Public Assessment Report

Decentralised Procedure

PERINDOPRIL ERUMINE 2 MG TABLETS
PERINDOPRIL ERUMINE 4 MG TABLETS
PERINDOPRIL ERUMINE 8 MG TABLETS

(Perindopril tert-butylamine)

Procedure No: UK/H/4521/001-3 & 4763/001-3/DC

UK Licence No: PL 17871/0139-41 & 0165-7

JENSON PHARMACEUTICAL SERVICES LIMITED
LAY SUMMARY

On 08 February 2012, Belgium, Czech Republic, France, Italy, Luxembourg, Netherlands, Poland, Slovakia and the UK agreed to grant Marketing Authorisations to Jenson Pharmaceutical Services Limited for the medicinal products Perindopril Erbumine 2 mg, 4 mg and 8 mg Tablets (PL 17871/0139-41 & 0165-7; UK/H/4521/001-3 &4763/001-3/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, Marketing Authorisations were granted in the UK on 28 February 2012. These are Prescription-Only Medicines (POM).

Perindopril Erbumine 2 mg, 4 mg and 8 mg tablets belongs to a group of medicines called angiotensin converting enzyme (ACE) inhibitors. They work by making blood vessels wider, which makes it easier for the heart to pump blood through them.

All strengths of this medicine are used:
- to treat high blood pressure (hypertension)
- 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 operation to improve the blood supply to the heart.

In addition, the 2 mg and 4 mg strength are also used to treat heart failure (a condition where the heart is unable to pump enough blood to meet the body’s needs).

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Perindopril Erbumine 2 mg, 4 mg and 8 mg Tablets outweigh the risks and Marketing Authorisations were granted.
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## Module 1

| **Product Name** | Perindopril Erbumine 2 mg tablets  
Perindopril Erbumine 4 mg tablets  
Perindopril Erbumine 8 mg tablets |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
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<tr>
<td><strong>Active Substances</strong></td>
<td>Perindopril tert-butylamine</td>
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<tr>
<td><strong>Form</strong></td>
<td>Tablets</td>
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<tr>
<td><strong>Strength</strong></td>
<td>2 mg, 4 mg and 8 mg.</td>
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<tr>
<td><strong>MA Holder</strong></td>
<td>Jenson Pharmaceutical Services Limited, Carradine House, 237 Regents Park Road, London, N3 3LF, UK.</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
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| **Concerned Member State (CMS)** | UK/H/4521/001/DC: France and the Netherlands  
UK/H/4521/002-3/DC: Belgium, Czech Republic, France, Italy, Luxembourg, Netherlands, Poland, Slovakia  
UK/H/4763/001/DC: France  
UK/H/4763/002-3/DC: Belgium and France |
| **Procedure Number** | UK/H/4521/001-3/DC  
UK/H/4763/001-3/DC |
| **Timetable** | Day 209– 08 February 2012 |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Perindopril Erbumine 2 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Perindopril Erbumine 2 mg tablets: Each tablet contains 2 mg of perindopril tert-butylamine salt (also known as erbumine), equivalent to 1.669 mg of perindopril.

Excipient with known effect:
Each tablet also contains 27.025 mg of lactose.
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablet.

Perindopril Erbumine 2 mg tablets are green mottled, round, tablets debossed with “PT” over “2” on one side of the tablet and “M” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Hypertension:
Treatment of hypertension.

Heart failure:
Treatment of symptomatic heart failure.

Stable coronary artery disease:
Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation.

4.2 Posology and method of administration

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

Hypertension
Perindopril Erbumine 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 Erbumine; 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 Erbumine (see section 4.4).

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

Symptomatic heart failure

It is recommended that Perindopril Erbumine, generally associated with a non-potassium-sparing diuretic and/or digoxin and/or a beta-blocker, be introduced under close medical supervision with a recommended starting dose of 2 mg taken in the morning. This dose may be increased after 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 section 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 Erbumine. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with Perindopril Erbumine (see section 4.4).

Stable coronary artery disease

Perindopril Erbumine 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”, below). 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

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ClCR &gt; 60</td>
<td>4 mg per day</td>
</tr>
<tr>
<td>30 &lt; ClCR &lt; 60</td>
<td>2 mg per day</td>
</tr>
<tr>
<td>15 &lt; ClCR &lt; 30</td>
<td>2 mg every other day</td>
</tr>
<tr>
<td>Haemodialysed patients *</td>
<td></td>
</tr>
<tr>
<td>ClCR &lt; 15</td>
<td>2 mg on the day of dialysis</td>
</tr>
</tbody>
</table>

* 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).

