 60$	2 mg per day
$15 < Cl_{CR} < 30$	2 mg every other day
Haemodialysed patients*, $Cl_{CR} < 15$	2 mg on the day of dialysis

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

Dosage adjustment in hepatic impairment:

No dosage adjustment is necessary in patients with hepatic impairment (see sections 4.4 and 5.2).

Children and adolescents:

Perindopril tert-butylamine is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

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 sections 4.4 and 4.6).

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 volumedepleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). 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 and 4.8). 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 erbumine. 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 may be necessary.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy:

As with other ACE inhibitors, Perindopril tert-butylamine 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) 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).

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 tert-butylamine 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 tert-butylamine 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 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 tert-butylamine 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 tert-butylamine (see 4.8). This may occur at any time during therapy. In such cases, Perindopril tert-butylamine 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).

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis:

Rarely, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Anaphylactic reactions during desensitisation:

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In the same patients, these reactions

have been avoided when the ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Hepatic failure:

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see 4.8).

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. Sporadic occurrences of haemolytic anaemia have been reported on patients with congenital G6-PD deficiency. 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 nonproductive, 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 tert-butylamine 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 abovementioned 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).

Lithium:

The combination of lithium and perindopril is generally not recommended (see 4.5).

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes:

The combination of perindopril and potassium sparing diuretics, potassium supplements or potassiumcontaining salt substitutes is generally not recommended (see 4.5).

Pregnancy:

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.(see sections 4.3 and 4.6).

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

Antihypertensive agents and vasodilators:

Concomitant use of these agents may increase the hypotensive effects of perindopril. Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

Antidiabetic agents:

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood-glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates:

Perindopril may be used concomitantly with acetylsalicylic acid (when used as a thrombolytic), thrombolytics, beta-blockers and/or nitrates.

Tricyclic antidepressants/Antipsychotics/Anesthetics:

Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Sympathomimetics:

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antacids may decrease the bioavailability of perindopril.

4.6 Pregnancy and lactation

Pregnancy:

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4).The use of ACE inhibitors is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy.

When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

ACE inhibitor/ AIIRAs therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also 5.3 'Preclinical safety data'). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see also section 4.3 and 4.4).

Lactation:

It is not known whether perindopril is excreted into human breast milk. Therefore the use of Perindopril tert-butylamine is not recommended in women who are breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

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

4.8 Undesirable effects

The frequency of adverse reactions listed below is defined using the following convention:

Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare (<1/10000), not known (cannot be estimated from the available data)

	common	uncommon	very rare
Psychiatric disorders		mood or sleep disturbances	
Nervous system disorders	headache, dizziness, vertigo, paresthaesia		
Eye disorders	vision disturbance		
Ear and labyrinth disorders	tinnitus		
Cardio-vascular disorders	hypotension and effects related to hypotension		arrhythmia, angina pectoris, myocardial

			infarction and stroke, possibly secondary to excessive hypotension in high-risk patients (see section 4.4).
Respiratory, thoracic and mediastinal disorders	cough, dyspnoea	bronchospasm	eosinophilic pneumonia, rhinitis
Gastro-intestinal disorders	nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea, constipation	dry mouth	pancreatitis
Hepato-biliary disorders			hepatitis either cytolytic or cholestatic (see section 4.4)
Skin and subcutaneous tissue disorders	rash, pruritus	angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see section).	erythema multiforme
Musculoskeletal, connective tissue and bone disorders		muscle cramps	
Renal and urinary disorders		renal insufficiency	acute renal failure
Reproductive system and breast disorders		impotence	
General	asthenia	sweating	

disorders			
Blood and the lymphatic system disorders			Decreases in haemoglobin and haematocrit, thrombocytopenia, leucopenia/ neutropenia, agranulocytosis or pancytopenia In patients with a congenital deficiency of G-6PDH, haemolytic anaemia has been reported (see section 4.4).

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 has been reported rarely.

Clinical trials:

During the randomised period of the EUROPA study, only serious adverse events were collected. Few patients experienced serious adverse events: 16 (0.3%) of the 6122 perindopril patients and 12 (0.2%) of the 6107 placebo patients. In perindopril-treated patients, hypotension was observed in 6 patients, angioedema in 3 patients and sudden cardiac arrest in 1 patient. More patients withdrew for cough, hypotension or other intolerance on perindopril than on placebo, 6.0% (n=366) versus 2.1% (n=129) respectively.

4.9 Overdose

Limited data are available for overdose in humans.

Symptoms associated with overdose of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

The recommended *treatment* of overdose 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

Pharmacotherapeutic group: C09AA - ACE inhibitors, plain; ATC code: C09A A04 perindopril

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 kallikreinkinin 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 tert-butylamine 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 tert-butylamine to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo.

Patients with stable coronary artery disease:

The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years.

Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to perindopril 8 mg (n=6110) or placebo (n=6108).

The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure. Overall, 90% of the patients had a previous myocardial infarction and/or a previous coronary revascularisation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers.

The main efficacy criterion was the composite of cardiovascular mortality, non fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with perindopril 8 mg once daily resulted in a significant absolute reduction in the primary endpoint of 1.9% (relative risk reduction of 20%, 95%CI [9.4; 28.6] – $p<0.001$).

In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2.2% corresponding to a RRR of 22.4% (95%CI [12.0; 31.6] – $p<0.001$) in the primary endpoint was observed by comparison to placebo.

5.2 Pharmacokinetic properties

After oral administration, the absorption of perindopril is rapid and the peak concentration complete within 1 hour. Bioavailability is 65 to 70 %.

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

As ingestion of food decreases conversion to perindoprilat, hence bioavailability, Perindopril tert-butylamine 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 and 4.4).

5.3 Preclinical safety data

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

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Silicified microcrystalline cellulose

Polacrillin potassium

Silicone dioxide

Colloidal anhydrous silica

Magnesium stearate

Hydroxypropylbetadex

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30° C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Aluminium/Aluminium blister.

Pack sizes: 7, 10, 14, 15, 20, 28, 30, 50, 56, 60, 90, 100, 112, 120 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited

37 Woolmer Way

Bordon

Hampshire

GU35 9QE

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/0758

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/04/2008

10 DATE OF REVISION OF THE TEXT

14/04/2008

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Perindopril 2 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains, 2 mg perindopril tert-butylamine, equivalent to 1.669 mg perindopril.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, round, biconvex tablet debossed with 2 on one side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Hypertension:

  Treatment of hypertension

- Heart failure:

  Treatment of symptomatic heart failure

- Stable coronary artery disease:

  Reduction of risk of cardiac events in patients with a history of myocardial infarction and/o revascularisation

4.2 Posology and method of administration

It is recommended that Perindopril tert-butylamine is taken once daily in the morning before a meal with sufficient amount of fluid (e.g. water).

The dose should be individualised according to the patient profile (see 4.4) and blood pressure response.

Hypertension:

Perindopril tert-butylamine 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 tert-butylamine; 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 (see section 4.4).

In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Perindopril tert-butylamine should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Perindopril tert-butylamine 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, generally associated with a nonpotassium-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).

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. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with Perindopril tert-butylamine (see section 4.4).

Stable coronary artery disease:

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

Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 mg once daily depending on renal function (see Table 1 "Dosage adjustment in renal impairment"). The dose should be increased only if the previous lower dose is well tolerated.

Dosage adjustment in renal impairment:

Dosage in patients with renal impairment should be based on creatinine clearance as outlined in table 1 below:

Table 1: dosage adjustment in renal impairment

creatinine clearance (ml/min)	*recommended dose*
$Cl_{CR} \geq 60$	4 mg per day
$30 < Cl_{CR} < 60$	2 mg per day
$15 < Cl_{CR} < 30$	2 mg every other day
Haemodialysed patients*, $Cl_{CR} < 15$	2 mg on the day of dialysis

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

Dosage adjustment in hepatic impairment:

No dosage adjustment is necessary in patients with hepatic impairment (see sections 4.4 and 5.2).

Children and adolescents:

Perindopril tert-butylamine is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

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 sections 4.4 and 4.6).

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 volumedepleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). 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 and 4.8). 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 erbumine. 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 may be necessary.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy:

As with other ACE inhibitors, Perindopril tert-butylamine 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) 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).

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 tert-butylamine 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 tert-butylamine 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 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 tert-butylamine 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 tert-butylamine (see 4.8). This may occur at any time during therapy. In such cases, Perindopril tert-butylamine 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).

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis:

Rarely, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Anaphylactic reactions during desensitisation:

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In the same patients, these reactions have been avoided when the ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Hepatic failure:

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see 4.8).

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. Sporadic occurrences of haemolytic anaemia have been reported on patients with congenital G6-PD deficiency. 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 nonproductive, 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 tert-butylamine 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 abovementioned 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).

Lithium:

The combination of lithium and perindopril is generally not recommended (see 4.5).

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes:

The combination of perindopril and potassium sparing diuretics, potassium supplements or potassiumcontaining salt substitutes is generally not recommended (see 4.5).

Pregnancy:

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.(see sections 4.3 and 4.6).

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

Antihypertensive agents and vasodilators:

Concomitant use of these agents may increase the hypotensive effects of perindopril. Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

Antidiabetic agents:

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood-glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates:

Perindopril may be used concomitantly with acetylsalicylic acid (when used as a thrombolytic), thrombolytics, beta-blockers and/or nitrates.

Tricyclic antidepressants/Antipsychotics/Anesthetics:

Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Sympathomimetics:

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antacids may decrease the bioavailability of perindopril.

4.6 Pregnancy and lactation

Pregnancy:

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4).The use of ACE inhibitors is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

ACE inhibitor/ AIIRAs therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also 5.3 'Preclinical safety data'). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see also section 4.3 and 4.4).

Lactation:

It is not known whether perindopril is excreted into human breast milk. Therefore the use of Perindopril tert-butylamine is not recommended in women who are breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

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

4.8 Undesirable effects

The frequency of adverse reactions listed below is defined using the following convention:

Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare (<1/10000), not known (cannot be estimated from the available data)

	common	uncommon	very rare
Psychiatric disorders		mood or sleep disturbances	
Nervous system disorders	headache, dizziness, vertigo, paresthaesia		
Eye disorders	vision disturbance		
Ear and labyrinth disorders	tinnitus		
Cardio-vascular disorders	hypotension and effects related to hypotension		arrhythmia, angina pectoris, myocardial infarction and stroke, possibly secondary to excessive hypotension in high-risk patients (see section 4.4).
Respiratory, thoracic and mediastinal disorders	cough, dyspnoea	bronchospasm	eosinophilic pneumonia, rhinitis
Gastro-intestinal	nausea, vomiting,	dry mouth	pancreatitis

disorders	abdominal pain, dysgeusia, dyspepsia, diarrhoea, constipation		
Hepato-biliary disorders			hepatitis either cytolytic or cholestatic (see section 4.4)
Skin and subcutaneous tissue disorders	rash, pruritus	angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see section).	erythema multiforme
Musculoskeletal, connective tissue and bone disorders		muscle cramps	
Renal and urinary disorders		renal insufficiency	acute renal failure
Reproductive system and breast disorders		impotence	
General disorders	asthenia	sweating	
Blood and the lymphatic system disorders			Decreases in haemoglobin and haematocrit, thrombocytopenia, leucopenia/ neutropenia, agranulocytosis or pancytopenia In patients with a congenital deficiency of G-6PDH, haemolytic

			anaemia has been reported (see section 4.4).

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 has been reported rarely.

Clinical trials:

During the randomised period of the EUROPA study, only serious adverse events were collected. Few patients experienced serious adverse events: 16 (0.3%) of the 6122 perindopril patients and 12 (0.2%) of the 6107 placebo patients. In perindopril-treated patients, hypotension was observed in 6 patients, angioedema in 3 patients and sudden cardiac arrest in 1 patient. More patients withdrew for cough, hypotension or other intolerance on perindopril than on placebo, 6.0% (n=366) versus 2.1% (n=129) respectively.

4.9 Overdose

Limited data are available for overdose in humans.

Symptoms associated with overdose of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

The recommended *treatment* of overdose 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

Pharmacotherapeutic group: C09AA - ACE inhibitors, plain; ATC code: C09A A04 perindopril

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 kallikreinkinin 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 tert-butylamine 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 tert-butylamine to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo.

Patients with stable coronary artery disease:

The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years.

Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to perindopril 8 mg (n=6110) or placebo (n=6108).

The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure. Overall, 90% of the patients had a previous myocardial infarction and/or a previous coronary revascularisation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers.

The main efficacy criterion was the composite of cardiovascular mortality, non fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with perindopril 8 mg once daily resulted in a significant absolute reduction in the primary endpoint of 1.9% (relative risk reduction of 20%, 95%CI [9.4; 28.6] – $p<0.001$).

In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2.2% corresponding to a RRR of 22.4% (95%CI [12.0; 31.6] – $p<0.001$) in the primary endpoint was observed by comparison to placebo.

5.2 Pharmacokinetic properties

After oral administration, the absorption of perindopril is rapid and the peak concentration complete within 1 hour. Bioavailability is 65 to 70 %.

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

As ingestion of food decreases conversion to perindoprilat, hence bioavailability, Perindopril tert-butylamine 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 and 4.4).

5.3 Preclinical safety data

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

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Silicified microcrystalline cellulose

Polacrillin potassium

Silicone dioxide

Colloidal anhydrous silica

Magnesium stearate

Hydroxypropylbetadex

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30° C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Aluminium/Aluminium blister.

Pack sizes: 7, 10, 14, 20, 28, 30, 50, 56, 60, 90, 100, 112, 500 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited

37 Woolmer Way

Bordon

Hampshire

GU35 9QE

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/0761

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/04/2008

10 DATE OF REVISION OF THE TEXT

14/04/2008

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Perindopril 2 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains, 2 mg perindopril tert-butylamine, equivalent to 1.669 mg perindopril.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, round, biconvex tablet debossed with 2 on one side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Hypertension:

  Treatment of hypertension

- Heart failure:

  Treatment of symptomatic heart failure

- Stable coronary artery disease:

  Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation

4.2 Posology and method of administration

It is recommended that Perindopril tert-butylamine is taken once daily in the morning before a meal with sufficient amount of fluid (e.g. water).

The dose should be individualised according to the patient profile (see 4.4) and blood pressure response.

Hypertension:

Perindopril tert-butylamine 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 tert-butylamine; 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 (see section 4.4).

In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Perindopril tert-butylamine should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Perindopril tert-butylamine 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, generally associated with a nonpotassium-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).

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. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with Perindopril tert-butylamine (see section 4.4).

Stable coronary artery disease:

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

Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 mg once daily depending on renal function (see Table 1 "Dosage adjustment in renal impairment"). The dose should be increased only if the previous lower dose is well tolerated.

Dosage adjustment in renal impairment:

Dosage in patients with renal impairment should be based on creatinine clearance as outlined in table 1 below:

Table 1: dosage adjustment in renal impairment

creatinine clearance (ml/min)	*recommended dose*
$Cl_{CR} \geq 60$	4 mg per day
$30 < Cl_{CR} < 60$	2 mg per day
$15 < Cl_{CR} < 30$	2 mg every other day
Haemodialysed patients*, $Cl_{CR} < 15$	2 mg on the day of dialysis

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

Dosage adjustment in hepatic impairment:

No dosage adjustment is necessary in patients with hepatic impairment (see sections 4.4 and 5.2).

Children and adolescents:

Perindopril tert-butylamine is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

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 sections 4.4 and 4.6).

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 volumedepleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). 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 and 4.8). 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 erbumine. 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 may be necessary.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy:

As with other ACE inhibitors, Perindopril tert-butylamine 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) 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).

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 tert-butylamine 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 tert-butylamine 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 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 tert-butylamine 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 tert-butylamine (see 4.8). This may occur at any time during therapy. In such cases, Perindopril tert-butylamine 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).

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis:

Rarely, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Anaphylactic reactions during desensitisation:

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In the same patients, these reactions have been avoided when the ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Hepatic failure:

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see 4.8).

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. Sporadic occurrences of haemolytic anaemia have been reported on patients with congenital G6-PD deficiency. 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 nonproductive, 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 tert-butylamine 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 abovementioned 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).

Lithium:

The combination of lithium and perindopril is generally not recommended (see 4.5).

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes:

The combination of perindopril and potassium sparing diuretics, potassium supplements or potassiumcontaining salt substitutes is generally not recommended (see 4.5).

Pregnancy:

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.(see sections 4.3 and 4.6).

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

Antihypertensive agents and vasodilators:

Concomitant use of these agents may increase the hypotensive effects of perindopril. Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

Antidiabetic agents:

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood-glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates:

Perindopril may be used concomitantly with acetylsalicylic acid (when used as a thrombolytic), thrombolytics, beta-blockers and/or nitrates.

Tricyclic antidepressants/Antipsychotics/Anesthetics:

Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Sympathomimetics:

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antacids may decrease the bioavailability of perindopril.

4.6 Pregnancy and lactation

Pregnancy:

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4).The use of ACE inhibitors is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

ACE inhibitor/ AIIRAs therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also 5.3 'Preclinical safety data'). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see also section 4.3 and 4.4).

Lactation:

It is not known whether perindopril is excreted into human breast milk. Therefore the use of Perindopril tert-butylamine is not recommended in women who are breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

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

4.8 Undesirable effects

The frequency of adverse reactions listed below is defined using the following convention:

Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare (<1/10000), not known (cannot be estimated from the available data)

	common	uncommon	very rare
Psychiatric disorders		mood or sleep disturbances	
Nervous system disorders	headache, dizziness, vertigo, paresthaesia		
Eye disorders	vision disturbance		
Ear and labyrinth disorders	tinnitus		
Cardio-vascular disorders	hypotension and effects related to hypotension		arrhythmia, angina pectoris, myocardial infarction and stroke, possibly secondary to excessive hypotension in high-risk patients (see section 4.4).
Respiratory, thoracic and mediastinal	cough, dyspnoea	bronchospasm	eosinophilic pneumonia, rhinitis

disorders			
Gastro-intestinal disorders	nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea, constipation	dry mouth	pancreatitis
Hepato-biliary disorders			hepatitis either cytolytic or cholestatic (see section 4.4)
Skin and subcutaneous tissue disorders	rash, pruritus	angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see section).	erythema multiforme
Musculoskeletal, connective tissue and bone disorders		muscle cramps	
Renal and urinary disorders		renal insufficiency	acute renal failure
Reproductive system and breast disorders		impotence	
General disorders	asthenia	sweating	
Blood and the lymphatic system disorders			Decreases in haemoglobin and haematocrit, thrombocytopenia, leucopenia/ neutropenia, agranulocytosis or pancytopenia In patients with a congenital

			deficiency of G-6PDH, haemolytic anaemia has been reported (see section 4.4).

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 has been reported rarely.
Clinical trials:
During the randomised period of the EUROPA study, only serious adverse events were collected. Few patients experienced serious adverse events: 16 (0.3%) of the 6122 perindopril patients and 12 (0.2%) of the 6107 placebo patients. In perindopril-treated patients, hypotension was observed in 6 patients, angioedema in 3 patients and sudden cardiac arrest in 1 patient. More patients withdrew for cough, hypotension or other intolerance on perindopril than on placebo, 6.0% (n=366) versus 2.1% (n=129) respectively.

4.9 Overdose

Limited data are available for overdose in humans.

Symptoms associated with overdose of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

The recommended *treatment* of overdose 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

Pharmacotherapeutic group: C09AA - ACE inhibitors, plain; ATC code: C09A A04 perindopril

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 kallikreinkinin 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 tert-butylamine 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 tert-butylamine to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo.

Patients with stable coronary artery disease:

The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years.

Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to perindopril 8 mg (n=6110) or placebo (n=6108).

The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure. Overall, 90% of the patients had a previous myocardial infarction and/or a previous coronary revascularisation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers.

The main efficacy criterion was the composite of cardiovascular mortality, non fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with perindopril 8 mg once daily resulted in a significant absolute reduction in the primary endpoint of 1.9% (relative risk reduction of 20%, 95%CI [9.4; 28.6] – $p<0.001$).

In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2.2% corresponding to a RRR of 22.4% (95%CI [12.0; 31.6] – $p<0.001$) in the primary endpoint was observed by comparison to placebo.

5.2 Pharmacokinetic properties

After oral administration, the absorption of perindopril is rapid and the peak concentration complete within 1 hour. Bioavailability is 65 to 70 %.

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

As ingestion of food decreases conversion to perindoprilat, hence bioavailability, Perindopril tert-butylamine 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 and 4.4).

5.3 Preclinical safety data

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

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Silicified microcrystalline cellulose

Polacrillin potassium

Silicone dioxide

Colloidal anhydrous silica

Magnesium stearate

Hydroxypropylbetadex

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30° C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Aluminium/Aluminium blister.

Pack sizes: 7, 10, 14, 15, 20, 28, 30, 50, 56, 60, 90, 100, 112, 120, 500 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited

37 Woolmer Way

Bordon

Hampshire

GU35 9QE

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/0764

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/04/2008

10 DATE OF REVISION OF THE TEXT

14/04/2008

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Perindopril 4 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains, 4 mg perindopril tert-butylamine, equivalent to 3.338 mg perindopril

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, round, biconvex tablet scored on one side and debossed with 4 on the reverse side. The tablet 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 infarction and/o revascularisation

4.2 Posology and method of administration

It is recommended that Perindopril tert-butylamine is taken once daily in the morning before a meal with sufficient amount of fluid (e.g. water).

The dose should be individualised according to the patient profile (see 4.4) and blood pressure response.

Hypertension:

Perindopril tert-butylamine 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 tert-butylamine; 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 (see section 4.4).

In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Perindopril tert-butylamine should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Perindopril tert-butylamine 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, generally associated with a nonpotassium-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).

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. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with Perindopril tert-butylamine (see section 4.4).

Stable coronary artery disease:

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

Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 mg once daily depending on renal function (see Table 1 "Dosage adjustment in renal impairment"). The dose should be increased only if the previous lower dose is well tolerated.

Dosage adjustment in renal impairment:

Dosage in patients with renal impairment should be based on creatinine clearance as outlined in table 1 below:

Table 1: dosage adjustment in renal impairment

creatinine clearance (ml/min)	*recommended dose*
$Cl_{CR} \geq 60$	4 mg per day
$30 < Cl_{CR} < 60$	2 mg per day
$15 < Cl_{CR} < 30$	2 mg every other day
Haemodialysed patients*, $Cl_{CR} < 15$	2 mg on the day of dialysis

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

Dosage adjustment in hepatic impairment:

No dosage adjustment is necessary in patients with hepatic impairment (see sections 4.4 and 5.2).

Children and adolescents:

Perindopril tert-butylamine is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

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 sections 4.4 and 4.6).

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 volumedepleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). 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 and 4.8). 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 erbumine. 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 may be necessary.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy:

As with other ACE inhibitors, Perindopril tert-butylamine 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) 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).

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 tert-butylamine 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 tert-butylamine 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 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 tert-butylamine 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 tert-butylamine (see 4.8). This may occur at any time during therapy. In such cases, Perindopril tert-butylamine 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).

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis:

Rarely, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Anaphylactic reactions during desensitisation:

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In the same patients, these reactions have been avoided when the ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Hepatic failure:

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see 4.8).

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. Sporadic occurrences of haemolytic anaemia have been reported on patients with congenital G6-PD deficiency. 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 nonproductive, 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 tert-butylamine 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 abovementioned 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).

Lithium:

The combination of lithium and perindopril is generally not recommended (see 4.5).

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes:

The combination of perindopril and potassium sparing diuretics, potassium supplements or potassiumcontaining salt substitutes is generally not recommended (see 4.5).

Pregnancy:

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.(see sections 4.3 and 4.6).