Paediatric population (less than 18 years of age)

Efficacy and safety of use in children and adolescents have not been established. Therefore, use in children and adolescents is not recommended.
Method of Administration

It is recommended that Perindopril Erbumine is taken once daily in the morning, before a meal.

4.3 Contraindications

- Hypersensitivity to perindopril, to any of the excipients (listed in section 6.1) 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 volume-depleted, e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 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 sections 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 sodium chloride 9 mg/ml (0.9%) solution. 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 Erbumine may be necessary.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

As with other ACE inhibitors, Perindopril Erbumine 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 section 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 section 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 Erbumine 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 Erbumine 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 Erbumine 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 anti-hypertensive agent.

Kidney transplantation

There is no experience regarding the administration of Perindopril Erbumine in patients with 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 Erbumine (see section 4.8). This may occur at any time during therapy. In such cases, Perindopril Erbumine 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.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).

Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

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 who have been treated with ACE inhibitors during desensitisation treatment (e.g. Hymenoptera venom) have displayed anaphylactoid reactions. In these patients, these reactions were prevented if the treatment with ACE inhibitors was temporarily stopped, but they reappeared in the event of unintended, repeated exposure.

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 section 4.8).

Neutropenia/Agranulocytosis/Thrombocytopenia/A Anaemia

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Perindopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If perindopril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (e.g. sore throat, fever).

Race

ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients. As with other ACE inhibitors, perindopril may be less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Cough

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/AAnaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Perindopril Erbumine 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, worsening of renal function, age (> 70 years), diabetes mellitus, inter-current events, in particular dehydration, acute cardiac decapsulation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). The use of potassium supplements, potassium sparing diuretics, or potassium containing salt substitutes particularly in patients with impaired renal function may lead to significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal arrhythmias. If concomitant use of the above-mentioned agents is deemed appropriate, they should be used with caution and regular monitoring of serum potassium is recommended. (see section 4.5)

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 section 4.5).

Lithium

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

Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes
The combination of perindopril and potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes is generally not recommended (see section 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).

**Excipients**

Due to the presence of lactose, patients with rare hereditary problems of galactose intolerance, glucose-galactose malabsorption, or the Lapp lactase deficiency should not take this medicinal product.

**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 medicinal products (NSAIDs), including aspirin ≥3 g/day**

When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the anti-hypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including a risk of acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function at the beginning of the treatment and periodically thereafter.

**Anti-hypertensive 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/Antaesthesia

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 anti-hypertensive effects of ACE inhibitors.

Gold:

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including perindopril.

4.6 Fertility, 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 trimesters of pregnancy (see sections 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.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human feto-toxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

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 sections 4.3 and 4.4).

Breast-feeding

Because no information is available regarding the use of Perindopril Erbumine during breast-feeding, Perindopril Erbumine is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on ability to drive and use machines

Perindopril Erbumine has no direct influence on the ability to drive and use machines but individual reactions related to low blood pressure may occur in some patients, particularly at the start of treatment or in combination with another antihypertensive medication.

4.8 Undesirable effects

The following undesirable effects have been observed during treatment with perindopril and ranked under the following frequency:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/100000); not known (cannot be estimated from the available data).
Blood and lymphatic system disorders

Decreases in haemoglobin and haematocrit, thrombocytopenia, leucopenia/neutropenia, and cases of agranulocytosis or pancytopenia have been reported very rarely. In patients with a congenital deficiency of G-6PDH, very rare cases of haemolytic anaemia have been reported (see section 4.4).

Metabolism and nutrition disorders

Not known: hypoglycaemia (see sections 4.4 and 4.5).

Psychiatric disorders

Uncommon: mood or sleep disturbances.

Nervous system disorders

Common: headache, dizziness, vertigo, paresthaesia.
Very rare: confusion.

Eye disorders

Common: vision disturbance.

Ear and labyrinth disorders

Common: tinnitus.

Cardiac disorders

Very rare: arrhythmia, angina pectoris and myocardial infarction, possibly secondary to excessive hypotension in high-risk patients (see section 4.4).

Vascular disorders

Common: hypotension and effects related to hypotension.
Very rare: stroke, possibly secondary to excessive hypotension in high-risk patients (see section 4.4).
Not known: vasculitis

Respiratory, thoracic and mediastinal disorders

Common: cough, dyspnoea.
Uncommon: bronchospasm.
Very rare: eosinophilic pneumonia, rhinitis.

Gastro-intestinal disorders

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

Hepato-biliary disorders

Very rare: hepatitis, either cytolytic or cholestatic (see section 4.4).

Skin and subcutaneous tissue disorders

Common: rash, pruritus.
Uncommon: angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see section 4.4).
Very rare: erythema multiforme.

Musculoskeletal and connective tissue disorders
Common: muscle cramps.

Renal and urinary disorders

Uncommon: renal insufficiency.
Very rare: acute renal failure.

Reproductive system and breast disorders

Uncommon: impotence.

General disorders and administration site conditions

Common: asthenia.
Uncommon: sweating.

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

The recommended treatment of overdosage is intravenous infusion of sodium chloride 9 mg/ml (0.9%) 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 section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitor, plain, ATC code: C09A A04

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

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

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

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

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

The anti-hypertensive 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 additivetype 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 Erbumine reduces cardiac work by a decrease in pre-load and after-load.

Studies in patients with heart failure have demonstrated:

- Decreased left and right ventricular filling pressures,
- Reduced total peripheral vascular resistance,
- Increased cardiac output and improved cardiac index.

In comparative studies, the first administration of 2 mg of perindopril to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo.

Patients with stable coronary artery disease

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

Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to 8 mg perindopril (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 8 mg perindopril 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 is achieved within 1 hour. The plasma half-life of perindopril is equal to 1 hour.

Perindopril is a pro-drug. Twenty seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.

As ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril erbumine should be administered orally in a single daily dose in the morning before a meal.

It has been demonstrated a linear relationship between the dose of perindopril and its plasma exposure.

The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Binding of perindoprilat to plasma proteins is 20%, principally to angiotensin-converting enzyme, but is concentration-dependent.

Perindoprilat is eliminated in the urine and the terminal half-life of the unbound fraction is approximately 17 hours, resulting in steady-state within 4 days.

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 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

- Cellulose, microcrystalline
- Sodium hydrogen carbonate
- Lactose anhydrous
- Silica, hydrophobic colloidal
- Magnesium stearate
- Aluminium lake of sodium copper chlorophyllin (E141)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25 °C
6.5 Nature and contents of container
Al/OPA/PVC-Al blister packs.

Pack sizes: 14, 30, 60, 90, 100 tablets.

Not all pack sizes and pack types may be marketed

6.6 Special precautions for disposal
No special requirements for disposal

7 MARKETING AUTHORISATION HOLDER
Jenson Pharmaceutical Services Limited
Carradine House,
237 Regents Park Road
London, N3 3LF, UK

8 MARKETING AUTHORIZATION NUMBER(S)
PL 17871/0139
PL 17871/0165

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
28/02/2012

10 DATE OF REVISION OF THE TEXT
28/02/2012
1 NAME OF THE MEDICINAL PRODUCT
Perindopril Erbumine 4 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Perindopril Erbumine 4 mg tablets: Each tablet contains 4 mg of perindopril tert-butylamine salt, equivalent to 3.338 mg of perindopril.

Excipient with known effect:
Each tablet also contains 54.050 mg of lactose.
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablet.

Perindopril Erbumine 4 mg tablets are green mottled, capsule shaped, tablets with side notch, debossed with “PT4” on one side of the tablet and “M” on the other side. The tablet can be divided into equal doses.

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

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

Hypertension

Perindopril Erbumine may be used in monotherapy or in combination with other classes of anti-hypertensive 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 Erbumine; 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 Erbumine (see section 4.4).

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

**Symptomatic heart failure**

It is recommended that Perindopril Erbumine, generally associated with a non-potassium-sparing diuretic and/or digoxin and/or a beta-blocker, be introduced under close medical supervision with a recommended starting dose of 2 mg taken in the morning. This dose may be increased after 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 section 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 Erbumine. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with Perindopril Erbumine (see section 4.4).

**Stable coronary artery disease**

Perindopril Erbumine 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”, below). 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>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{Cl}_{\text{CR}} \geq 60 )</td>
<td>4 mg per day</td>
</tr>
<tr>
<td>( 30 \lt \text{Cl}_{\text{CR}} \lt 60 )</td>
<td>2 mg per day</td>
</tr>
<tr>
<td>( 15 \lt \text{Cl}_{\text{CR}} \lt 30 )</td>
<td>2 mg every other day</td>
</tr>
<tr>
<td>Haemodialysed patients *</td>
<td></td>
</tr>
<tr>
<td>( \text{Cl}_{\text{CR}} \lt 15 )</td>
<td>2 mg on the day of dialysis</td>
</tr>
</tbody>
</table>

* 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).