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

Antihypertensive agents and vasodilators:

Concomitant use of these agents may increase the hypotensive effects of perindopril. Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

Antidiabetic agents:

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood-glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates:

Perindopril may be used concomitantly with acetylsalicylic acid (when used as a thrombolytic), thrombolytics, beta-blockers and/or nitrates.

Tricyclic antidepressants/Antipsychotics/Anesthetics:

Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Sympathomimetics:

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antacids may decrease the bioavailability of perindopril.

4.6 Pregnancy and lactation

Pregnancy:

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4).The use of ACE inhibitors is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

ACE inhibitor/ AIIRAs therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also 5.3 'Preclinical safety data'). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see also section 4.3 and 4.4).

Lactation:

It is not known whether perindopril is excreted into human breast milk. Therefore the use of Perindopril tert-butylamine is not recommended in women who are breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

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

4.8 Undesirable effects

The frequency of adverse reactions listed below is defined using the following convention:

Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare (<1/10000), not known (cannot be estimated from the available data)

	common	uncommon	very rare
Psychiatric disorders		mood or sleep disturbances	
Nervous system disorders	headache, dizziness, vertigo, paresthaesia		
Eye disorders	vision disturbance		
Ear and labyrinth disorders	tinnitus		
Cardio-vascular disorders	hypotension and effects related to hypotension		arrhythmia, angina pectoris, myocardial infarction and stroke, possibly secondary to

			excessive hypotension in high-risk patients (see section 4.4).
Respiratory, thoracic and mediastinal disorders	cough, dyspnoea	bronchospasm	eosinophilic pneumonia, rhinitis
Gastro-intestinal disorders	nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea, constipation	dry mouth	pancreatitis
Hepato-biliary disorders			hepatitis either cytolytic or cholestatic (see section 4.4)
Skin and subcutaneous tissue disorders	rash, pruritus	angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see section).	erythema multiforme
Musculoskeletal, connective tissue and bone disorders		muscle cramps	
Renal and urinary disorders		renal insufficiency	acute renal failure
Reproductive system and breast disorders		impotence	
General disorders	asthenia	sweating	
Blood and the lymphatic			Decreases in haemoglobin

system disorders			and haematocrit, thrombocytopenia, leucopenia/ neutropenia, agranulocytosis or pancytopenia In patients with a congenital deficiency of G-6PDH, haemolytic anaemia has been reported (see section 4.4).

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 has been reported rarely.

Clinical trials:

During the randomised period of the EUROPA study, only serious adverse events were collected. Few patients experienced serious adverse events: 16 (0.3%) of the 6122 perindopril patients and 12 (0.2%) of the 6107 placebo patients. In perindopril-treated patients, hypotension was observed in 6 patients, angioedema in 3 patients and sudden cardiac arrest in 1 patient. More patients withdrew for cough, hypotension or other intolerance on perindopril than on placebo, 6.0% (n=366) versus 2.1% (n=129) respectively.

4.9 Overdose

Limited data are available for overdose in humans.

Symptoms associated with overdose of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

The recommended *treatment* of overdose 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

Pharmacotherapeutic group: C09AA - ACE inhibitors, plain; ATC code: C09A A04 perindopril

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 kallikreinkinin 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 tert-butylamine 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 tert-butylamine to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo.

Patients with stable coronary artery disease:

The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years.

Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to perindopril 8 mg (n=6110) or placebo (n=6108).

The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure. Overall, 90% of the patients had a previous myocardial infarction and/or a previous coronary revascularisation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers.

The main efficacy criterion was the composite of cardiovascular mortality, non fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with perindopril 8 mg once daily resulted in a significant absolute reduction in the primary endpoint of 1.9% (relative risk reduction of 20%, 95%CI [9.4; 28.6] – $p<0.001$).

In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2.2% corresponding to a RRR of 22.4% (95%CI [12.0; 31.6] – $p<0.001$) in the primary endpoint was observed by comparison to placebo.

5.2 Pharmacokinetic properties

After oral administration, the absorption of perindopril is rapid and the peak concentration complete within 1 hour. Bioavailability is 65 to 70 %.

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

As ingestion of food decreases conversion to perindoprilat, hence bioavailability, Perindopril tert-butylamine 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 and 4.4).

5.3 Preclinical safety data

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

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Silicified microcrystalline cellulose

Polacrillin potassium

Silicone dioxide

Colloidal anhydrous silica

Magnesium stearate

Hydroxypropylbetadex

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30° C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Aluminium/Aluminiumblister.

Pack sizes: 7, 10, 14, 15, 20, 28, 30, 50, 56, 60, 90, 100, 112, 120 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited

37 Woolmer Way

Bordon

Hampshire

GU35 9QE

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/0759

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/04/2008

10 DATE OF REVISION OF THE TEXT

14/04/2008

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Perindopril 4 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains, 4 mg perindopril tert-butylamine, equivalent to 3.338 mg perindopril

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, round, biconvex tablet scored on one side and debossed with 4 on the reverse side. The tablet 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 infarction and/or revascularisation

4.2 Posology and method of administration

It is recommended that Perindopril tert-butylamine is taken once daily in the morning before a meal with sufficient amount of fluid (e.g. water).

The dose should be individualised according to the patient profile (see 4.4) and blood pressure response.

Hypertension:

Perindopril tert-butylamine 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 tert-butylamine; 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 (see section 4.4).

In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Perindopril tert-butylamine should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Perindopril tert-butylamine 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, generally associated with a nonpotassium-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).

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. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with Perindopril tert-butylamine (see section 4.4).

Stable coronary artery disease:

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

Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 mg once daily depending on renal function (see Table 1 "Dosage adjustment in renal impairment"). The dose should be increased only if the previous lower dose is well tolerated.

Dosage adjustment in renal impairment:

Dosage in patients with renal impairment should be based on creatinine clearance as outlined in table 1 below:

Table 1: dosage adjustment in renal impairment

creatinine clearance (ml/min)	*recommended dose*
$Cl_{CR} \geq 60$	4 mg per day
$30 < Cl_{CR} < 60$	2 mg per day
$15 < Cl_{CR} < 30$	2 mg every other day
Haemodialysed patients*, $Cl_{CR} < 15$	2 mg on the day of dialysis

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

Dosage adjustment in hepatic impairment:

No dosage adjustment is necessary in patients with hepatic impairment (see sections 4.4 and 5.2).

Children and adolescents:

Perindopril tert-butylamine is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

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 sections 4.4 and 4.6).

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 volumedepleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). 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 and 4.8). 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 erbumine. 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 may be necessary.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy:

As with other ACE inhibitors, Perindopril tert-butylamine 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) 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).

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 tert-butylamine 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 tert-butylamine 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 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 tert-butylamine 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 tert-butylamine (see 4.8). This may occur at any time during therapy. In such cases, Perindopril tert-butylamine 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).

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis:

Rarely, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Anaphylactic reactions during desensitisation:

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In the same patients, these reactions have been avoided when the ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Hepatic failure:

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see 4.8).

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. Sporadic occurrences of haemolytic anaemia have been reported on patients with congenital G6-PD deficiency. 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 nonproductive, 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 tert-butylamine 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 abovementioned 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).

Lithium:

The combination of lithium and perindopril is generally not recommended (see 4.5).

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes:

The combination of perindopril and potassium sparing diuretics, potassium supplements or potassiumcontaining salt substitutes is generally not recommended (see 4.5).

Pregnancy:

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.(see sections 4.3 and 4.6).

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

Antihypertensive agents and vasodilators:

Concomitant use of these agents may increase the hypotensive effects of perindopril. Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

Antidiabetic agents:

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood-glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates:

Perindopril may be used concomitantly with acetylsalicylic acid (when used as a thrombolytic), thrombolytics, beta-blockers and/or nitrates.

Tricyclic antidepressants/Antipsychotics/Anesthetics:

Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Sympathomimetics:

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antacids may decrease the bioavailability of perindopril.

4.6 Pregnancy and lactation

Pregnancy:

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4).The use of ACE inhibitors is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

ACE inhibitor/ AIIRAs therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also 5.3 'Preclinical safety data'). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see also section 4.3 and 4.4).

Lactation:

It is not known whether perindopril is excreted into human breast milk. Therefore the use of Perindopril tert-butylamine is not recommended in women who are breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

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

4.8 Undesirable effects

The frequency of adverse reactions listed below is defined using the following convention:

Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare (<1/10000), not known (cannot be estimated from the available data)

	common	uncommon	very rare
Psychiatric disorders		mood or sleep disturbances	
Nervous system disorders	headache, dizziness, vertigo, paresthaesia		
Eye disorders	vision disturbance		
Ear and labyrinth disorders	tinnitus		
Cardio-vascular disorders	hypotension and effects related to hypotension		arrhythmia, angina pectoris, myocardial infarction and stroke, possibly secondary to

			excessive hypotension in high-risk patients (see section 4.4).
Respiratory, thoracic and mediastinal disorders	cough, dyspnoea	bronchospasm	eosinophilic pneumonia, rhinitis
Gastro-intestinal disorders	nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea, constipation	dry mouth	pancreatitis
Hepato-biliary disorders			hepatitis either cytolytic or cholestatic (see section 4.4)
Skin and subcutaneous tissue disorders	rash, pruritus	angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see section).	erythema multiforme
Musculoskeletal, connective tissue and bone disorders		muscle cramps	
Renal and urinary disorders		renal insufficiency	acute renal failure
Reproductive system and breast disorders		impotence	
General disorders	asthenia	sweating	
Blood and the lymphatic			Decreases in haemoglobin

system disorders			and haematocrit, thrombocytopenia, leucopenia/ neutropenia, agranulocytosis or pancytopenia In patients with a congenital deficiency of G-6PDH, haemolytic anaemia has been reported (see section 4.4).

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 has been reported rarely.

Clinical trials:

During the randomised period of the EUROPA study, only serious adverse events were collected. Few patients experienced serious adverse events: 16 (0.3%) of the 6122 perindopril patients and 12 (0.2%) of the 6107 placebo patients. In perindopril-treated patients, hypotension was observed in 6 patients, angioedema in 3 patients and sudden cardiac arrest in 1 patient. More patients withdrew for cough, hypotension or other intolerance on perindopril than on placebo, 6.0% (n=366) versus 2.1% (n=129) respectively.

4.9 Overdose

Limited data are available for overdose in humans.

Symptoms associated with overdose of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

The recommended *treatment* of overdose 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

Pharmacotherapeutic group: C09AA - ACE inhibitors, plain; ATC code: C09A A04 perindopril

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 kallikreinkinin 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 tert-butylamine 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 tert-butylamine to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo.

Patients with stable coronary artery disease:

The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years.

Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to perindopril 8 mg (n=6110) or placebo (n=6108).

The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure. Overall, 90% of the patients had a previous myocardial infarction and/or a previous coronary revascularisation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers.

The main efficacy criterion was the composite of cardiovascular mortality, non fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with perindopril 8 mg once daily resulted in a significant absolute reduction in the primary endpoint of 1.9% (relative risk reduction of 20%, 95%CI [9.4; 28.6] – $p<0.001$).

In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2.2% corresponding to a RRR of 22.4% (95%CI [12.0; 31.6] – $p<0.001$) in the primary endpoint was observed by comparison to placebo.

5.2 Pharmacokinetic properties

After oral administration, the absorption of perindopril is rapid and the peak concentration complete within 1 hour. Bioavailability is 65 to 70 %.

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

As ingestion of food decreases conversion to perindoprilat, hence bioavailability, Perindopril tert-butylamine 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 and 4.4).

5.3 Preclinical safety data

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

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Silicified microcrystalline cellulose

Polacrillin potassium

Silicone dioxide

Colloidal anhydrous silica

Magnesium stearate

Hydroxypropylbetadex

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30° C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Aluminium/Aluminium blister.

Pack sizes: 7, 10, 14, 20, 28, 30, 50, 56, 60, 90, 100, 112, 500 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited

37 Woolmer Way

Bordon

Hampshire

GU35 9QE

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/0762

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/04/2008

10 DATE OF REVISION OF THE TEXT

14/04/2008

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Perindopril 4 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains, 4 mg perindopril tert-butylamine, equivalent to 3.338 mg perindopril

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, round, biconvex tablet scored on one side and debossed with 4 on the reverse side. The tablet 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 infarction and/o revascularisation

4.2 Posology and method of administration

It is recommended that Perindopril tert-butylamine is taken once daily in the morning before a meal with sufficient amount of fluid (e.g. water).

The dose should be individualised according to the patient profile (see 4.4) and blood pressure response.

Hypertension:

Perindopril tert-butylamine 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 tert-butylamine; 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 (see section 4.4).

In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Perindopril tert-butylamine should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Perindopril tert-butylamine 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, generally associated with a nonpotassium-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).

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. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with Perindopril tert-butylamine (see section 4.4).

Stable coronary artery disease:

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

Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 mg once daily depending on renal function (see Table 1 "Dosage adjustment in renal impairment"). The dose should be increased only if the previous lower dose is well tolerated.

Dosage adjustment in renal impairment:

Dosage in patients with renal impairment should be based on creatinine clearance as outlined in table 1 below:

Table 1: dosage adjustment in renal impairment

creatinine clearance (ml/min)	*recommended dose*
$Cl_{CR} \geq 60$	4 mg per day
$30 < Cl_{CR} < 60$	2 mg per day
$15 < Cl_{CR} < 30$	2 mg every other day
Haemodialysed patients*, $Cl_{CR} < 15$	2 mg on the day of dialysis

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

Dosage adjustment in hepatic impairment:

No dosage adjustment is necessary in patients with hepatic impairment (see sections 4.4 and 5.2).

Children and adolescents:

Perindopril tert-butylamine is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

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 sections 4.4 and 4.6).

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 volumedepleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). 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 and 4.8). 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 erbumine. 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 may be necessary.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy:

As with other ACE inhibitors, Perindopril tert-butylamine 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) 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).

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 tert-butylamine 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 tert-butylamine 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 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 tert-butylamine 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 tert-butylamine (see 4.8). This may occur at any time during therapy. In such cases, Perindopril tert-butylamine 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).

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis:

Rarely, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Anaphylactic reactions during desensitisation:

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In the same patients, these reactions have been avoided when the ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Hepatic failure:

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see 4.8).

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. Sporadic occurrences of haemolytic anaemia have been reported on patients with congenital G6-PD deficiency. 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 nonproductive, 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 tert-butylamine 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 abovementioned 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).

Lithium:

The combination of lithium and perindopril is generally not recommended (see 4.5).

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes:

The combination of perindopril and potassium sparing diuretics, potassium supplements or potassiumcontaining salt substitutes is generally not recommended (see 4.5).

Pregnancy:

ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.(see sections 4.3 and 4.6).

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 $\geq$ 3 g/day:

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

Antihypertensive agents and vasodilators:

Concomitant use of these agents may increase the hypotensive effects of perindopril. Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

Antidiabetic agents:

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood-glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates:

Perindopril may be used concomitantly with acetylsalicylic acid (when used as a thrombolytic), thrombolytics, beta-blockers and/or nitrates.

Tricyclic antidepressants/Antipsychotics/Anesthetics:

Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Sympathomimetics:

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antacids may decrease the bioavailability of perindopril.

4.6 Pregnancy and lactation

Pregnancy:

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4).The use of ACE inhibitors is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

ACE inhibitor/ AIIRAs therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also 5.3 'Preclinical safety data'). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see also section 4.3 and 4.4).

Lactation:

It is not known whether perindopril is excreted into human breast milk. Therefore the use of Perindopril tert-butylamine is not recommended in women who are breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

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

4.8 Undesirable effects

The frequency of adverse reactions listed below is defined using the following convention:

Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare (<1/10000), not known (cannot be estimated from the available data)

	common	uncommon	very rare
Psychiatric disorders		mood or sleep disturbances	
Nervous system disorders	headache, dizziness, vertigo, paresthaesia		
Eye disorders	vision disturbance		
Ear and labyrinth disorders	tinnitus		
Cardio-vascular disorders	hypotension and effects related to hypotension		arrhythmia, angina pectoris, myocardial infarction and stroke, possibly secondary to

			excessive hypotension in high-risk patients (see section 4.4).
Respiratory, thoracic and mediastinal disorders	cough, dyspnoea	bronchospasm	eosinophilic pneumonia, rhinitis
Gastro-intestinal disorders	nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea, constipation	dry mouth	pancreatitis
Hepato-biliary disorders			hepatitis either cytolytic or cholestatic (see section 4.4)
Skin and subcutaneous tissue disorders	rash, pruritus	angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see section).	erythema multiforme
Musculoskeletal, connective tissue and bone disorders		muscle cramps	
Renal and urinary disorders		renal insufficiency	acute renal failure
Reproductive system and breast disorders		impotence	
General disorders	asthenia	sweating	
Blood and the lymphatic			Decreases in haemoglobin

system disorders			and haematocrit, thrombocytopenia, leucopenia/ neutropenia, agranulocytosis or pancytopenia In patients with a congenital deficiency of G-6PDH, haemolytic anaemia has been reported (see section 4.4).

Investigations:

Increases in blood urea and plasma creatinine, hyperkalaemia reversible on discontinuation may occur, especially in the presence of renal insufficiency, severe heart failure and renovascular hypertension.

Elevation of liver enzymes and serum bilirubin have been reported rarely.

Clinical trials:

During the randomised period of the EUROPA study, only serious adverse events were collected. Few patients experienced serious adverse events: 16 (0.3%) of the 6122 perindopril patients and 12 (0.2%) of the 6107 placebo patients. In perindopril-treated patients, hypotension was observed in 6 patients, angioedema in 3 patients and sudden cardiac arrest in 1 patient. More patients withdrew for cough, hypotension or other intolerance on perindopril than on placebo, 6.0% (n=366) versus 2.1% (n=129) respectively.

4.9 Overdose

Limited data are available for overdose in humans.

Symptoms associated with overdose of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

The recommended *treatment* of overdose 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

Pharmacotherapeutic group: C09AA - ACE inhibitors, plain; ATC code: C09A A04 perindopril

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 kallikreinkinin 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 tert-butylamine 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 tert-butylamine to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo.

Patients with stable coronary artery disease:

The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years.

Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to perindopril 8 mg (n=6110) or placebo (n=6108).

The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure. Overall, 90% of the patients had a previous myocardial infarction and/or a previous coronary revascularisation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers.

The main efficacy criterion was the composite of cardiovascular mortality, non fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with perindopril 8 mg once daily resulted in a significant absolute reduction in the primary endpoint of 1.9% (relative risk reduction of 20%, 95%CI [9.4; 28.6] – $p<0.001$).

In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2.2% corresponding to a RRR of 22.4% (95%CI [12.0; 31.6] – $p<0.001$) in the primary endpoint was observed by comparison to placebo.

5.2 Pharmacokinetic properties

After oral administration, the absorption of perindopril is rapid and the peak concentration complete within 1 hour. Bioavailability is 65 to 70 %.

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

As ingestion of food decreases conversion to perindoprilat, hence bioavailability, Perindopril tert-butylamine 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 and 4.4).

5.3 Preclinical safety data

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

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Silicified microcrystalline cellulose

Polacrillin potassium

Silicone dioxide

Colloidal anhydrous silica

Magnesium stearate

Hydroxypropylbetadex

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30° C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Aluminium/Aluminium blister.

Pack sizes: 7, 10, 14, 15, 20, 28, 30, 50, 56, 60, 90, 100, 112, 120, 500 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited

37 Woolmer Way

Bordon

Hampshire

GU35 9QE

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/0765

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/04/2008

10 DATE OF REVISION OF THE TEXT

14/04/2008

Module 3
Patient Information Leaflet

Package leaflet: Information for the user

SZD0000LT000

Perindopril 2 mg Tablets
Perindopril 4 mg Tablets

Perindopril tert-butylamine

Read all of this leaflet carefully before you start taking the medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please 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 your pharmacist

In this leaflet:
1. What Perindopril is and what it is used for
2. Before you take Perindopril
3. How to take Perindopril
4. Possible side effects
5. How to store Perindopril
6. Further information

SANDOZ

1 What Perindopril is and what it is used for

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

Perindopril tablets are used:
- to treat high blood pressure (hypertension).
- to treat heart failure (a condition where the heart is unable to pump enough blood to meet the body's needs).
- to reduce the risk of cardiac events, 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

Do not take Perindopril
- if you are **allergic (hypersensitive)** to Perindopril or any of the other ingredients in the tablet **or any other ACE inhibitor** (see section 6).
- if you have **had symptoms** such as **wheezing, swelling of the face, tongue or throat, intense itching, skin rashes, fainting** or **dizziness** with previous ACE inhibitor treatment or have had these symptoms in any other circumstances (this is a condition called angioedema).
- if you have hereditary tendency to tissue swelling or **tissue swelling** of unknown origin (hereditary or idiopactic angioedema).
- if you are in **the second** or **the third trimester of pregnancy.**

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

Take special care with Perindopril
You should check with your doctor **BEFORE** taking Perindopril if you:
- are in **risk of an excessive fall in the blood pressure.** This may be case, among others, if you suffer from heart failure, impaired renal function or disorders in the salt and fluid balance, e.g. because you take diuretics (medicines that increase urine production) or keep low-salt diet or as a consequence of vomiting or diarrhoea.
- have aortic stenosis **(narrowing of the main blood vessel leading from the heart)**, mitral valv stenosis **(narrowing of heart's mitral valve)**, hypertrophic cardiomyopathy **(cardiac muscle disease)** or renal artery stenosis **(narrowing of the artery supplying the kidney with blood).**
- have hypersensitivity reactions or tissue swelling (angioedema) during treatment with perindopril or other ACE inhibitors. Angioneurotic oedema more frequently occur in patients with black skin colour than in patients with non-black skin colour.
- have a **heart problem.**
- have a **liver problem.**
- have a **kidney problem**.
- are **receiving dialysis.**
- suffer from a **collagen disease** such as systemic lupus erythematosus or scleroderma.
- are on a **salt restricted** diet or use **salt substitutes which contain potassium**.
- suffer from a **diabetes which is not well controlled.**
- are **planning pregnancy** or are in the **first trimester of pregnancy.**
- are **breast-feeding.**

Perindopril tablets are **not recommended** for **children.**

You should also inform your doctor or medical staff that you are taking Perindopril
- if you had an episode of **chest pains** (angina pectoris).
- if you are to **undergo anaesthesia** and/or **surgery.**
- if you have suffered from recent **diarrhoea** or **vomiting.**
- if you are going to have **desensitization** treatment to reduce the effects of an allergy to bee or wasp stings.
- if you are to **undergo LDL apheresis** (which is removal of cholesterol from your blood by a machine).
- if your **blood pressure is not sufficiently lowered** due to your ethnic affiliation (particularly in patients with black skin colour).
- if you have **persistent dry cough.**

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, herbal medicines or natural products. In particular, you should check with your doctor if you are taking any of the following to be sure that it is safe to take Perindopril:

- other medicines for **treating high blood pressure** including diuretics **(water tablets)**
- **potassium-sparing diuretics** (e.g. spironolactone, triamterene or amiloride); **potassium supplements** and **potassium-containing salt substitutes**
- medicines for the **treatment of diabetes** (insulin or tablets) to **lower blood sugar**
- lithium for **treatment of mania** or **depression**
- medicines for the **treatment of mental disorders** such as depression, anxiety, schizophrenia or other psychoses
- allopurinol used for the **treatment of gout**
- immunosuppressants used for the **treatment of auto-immune disorders** (e.g. rheumatoid arthritis) or **following transplant surgery**
- procainamide, a **treatment for irregular heartbeat**
- non-steroidal anti-inflammatory drugs (NSAIDs) **medications for pain relief**, including aspirin (if dose is higher or equal to 3g/day)
- medicines used for the treatment of **low blood pressure, shock** or **asthma** (e.g. ephedrine, noradrenaline or adrenaline)
- vasodilators including nitrates **(product that make the blood vessels become wider)**
- heparin (blood **thinning medication**)

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

Tell your doctor or dentist **before** having an **anaesthetic** or **surgery**, because your blood pressure may fall suddenly during the anaesthesia.