**Paediatric population (less than 18 years of age)**

Efficacy and safety of use in children and adolescents have not been established. Therefore, use in children and adolescents is not recommended.
Method of Administration

It is recommended that Perindopril Erbumine is taken once daily in the morning, before a meal.

4.3 Contraindications

- Hypersensitivity to perindopril, to any of the excipients (listed in section 6.1) 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 volume-depleted, for example 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 sections 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 sodium chloride 9 mg/ml (0.9%) solution. 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 Erbumine may be necessary.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

As with other ACE inhibitors, Perindopril Erbumine 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 section 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 section 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 Erbumine 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
Erbumine 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 Erbumine 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 anti-hypertensive agent.

Kidney transplantation

There is no experience regarding the administration of Perindopril Erbumine in patients with 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 Erbumine (see section
4.8). This may occur at any time during therapy. In such cases, Perindopril Erbumine 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.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of
angioedema while receiving an ACE inhibitor (see section 4.3).

Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients
presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior
facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures
including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the
ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on
ACE inhibitors presenting with abdominal pain.

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 who have been treated with ACE inhibitors during desensitisation treatment (e.g.
Hymenoptera venom) have displayed anaphylactoid reactions. In these patients, these reactions were
prevented if the treatment with ACE inhibitors was temporarily stopped, but they reappeared in the
event of unintended, repeated exposure.

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 section 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. 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 (e.g. sore throat, fever).

Race

ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients. As with other ACE inhibitors, perindopril may be less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Cough

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Antaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Perindopril Erbumine 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, worsening of renal function, age (> 70 years), diabetes mellitus, inter-current events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). The use of potassium supplements, potassium sparing diuretics, or potassium containing salt substitutes particularly in patients with impaired renal function may lead to significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal arrhythmias. If concomitant use of the above-mentioned agents is deemed appropriate, they should be used with caution and regular monitoring of serum potassium is recommended. (see section 4.5)

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 section 4.5).

Lithium

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

Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes
The combination of perindopril and potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes is generally not recommended (see section 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).

**Excipients**

Due to the presence of lactose, patients with rare hereditary problems of galactose intolerance, glucose-galactose malabsorption, or the Lapp lactase deficiency should not take this medicinal product.

### 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 medicinal products (NSAIDs), including aspirin ≥3 g/day**

When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the anti-hypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including a risk of acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function at the beginning of the treatment and periodically thereafter.

**Anti-hypertensive 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/Antiasthetics

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 anti-hypertensive effects of ACE inhibitors.

Gold:

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including perindopril.

4.6 Fertility, 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 trimesters of pregnancy (see sections 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.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human feto-toxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

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 sections 4.3 and 4.4).

Breast-feeding

Because no information is available regarding the use of Perindopril Erbumine during breast-feeding, Perindopril Erbumine is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on ability to drive and use machines

Perindopril Erbumine has no direct influence on the ability to drive and use machines but individual reactions related to low blood pressure may occur in some patients, particularly at the start of treatment or in combination with another antihypertensive medication.

4.8 Undesirable effects

The following undesirable effects have been observed during treatment with perindopril and ranked under the following frequency:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000); not known (cannot be estimated from the available data).
Blood and lymphatic system disorders

Decreases in haemoglobin and haematocrit, thrombocytopenia, leucopenia/neutropenia, and cases of agranulocytosis or pancytopenia have been reported very rarely. In patients with a congenital deficiency of G-6PDH, very rare cases of haemolytic anaemia have been reported (see section 4.4).

Metabolism and nutrition disorders

Not known: hypoglycaemia (see sections 4.4 and 4.5).

Psychiatric disorders

Uncommon: mood or sleep disturbances.

Nervous system disorders

Common: headache, dizziness, vertigo, paresthaesia.
Very rare: confusion.

Eye disorders

Common: vision disturbance.

Ear and labyrinth disorders

Common: tinnitus.

Cardiac disorders

Very rare: arrhythmia, angina pectoris and myocardial infarction, possibly secondary to excessive hypotension in high-risk patients (see section 4.4).