Taking Perindopril with food and drink
It is recommended that Perindopril should be taken before a meal with sufficient amount of fluid (e.g. water) in order to reduce the influence of food on the way in which the medicine works.
Potassium containing food additives or salt substitutes should not be used if you use Perindopril. The blood potassium concentration can be elevated too high. Also large amounts of (plain) salt (NaCl) in the diet may reduce the antihypertensive effect of Perindopril.

Pregnancy and breast-feeding
You **can not take** Perindopril if you are in **the second** or **the third trimester of pregnancy.**
If you are **planning to become pregnant** or are in **the first trimester** of pregnancy it is **not recommended** to take Perindopril, ask your doctor before starting treatment.

If you **become pregnant** while taking Perindopril **stop taking it immediately** and tell your doctor.

You should **not take** Perindopril if you are **breast-feeding.**

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

Driving and using machines
No studies on the effects on the ability to drive and use machines have been performed.
However, Perindopril does not affects alertness but different reactions such as dizziness or weakness in relation to the decrease in blood pressure may occur in certain patients, especially in the beginning of treatment or when increasing the dose. If affected, your ability to drive or to operate machinery may be impaired.

Continued on the next page >>

3 How to take Perindopril

Always take this medicine exactly as your doctor told you. Please ask your doctor or pharmacist if you are not sure.
Perindopril may be used on its own or with other medicines which lower blood pressure.

The usual dosages for Perindopril are as follows:
High blood pressure: the usual starting and maintenance dose for treatment in adults is 4 mg once a day. After a month, this can be increased to 8 mg a day which is the maximum recommended dose.

If you are 65 or over, the usual starting dose is 2 mg once a day. After a month, this can be increased to 4 mg a day and if necessary to 8 mg a day.

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

Stable coronary artery disease: the usual starting dose is 4 mg once daily. After two weeks and if 4 mg is well tolerated, this can be increased to 8 mg once daily.
If you are 65 or over, the usual starting dose is 2 mg once daily. After one week, this can be increased to 4 mg once daily and after a further week to 8 mg once daily.
Your doctor may give you a blood test to check that your kidneys are working properly before increasing the dose to 8 mg.
In case of impaired renal or hepatic function, your doctor will adjust the dose of Perindopril for you.
Treatment of these conditions is usually life-long.
Take your tablet(s) with a glass of water, preferably at the same time each day, in the morning, before a meal. If you are taking water tablets (diuretics), your doctor may decide to reduce or even discontinue these at beginning of your treatment with Perindopril.

Perindopril is not suitable for use in children.

If you take more Perindopril than you should
If you take too many tablets, contact your nearest hospital casualty department or tell your doctor immediately. The most likely effect in case of overdose is low blood pressure. If marked low blood pressure occurs (symptoms such as dizziness or faintness), lying down with the legs raised can help.

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

If you stop taking Perindopril
Always consult your doctor, if you wish to stop taking this medicine. Even if you feel well, it may be necessary to continue taking this medicine.

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

4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

This side effect occurs uncommonly (affecting less then 1 in every 100 people). However, if you notice any of the following side effects, contact your doctor immediately:
- swelling of the face, lips, mouth, tongue or throat
- difficulty in breathing
- dizziness or fainting
- unusually fast or irregular heart beat

These are symptoms of a serious reaction (angioedema) which can occur with all other drugs of this type (ACE inhibitors). It must be treated immediately, usually in hospital.

Other possible side effects
Common (affecting less than 1 in every 10 people):
- cough, shortness of breath
- light-headedness due to low blood pressure (particularly after the first few doses, if the dose is increased or when water tablets are also taken)
- headache, dizziness, vertigo, tiredness, pins and needles, muscle cramps, visual disturbances (e.g. blurred vision, eye pain), tinnitus (sensation of noises in the ears)
- nausea, vomiting, abdominal pain, changes in your sense of taste, feeling of indigestion, diarrhoea, constipation
- skin rashes, itching

Uncommon (affecting less than 1 in every 100 people):
- changes in mood or sleep
- bronchospasm (tightening of the chest, wheezing and shortness of breath)
- dry mouth
- kidney problems
- impotence
- sweating

Very rare (affecting less than 1 in every 10.000 people):
- confusion
- irregular heart beat, heart attack and stroke (these have been reported with ACE inhibitors in association with low blood pressure)
- angina pectoris (chest tightness)
- eosinophilic pneumonia (a rare type of pneumonia), rhinitis (blocked up or runny nose)
- pancreatitis (inflammation of the pancreas)
- hepatitis (inflammation of the liver)
- erythemy multiforme (skin reaction disorder resulting from allergic reaction provoked by many different causes)
- changes in the blood cell count: your doctor may decide to carry out blood tests at intervals to monitor 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

Keep out of the reach and sight of children.

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

Do not store above 30° C.
Store in the original package in order to protect from moisture.

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 contains:
The active substance is: perindopril tert-butylamine.

Perindopril 2 mg Tablets:
Each tablet contains, 2 mg perindopril tert-butylamine , equivalent to 1.669 mg perindopril.

Perindopril 4 mg Tablets:
Each tablet contains, 4 mg perindopril tert-butylamine, equivalent to 3.338 mg perindopril.

The other ingredients are: microcrystalline cellulose, silicified microcrystalline cellulose, polacrillin potassium, silicone dioxide, colloidal anhydrous silica, magnesium stearate and hydroxypropylbetadex.

What Perindopril looks like and contents of the pack
Perindopril 2 mg Tablets are white, round, biconvex tablet debossed with 2 on one side.
Perindopril 4 mg Tablets are white, round, biconvex tablet scored on one side and debossed with 4 on the reverse side. The tablet can be divided into equal halves.

Aluminium/Aluminium blister.

Pack sizes: 7, 10, 14, 15, 20, 28, 30, 50, 56, 60, 90, 100, 112 and 120 tablets

Not all pack sizes may be marketed.

Marketing authorization holder and Manufacturer
Marketing authorization holder:
Sandoz Ltd, 37 Woolmer Way, Bordon, Hampshire, GU35 9QE.

Manufacturer:
Lek Pharmaceuticals d.d., Verovskova 57, 1526 Ljubljana, Slovenia ***or***
LEK S.A., ul. Podlipie 16, 95-010 Stryków, Poland ***or***
LEK S.A., ul. Domaniewska 50 C, 02-672 Warsaw, Poland ***or***
Salutas Pharma GmbH, Otto-von-Guericke-Allee 1, 39179 Barleben, Germany ***or***
Salutas Pharma GmbH, Dieselstrasse 5, 70839 Gerlingen, Germany.

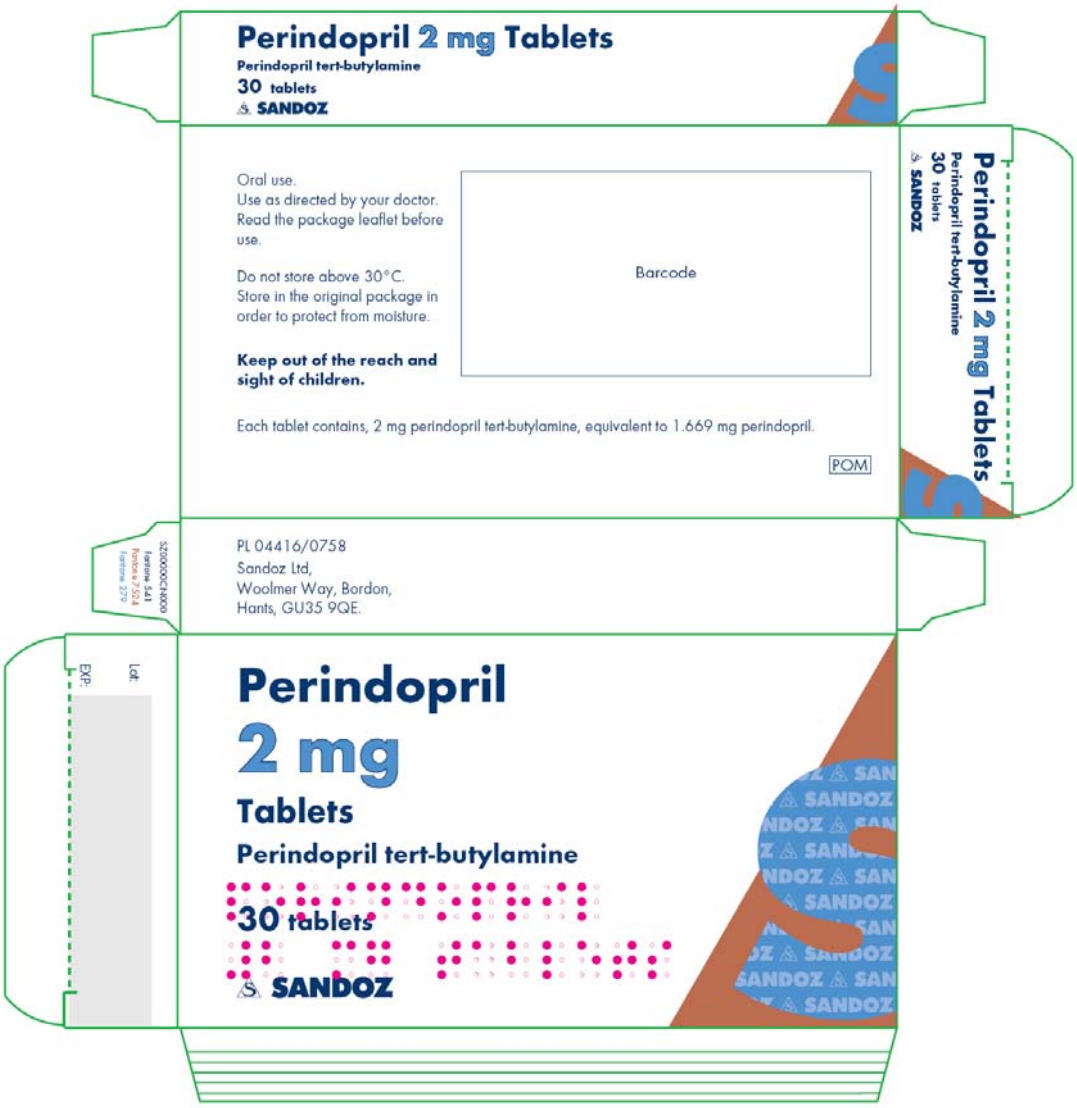
This medicinal product is authorised in the Member States of the EEA under the following names:

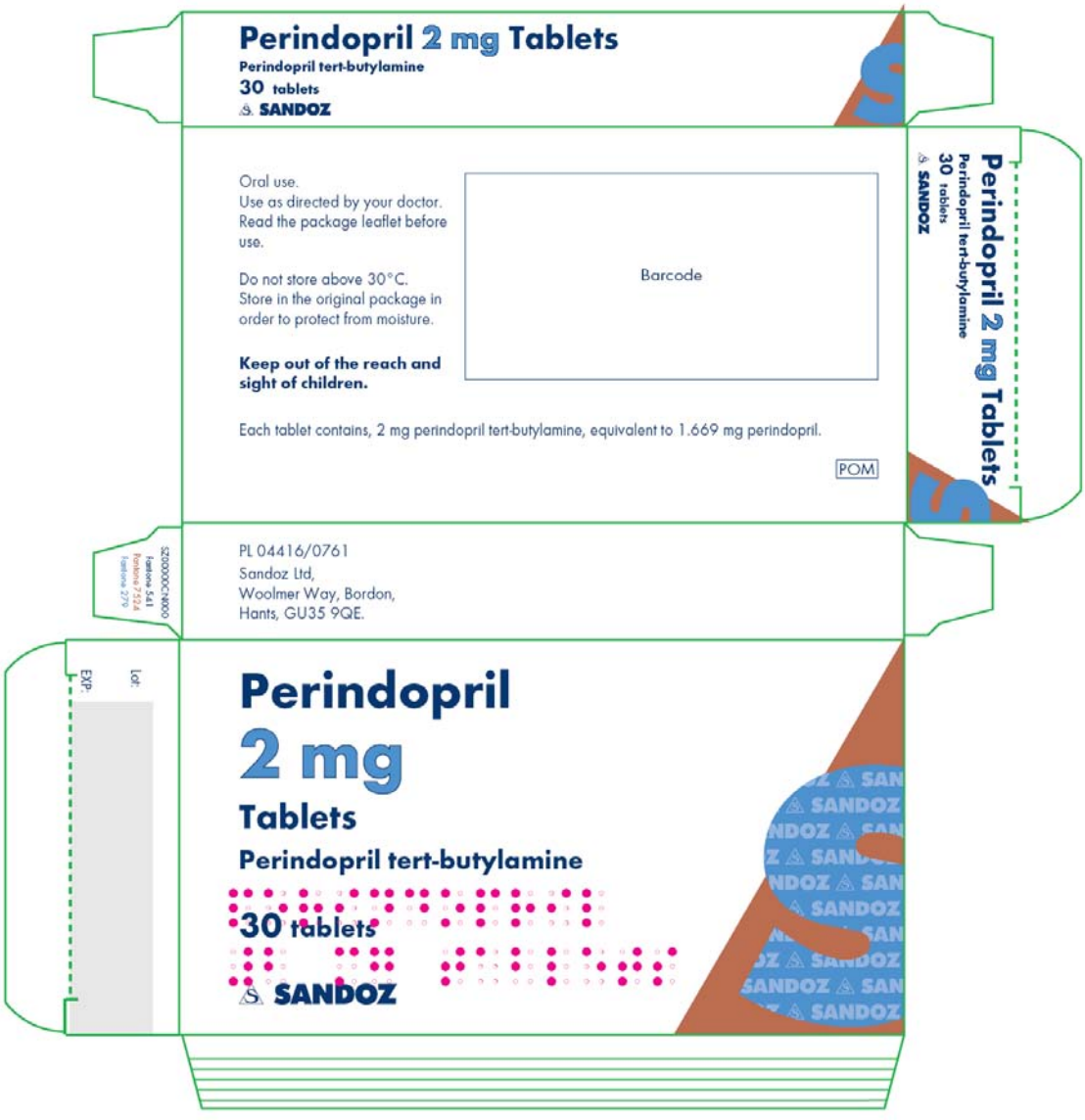
Germany:	PerindoHEXAL 4 mg Tabletten
Denmark:	Perindoxal
Finland:	Perindoxal
France:	PERINDOPRIL GeNeRes 2 mg, comprimé PERINDOPRIL GeNeRes 4 mg, comprimé sécable
Ireland:	Pendrex 2 mg Tablets Pendrex 4 mg Tablets
Hungary:	Perindopril Sandoz
Italy:	PERINDOPRIL Hexal 4 mg compresse
Luxembourg:	PerindoHEXAL 4 mg Tabletten
Lithuania:	Perindopril Sandoz 4mg tabletės
Latvia:	Perindopril Sandoz 4mg tabletes
Poland:	Perindopril -1A Pharma

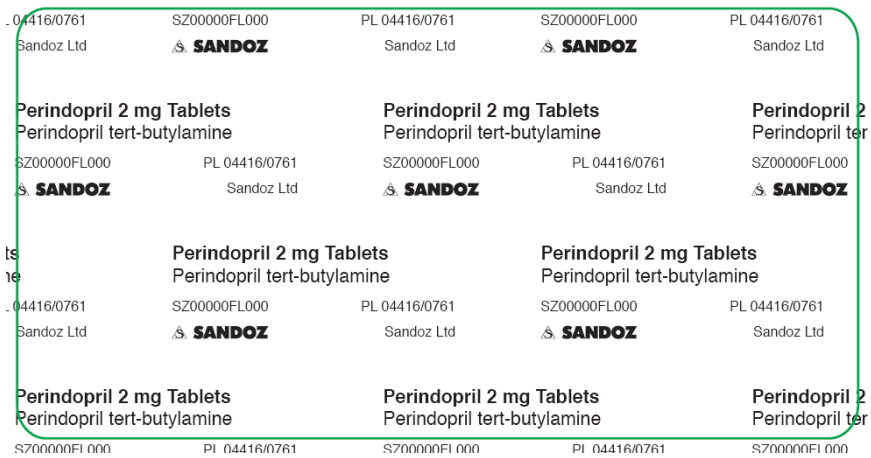
This leaflet was last approved in 01/2008 *(to be amended after the approval).*

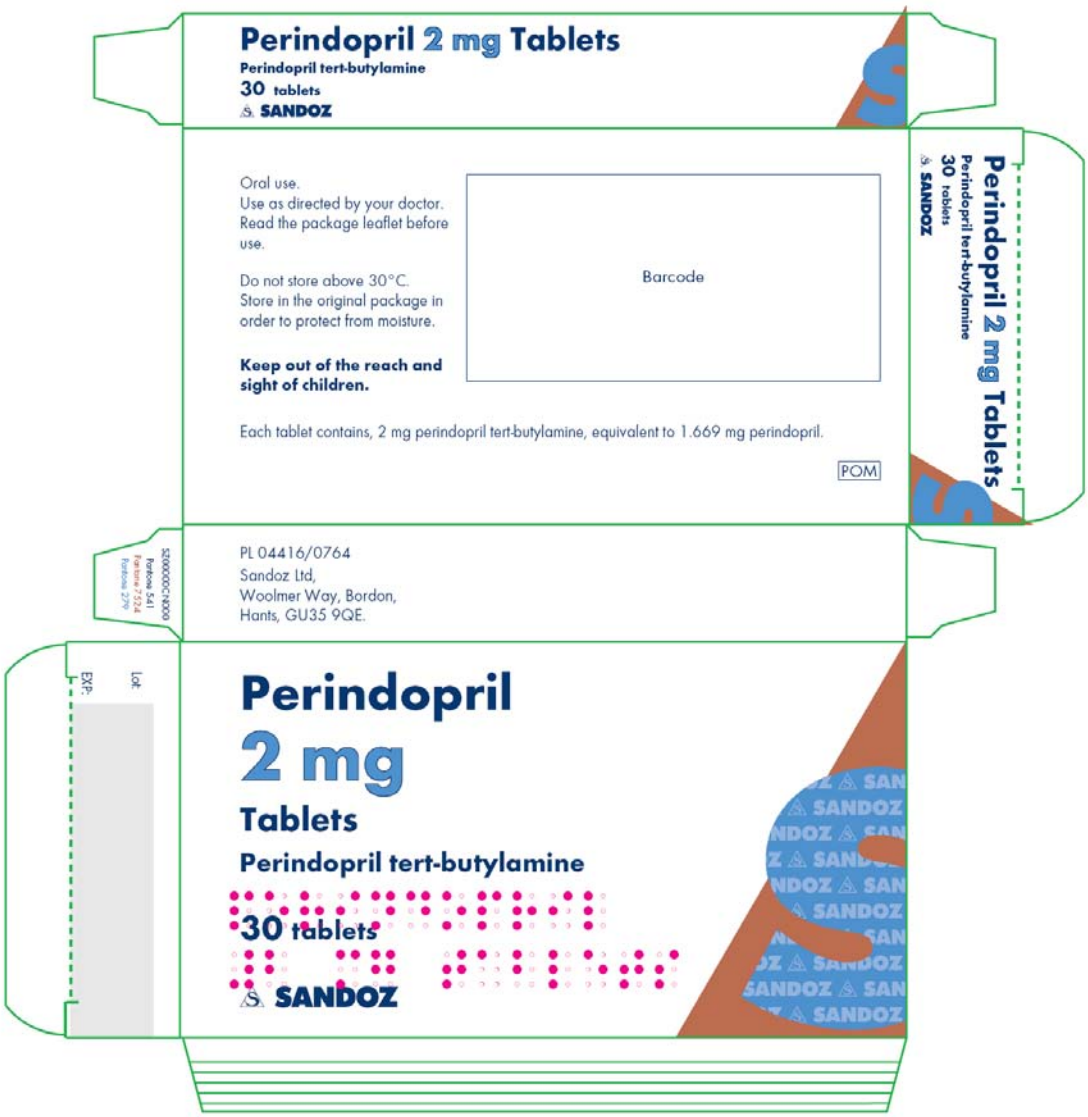
SZ00000LT000

Module 4
Labelling – Perindopril 2mg Tablets



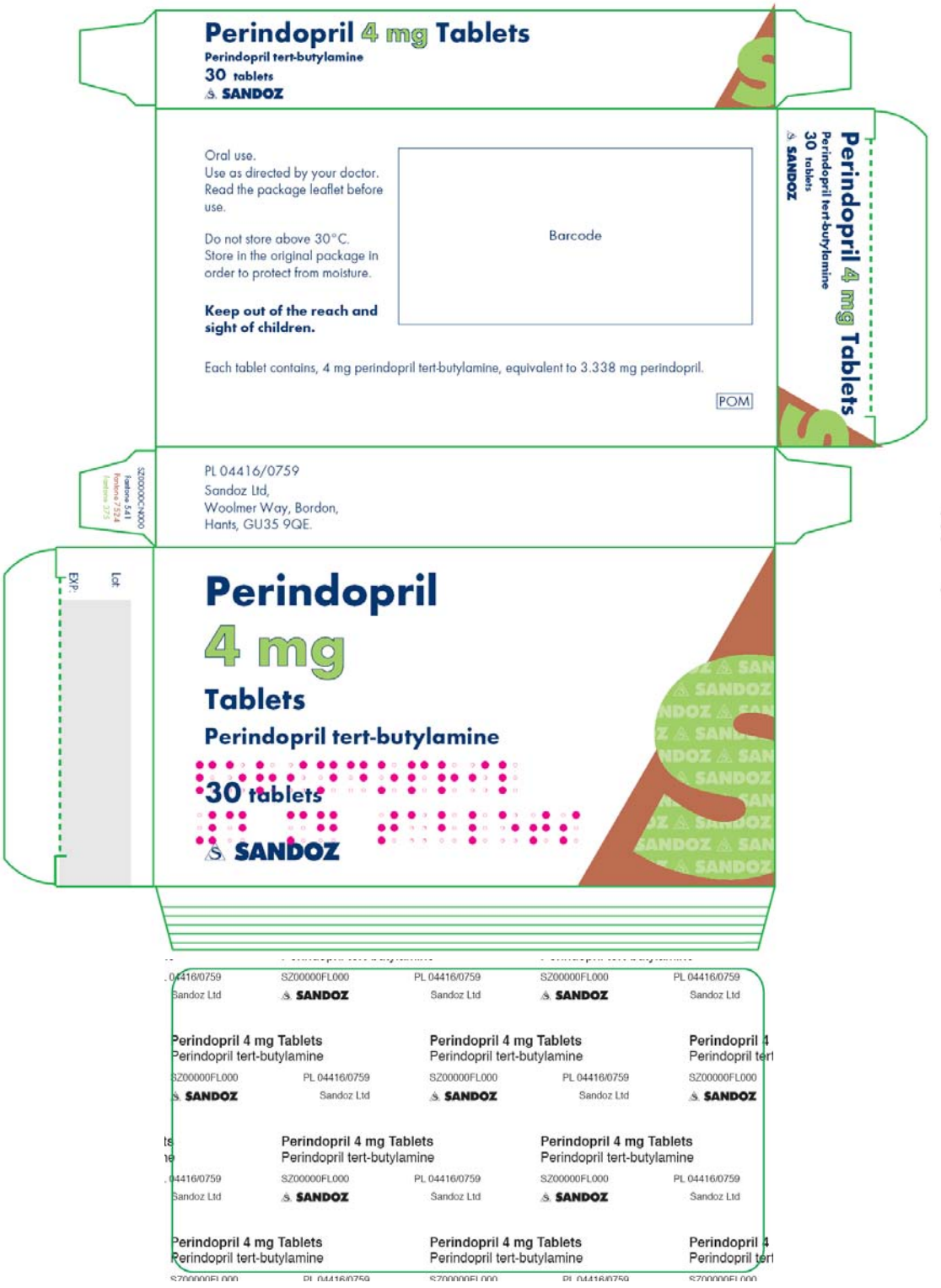

Perindopril 2 mg Tablets
Perindopril tert-butylamine
30 tablets
SANDOZ
Oral use.
Use as directed by your doctor.
Read the package leaflet before use.
Do not store above 30°C.
Store in the original package in order to protect from moisture.
Keep out of the reach and sight of children.
Barcode
Each tablet contains, 2 mg perindopril tert-butylamine, equivalent to 1.669 mg perindopril.
POM
PL 04416/0761
Sandoz Ltd,
Woolmer Way, Bordon,
Hants, GU35 9QE.
EXP
Lot
Perindopril
2 mg
Tablets
Perindopril tert-butylamine
30 tablets
SANDOZ