Vascular disorders

Common: hypotension and effects related to hypotension.
Very rare: stroke, possibly secondary to excessive hypotension in high-risk patients (see section 4.4).
Not known: vasculitis

Respiratory, thoracic and mediastinal disorders

Common: cough, dyspnoea.
Uncommon: bronchospasm.
Very rare: eosinophilic pneumonia, rhinitis.

Gastro-intestinal disorders

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

Hepato-biliary disorders

Very rare: hepatitis, either cytolytic or cholestatic (see section 4.4).

Skin and subcutaneous tissue disorders

Common: rash, pruritus.
Uncommon: angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see section 4.4).
Very rare: erythema multiforme.

Musculoskeletal and connective tissue disorders
Common: muscle cramps.

Renal and urinary disorders

Uncommon: renal insufficiency.
Very rare: acute renal failure.

Reproductive system and breast disorders

Uncommon: impotence.

General disorders and administration site conditions

Common: asthenia.
Uncommon: sweating.

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

The recommended treatment of overdosage is intravenous infusion of sodium chloride 9 mg/ml (0.9%) 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 section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitor, plain, ATC code: C09A A04

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

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

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

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

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

The anti-hypertensive 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 additivetype 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 Erbumine reduces cardiac work by a decrease in pre-load and after-load.

Studies in patients with heart failure have demonstrated:

- Decreased left and right ventricular filling pressures,
- Reduced total peripheral vascular resistance,
- Increased cardiac output and improved cardiac index.

In comparative studies, the first administration of 2 mg of perindopril to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo.

Patients with stable coronary artery disease

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

Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to 8 mg perindopril (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 8 mg perindopril 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 is achieved within 1 hour. The plasma half-life of perindopril is equal to 1 hour.

Perindopril is a pro-drug. Twenty seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.

As ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril erbumine should be administered orally in a single daily dose in the morning before a meal.

It has been demonstrated a linear relationship between the dose of perindopril and its plasma exposure.

The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Binding of perindoprilat to plasma proteins is 20%, principally to angiotensin-converting enzyme, but is concentration-dependent.

Perindoprilat is eliminated in the urine and the terminal half-life of the unbound fraction is approximately 17 hours, resulting in steady-state within 4 days.

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 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

Cellulose, microcrystalline,
Sodium hydrogen carbonate,
Lactose anhydrous,
Silica, hydrophobic colloidal,
Magnesium stearate
Aluminium lake of sodium copper chlorophyllin (E141)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25 °C
6.5 Nature and contents of container
Al/OPA/PVC-Al blister packs.

Pack sizes: 14, 30, 60, 90, 100 tablets.

Not all pack sizes and pack types may be marketed

6.6 Special precautions for disposal
No special requirements for disposal

7 MARKETING AUTHORISATION HOLDER
Jenson Pharmaceutical Services Limited
Carradine House,
237 Regents Park Road
London, N3 3LF, UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 17871/0140
PL 17871/0166

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
28/02/2012

10 DATE OF REVISION OF THE TEXT
28/02/2012
1 NAME OF THE MEDICINAL PRODUCT
Perindopril Erbumine 8 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Perindopril Erbumine 8 mg tablets: Each tablet contains 8 mg of perindopril tert-butylamine salt, equivalent to 6.676 mg of perindopril.

Excipient with known effect:
Each 8 mg tablet also contains 108.100 mg of lactose.
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablet.

Perindopril Erbumine 8 mg tablets are green mottled, round, tablets debossed with “PT8” on one side of the tablet and “M” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Hypertension:
Treatment of hypertension.

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

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

Hypertension
Perindopril Erbumine may be used in monotherapy or in combination with other classes of anti-hypertensive 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 Erbumine; 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 Erbumine (see section 4.4).

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

Stable coronary artery disease
Perindopril Erbumine 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”, below). 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

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ClCR ≥ 60</td>
<td>4 mg per day</td>
</tr>
<tr>
<td>30 &lt; ClCR &lt; 60</td>
<td>2 mg per day</td>
</tr>
<tr>
<td>15 &lt; ClCR &lt; 30</td>
<td>2 mg every other day</td>
</tr>
<tr>
<td>Haemodialysed patients *</td>
<td></td>
</tr>
<tr>
<td>ClCR &lt; 15</td>
<td>2 mg on the day of dialysis</td>
</tr>
</tbody>
</table>

* 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).

Paediatric population (less than 18 years of age)

Efficacy and safety of use in children and adolescents have not been established. Therefore, use in children and adolescents is not recommended.

Method of Administration

It is recommended that Perindopril Erbumine is taken once daily in the morning, before a meal.