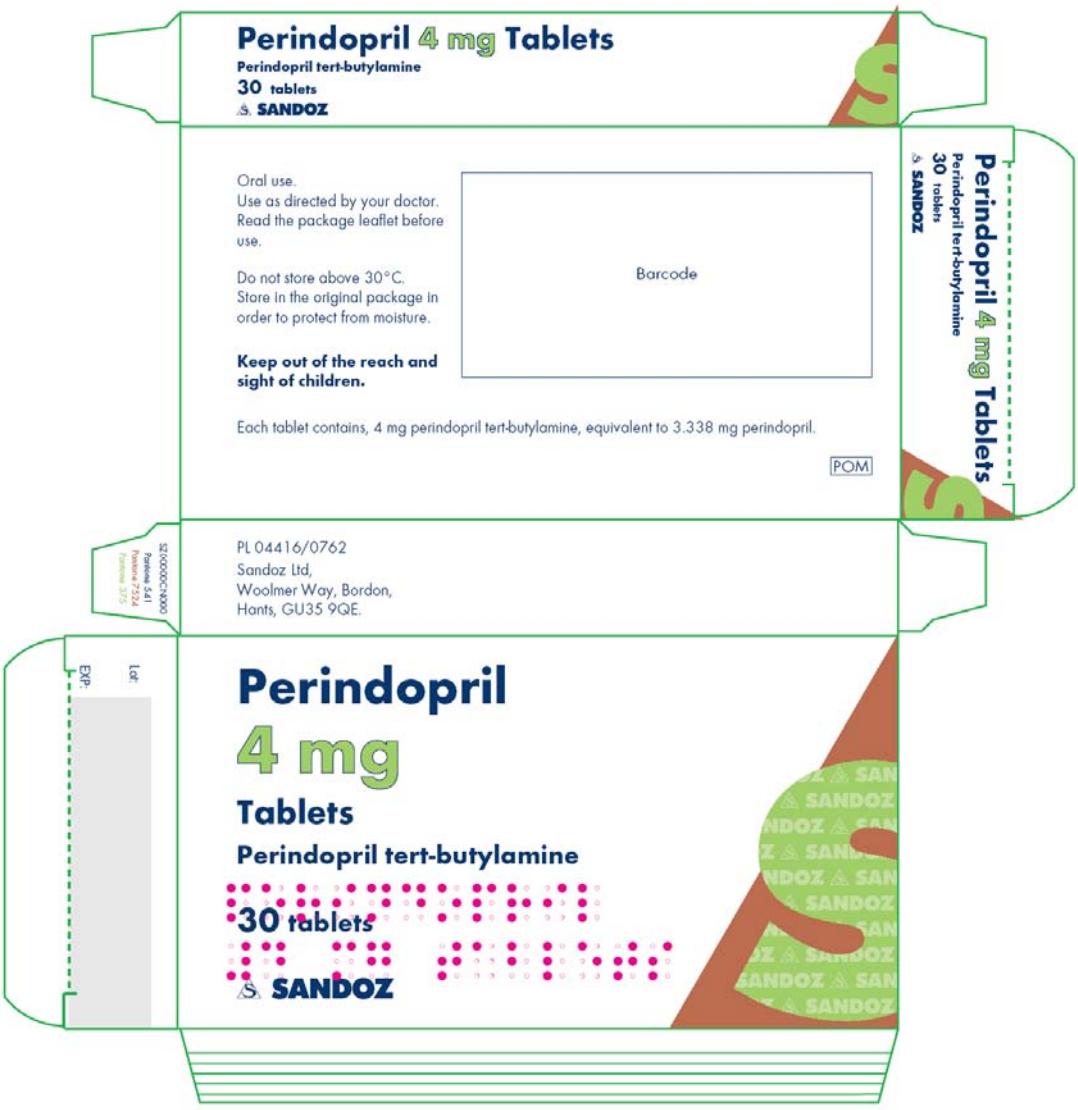

SZ00000FL000
PL 04416/0761
Sandoz Ltd
SANDOZ
Perindopril 2 mg Tablets
Perindopril tert-butylamine


Perindopril 2 mg Tablets
Perindopril tert-butylamine
30 tablets
SANDOZ
Oral use.
Use as directed by your doctor.
Read the package leaflet before use.
Do not store above 30°C.
Store in the original package in order to protect from moisture.
Keep out of the reach and sight of children.
Barcode
Each tablet contains, 2 mg perindopril tert-butylamine, equivalent to 1.669 mg perindopril.
POM
PL 04416/0764
Sandoz Ltd,
Woolmer Way, Bordon,
Hants, GU35 9QE.
EXP
Lot
Perindopril
2 mg
Tablets
Perindopril tert-butylamine
30 tablets
SANDOZ

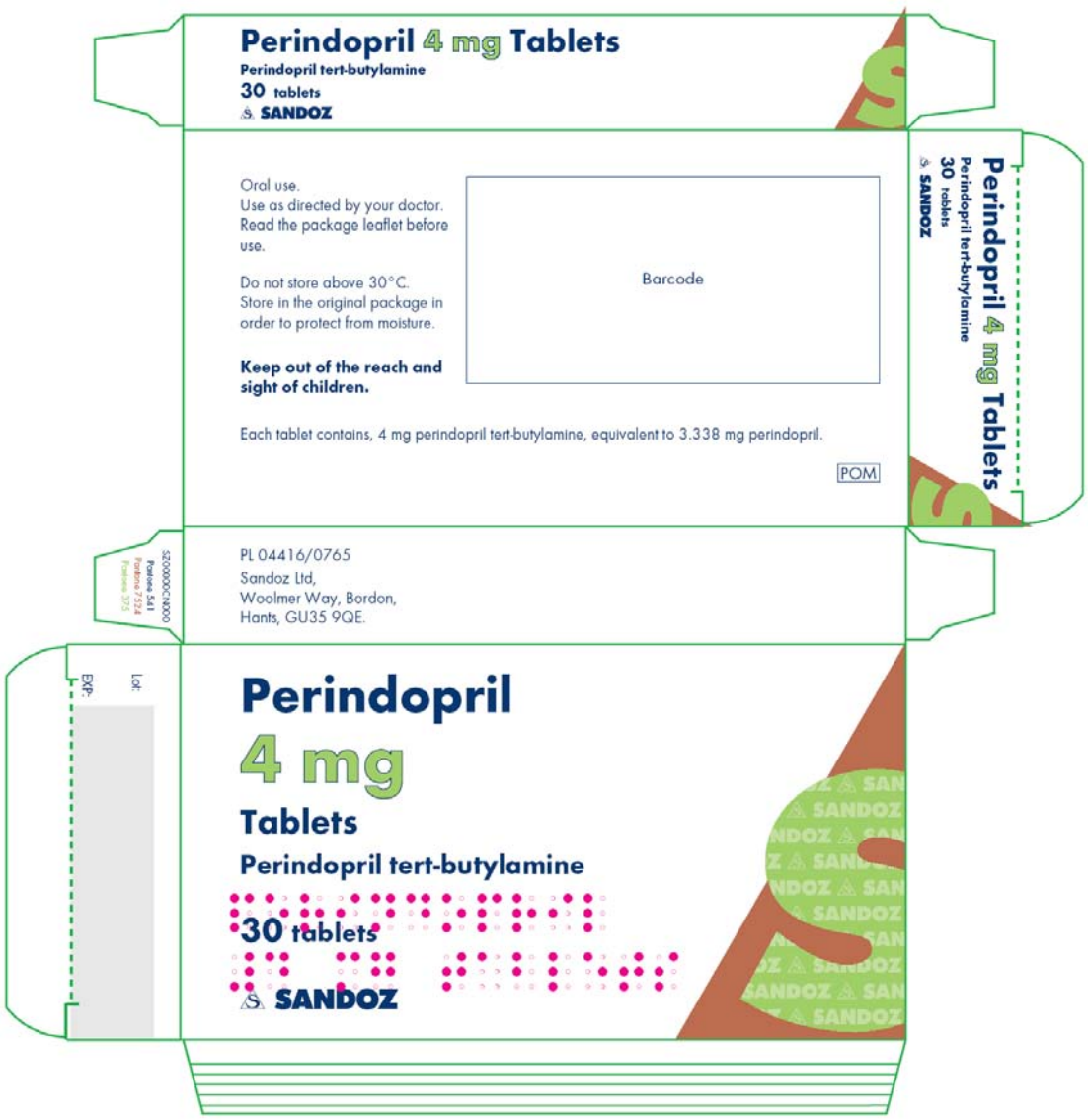

04416/0764
SZ00000FL000
PL 04416/0764
SZ00000FL000
PL 04416/0764
Sandoz Ltd
SANDOZ
Sandoz Ltd
SANDOZ
Sandoz Ltd
Perindopril 2 mg Tablets
Perindopril tert-butylamine
Perindopril 2 mg Tablets
Perindopril tert-butylamine
Perindopril 2
Perindopril ter
SZ00000FL000
PL 04416/0764
SZ00000FL000
PL 04416/0764
SZ00000FL000
SANDOZ
Sandoz Ltd
SANDOZ
Sandoz Ltd
SANDOZ
Perindopril 2 mg Tablets
Perindopril tert-butylamine
Perindopril 2 mg Tablets
Perindopril tert-butylamine
04416/0764
SZ00000FL000
PL 04416/0764
SZ00000FL000
PL 04416/0764
Sandoz Ltd
SANDOZ
Sandoz Ltd
SANDOZ
Sandoz Ltd
Perindopril 2 mg Tablets
Perindopril tert-butylamine
Perindopril 2 mg Tablets
Perindopril tert-butylamine
Perindopril 2
Perindopril ter
SZ00000FL000
PL 04416/0764
SZ00000FL000
PL 04416/0764
SZ00000FL000

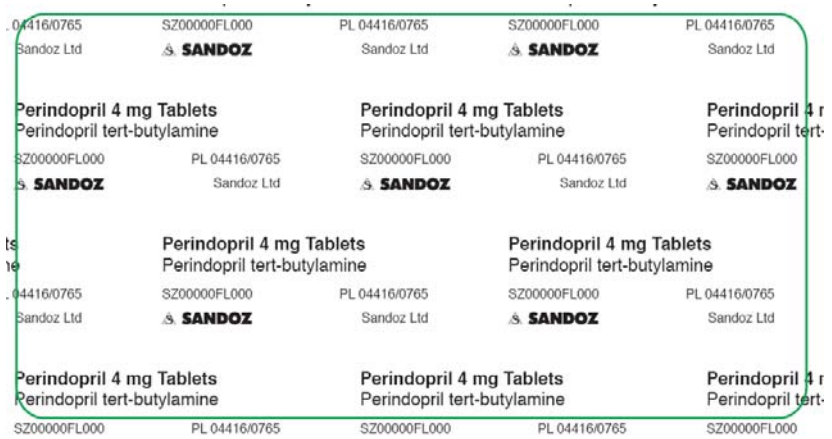
Labelling – Perindopril 4mg Tablets




Perindopril 4 mg Tablets
Perindopril tert-butylamine
30 tablets
SANDOZ
Oral use.
Use as directed by your doctor.
Read the package leaflet before use.
Do not store above 30°C.
Store in the original package in order to protect from moisture.
Keep out of the reach and sight of children.
Barcode
Each tablet contains, 4 mg perindopril tert-butylamine, equivalent to 3.338 mg perindopril.
POM
PL 04416/0762
Sandoz Ltd,
Woolmer Way, Bordon,
Hants, GU35 9QE.
EXP:
Lot:
Perindopril
4 mg
Tablets
Perindopril tert-butylamine
30 tablets
SANDOZ


PL 04416/0762
SZ00000FL000
Sandoz Ltd
SANDOZ
Perindopril 4 mg Tablets
Perindopril tert-butylamine


Perindopril 4 mg Tablets
Perindopril tert-butylamine
30 tablets
SANDOZ
Oral use.
Use as directed by your doctor.
Read the package leaflet before use.
Do not store above 30°C.
Store in the original package in order to protect from moisture.
Keep out of the reach and sight of children.
Barcode
Each tablet contains, 4 mg perindopril tert-butylamine, equivalent to 3.338 mg perindopril.
POM
PL 04416/0765
Sandoz Ltd,
Woolmer Way, Bordon,
Hants, GU35 9QE.
EXP
Lot
Perindopril
4 mg
Tablets
Perindopril tert-butylamine
30 tablets
SANDOZ


PL 04416/0765
SZ00000FL000
Sandoz Ltd
SANDOZ
Perindopril 4 mg Tablets
Perindopril tert-butylamine

Module 5

Scientific Discussion During Initial Procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal products Perindopril 2mg Tablets (Pl 04416/0758, PL 04416/0761 and PL 04416/0764) and Perindopril 4mg Tablets (PL 04416/0759, PL 04416/0762 and PL 04416/0765) on 14 March 2008. The products are prescription-only medicines.

These applications were submitted as generic applications under Article 10.1 of 2001/83 EC, as amended, referring to Coversyl 2mg and 4mg Tablets (Les Laboratoires Servier), which were granted licences in the UK in December 1989.

The products contain the active ingredient perindopril and are indicated for the treatment of hypertension and symptomatic heart failure as well as for the reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation.

Perindopril is an ACE inhibitor that inhibits the conversion of angiotensin I into angiotensin II. Inhibition of ACE leads to reduced plasma level of angiotensin II which consequentially increases plasma rennin activity (by inhibition of the negative feedback of rennin release). Perindopril acts through its active metabolite, perindoprilat. Other metabolites are inactive.

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

No clinical studies were conducted, which is acceptable given that the applications referred 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 Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of the product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

The decentralised procedure was completed at Day 210 (22 January 2008), with the RMS and the CMS agreeing that the licences were approvable. The national phase of the decentralised procedure was completed in the UK on 14 March 2008.

II ABOUT THE PRODUCT

Name of the product in the Reference Member State	Perindopril 2mg Tablets
Name(s) of the active substance(s) (INN)	Perindopril tert-butylamine
Pharmacotherapeutic classification (ATC code)	ACE inhibitors (C09A A04)
Pharmaceutical form and strength(s)	2mg Tablet
Reference numbers for the Decentralised Procedure	UK/H/0965-7/01/DC
Reference Member State	United Kingdom
Concerned Member States	PL 04416/0758 UK/H/0965/01/DC Belgium, Czech Republic, Denmark, Finland, France, Netherlands, Poland, Portugal, Slovenia and Slovakia. PL 04416/0761 UK/H/0966/01/DC Czech Republic, Germany, Hungary and Slovakia. PL 04416/0764 UK/H/0967/01/DC Denmark, Finland, France, Hungary, Ireland and Poland.
Marketing Authorisation Number(s)	PL 04416/0758 PL 04416/0761 PL 04416/0764
Name and address of the authorisation holder	Sandoz Ltd 37 Woolmer Way Bordon Hampshire GU35 9QE

Name of the product in the Reference Member State	Perindopril 4mg Tablets
Name(s) of the active substance(s) (INN)	Perindopril tert-butylamine
Pharmacotherapeutic classification (ATC code)	ACE inhibitors (C09A A04)
Pharmaceutical form and strength(s)	4mg Tablet
Reference numbers for the Decentralised Procedure	UK/H/0965-7/02/DC
Reference Member State	United Kingdom
Concerned Member States	PL 04416/0759 UK/H/0965/02/DC Belgium, Czech Republic, Denmark, Finland, France, Italy, Netherlands, Poland, Portugal, Slovenia and Slovakia. PL 04416/0762 UK/H/0966/02/DC Czech Republic, Germany, Hungary, Lithuania, Latvia and Slovakia. PL 04416/0765 UK/H/0967/02/DC Germany, Denmark, Finland, France, Hungary, Ireland, Italy, Lithuania, Luxembourg, Latvia and Poland.
Marketing Authorisation Number(s)	PL 04416/0759 PL 04416/0762 PL 04416/0765
Name and address of the authorisation holder	Sandoz Ltd 37 Woolmer Way Bordon Hampshire GU35 9QE

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

Perindopril tert-butylamine
Perindopril tert-butylamine is presented as a complex with cyclodextrin. Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Analytical methods have been validated and are satisfactory for ensuring compliance with the relevant specifications.

DRUG PRODUCT

Other Ingredients
The excipients present are microcrystalline cellulose, silicified microcrystalline cellulose, polacrillin potassium, silicone dioxide, colloidal anhydrous silica, magnesium stearate and hydroxypropylebetadex.

The excipients used comply with their respective European Pharmacopoiea monographs with the exception of silicified microcrystalline cellulose which complies with a satisfactory in-house specification. Satisfactory certificates of analysis have been provided.

None of the excipients used contain material of animal or human origin.

Pharmaceutical Development
The applicant has provided suitable product development rationale and data.

Dissolution Profiles
Dissolution profiles for the drug product were found to be similar to the reference product.

Impurity Profiles
The impurity profiles for the drug product and reference product were comparable.

Manufacture
Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. Suitable in-process controls are applied during the manufacturing process to ensure the quality of the product.

The manufacturing process has been validated and the results are satisfactory.

Control of Drug Product
The proposed finished product specification is acceptable and provides an assurance of the quality of the finished product. The analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed specification.

Reference Standards or Materials
Certificates of analysis for all reference standards used have been provided and are satisfactory.

Container Closure System
The finished product is packaged in an Aluminium/Aluminum blister in pack sizes of 7, 10, 14, 20, 28, 30, 50, 56, 60, 90, 100 and 112 tablets (PL 04416/0758, PL 04416/0759, PL 04416/0764 and PL 04416/0765 are also available in pack sizes of 15 and 120 tablets and PL 04416/0761, PL 04416/0762, PL 04416/0764 and PL 04416/0765 are also available in pack sizes of 500 tablets). Satisfactory specifications and certificates of analysis have been provided for the packaging components. All primary product packaging complies with EU legislation regarding contact with food.

Stability of the Drug Product
The stability data provided support a shelf-life of 2 years, with the storage conditions ‘Do not store above 30°C. Store in the original package in order to protect from moisture’.

Bioequivalence/Bioavailability
Refer to Clinical Aspects (III.3).

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

A patient information leaflet (PIL) has been submitted to the MHRA along with a bridging report which refers to the results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC performed on the PIL of a similar product. The results indicate that the applicant’s PIL 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 on the information that it contains.

CONCLUSION

It is recommended that Marketing Authorisations are granted for these applications.

III.2 NON-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of perindopril tert-butylamine are well known. As perindopril tert-butylamine is a widely used, well-known active substance, no further studies were required. An adequate overview based on literature review has been provided.

Sections 4.6 and 5.3 of the Summary of Product Characteristics are in line with those for the reference products.

There are no objections to the approval of Perindopril 2mg and 4mg Tablets from a non-clinical point of view.

II.3 CLINICAL ASPECTS

CLINICAL PHARMACOLOGY

The applicant has provided biowaiver justification for Perindopril 2mg Tablets. The bioequivalence study used 4mg tablets only given as single dose.
The applicant argues that the kinetics of perindopril are linear and that biowaver criteria fulfil the requirements in section 5.4 of the CPMP/EWP/QWP/1401/98 document. The qualitative composition of the strengths and the ratio between amounts of the active substance and excipients are the same. The dissolution profiles are similar under identical conditions for the additional strength.

Pharmacokinetics

The applicant has provided an open-label, single-dose, randomised, 2-way crossover study. All subjects received study medication in a fasted state. The washout period was 21 days. The sampling period was up to 144 hours post-dose

Test and reference products
Perindopril 4mg Tablets were compared to Coversyl 4mg Tablets (Les Laboratoires Servier).

Population studied
Subjects were healthy male volunteers, aged 18-45 years with a BMI between 19 and 30. A total of 40 subjects were recruited and randomised. In all, 36 subjects completed the study.

Analytical methods
Plasma samples were used for analysis. Both perindopril and perindoprilat were measured by LC-MS/MS. The sample analysis calibration curve range for perindopril and peridoprilat were 1.0-200.0 ng/ml and 0.2-40.0 ng/ml respectively.

Pharmacokinetic Variables
The pharmacokinetic variables measured were AUC_t, AUC_i, C_{max} (primary parameters for C_{max} perindopril and perindoprilat). The secondary parameters measures were t_{max}, kel, $t_{½}$, RAUC, R_{start} and R_{end}, for perindopril and perindoprilat.

Statistical methods
The statistical methods used were average bioequivalence analysis using PROC GLM in SAS on ln-transformed AUC_t, AUC_i and C_{max}. Descriptive statistics was used for all pharmacokinetic parameters and non-parametric analysis was performed for t_{max}.
The acceptance criteria was 90% confidence interval within 80 – 125% range.

Results

The results from the bioequivalence study are shown in the table below.

Parameter	**Perindopril** Test vs. Reference	**Perindoprilat** Test vs. Reference
AUC_t	102% (98% - 106%)	93% (83% - 104%)
AUC_i	102% (98% - 106%)	99% (95% - 102%)
C_{max}	94% (88% - 100%)	93% (80% - 107%)

Based on the submitted bioequivalence study, Perindopril 4mg Tablets are considered to be bioequivalent with Coversyl 4mg Tablets. The results can be extrapolated to the 2mg strength.

Pharmacodynamics

No new pharmacodynamic data have been provided and none are required for an application of this type.

EFFICACY
No new clinical data have been submitted and none are required for this product. The efficacy of peridopril has been established through its use in clinical practice for many years.

SAFETY

No new clinical data have been submitted and none are required for this product. The safety of peridopril has been established through its use in clinical practice for many years.

EXPERT REPORT

A satisfactory clinical expert report has been submitted, which has been written by an appropriately qualified medical practitioner. This report is an adequate overview of the clinical pharmacology, efficacy and safety.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

This is satisfactory and consistent with the SPC for the reference product.

PATIENT INFORMATION LEAFLET (PIL)

This is satisfactory and consistent with the SPC.

LABELLING

These are satisfactory.

CONCLUSION

There are no clinical objections to the grant of Marketing Authorisations for these applications.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Perindopril 2mg and 4mg 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 4mg Tablets and Coversyl 4mg Tablets (Les Laboratoires Servier). Given that linear kinetics apply between the 2mg and 4mg Tablets, that proportional formulae for the tablets have been used, the method of manufacture is the same and that similar dissolution results have been shown for the two strengths, a separate bioequivalence study using the 2mg Tablet is not considered necessary.

No new or unexpected safety concerns arose from these applications.

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

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the reference products are interchangeable. Clinical experience with perindopril 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