4.3 Contraindications

• Hypersensitivity to perindopril, to any of the excipients (listed in section 6.1) 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 volume-depleted, e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 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 sections 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 sodium chloride 9 mg/ml (0.9%) solution. 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 Erbumine may be necessary.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

As with other ACE inhibitors, Perindopril Erbumine 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 section 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 section 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 Erbumine 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 Erbumine 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 Erbumine 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 anti-hypertensive agent.

Kidney transplantation

There is no experience regarding the administration of Perindopril Erbumine in patients with 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 Erbumine (see section 4.8). This may occur at any time during therapy. In such cases, Perindopril Erbumine 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.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).

Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

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 who have been treated with ACE inhibitors during desensitisation treatment (e.g. Hymenoptera venom) have displayed anaphylactoid reactions. In these patients, these reactions were prevented if the treatment with ACE inhibitors was temporarily stopped, but they reappeared in the event of unintended, repeated exposure.

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 section 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. 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 (e.g. sore throat, fever).

Race

ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients. As with other ACE inhibitors, perindopril may be less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Cough
Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

**Surgery/Antaesthesia**

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Perindopril Erbumine 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, worsening of renal function, age (> 70 years), diabetes mellitus, inter-current events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). The use of potassium supplements, potassium sparing diuretics, or potassium containing salt substitutes particularly in patents with impaired renal function may lead to significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal arrhythmias. If concomitant use of the above-mentioned agents is deemed appropriate, they should be used with caution and regular monitoring of serum potassium is recommended. (see section 4.5)

**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 section 4.5).

**Lithium**

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

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

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

**Excipients**

Due to the presence of lactose, patients with rare hereditary problems of galactose intolerance, glucose-galactose malabsorption, or the Lapp lactase deficiency should not take this medicinal product.

### 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 medicinal products (NSAIDs), including aspirin ≥3 g/day**

When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the anti-hypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including a risk of acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function at the beginning of the treatment and periodically thereafter.

**Anti-hypertensive 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/Antaesthetics**

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 anti-hypertensive effects of ACE inhibitors.

**Gold**

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including perindopril.

### 4.6 Fertility, 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 trimesters of pregnancy (see sections 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.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human feto-toxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

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 sections 4.3 and 4.4).

**Breast-feeding**

Because no information is available regarding the use of Perindopril Erbumine during breast-feeding, Perindopril Erbumine is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

### 4.7 Effects on ability to drive and use machines

Perindopril Erbumine has no direct influence on the ability to drive and use machines but individual reactions related to low blood pressure may occur in some patients, particularly at the start of treatment or in combination with another antihypertensive medication.

### 4.8 Undesirable effects

The following undesirable effects have been observed during treatment with perindopril and ranked under the following frequency:

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

**Blood and lymphatic system disorders**

Decreases in haemoglobin and haematocrit, thrombocytopenia, leucopenia/neutropenia, and cases of agranulocytosis or pancytopenia have been reported very rarely. In patients with a congenital deficiency of G-6PDH, very rare cases of haemolytic anaemia have been reported (see section 4.4).

**Metabolism and nutrition disorders**

Not known: hypoglycaemia (see sections 4.4 and 4.5).

**Psychiatric disorders**

Uncommon: mood or sleep disturbances.

**Nervous system disorders**


**Eye disorders**

Common: vision disturbance.

**Ear and labyrinth disorders**
Common: tinnitus.

Cardiac disorders

Very rare: arrhythmia, angina pectoris and myocardial infarction, possibly secondary to excessive hypotension in high-risk patients (see section 4.4).

Vascular disorders

Common: hypotension and effects related to hypotension.
Very rare: stroke, possibly secondary to excessive hypotension in high-risk patients (see section 4.4).
Not known: vasculitis

Respiratory, thoracic and mediastinal disorders

Common: cough, dyspnoea.
Uncommon: bronchospasm.
Very rare: eosinophilic pneumonia, rhinitis.

Gastro-intestinal disorders

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

Hepato-biliary disorders

Very rare: hepatitis, either cytolytic or cholestatic (see section 4.4).

Skin and subcutaneous tissue disorders

Common: rash, pruritus.
Uncommon: angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see section 4.4).
Very rare: erythema multiforme.

Musculoskeletal and connective tissue disorders

Common: muscle cramps.

Renal and urinary disorders

Uncommon: renal insufficiency.
Very rare: acute renal failure.

Reproductive system and breast disorders

Uncommon: impotence.

General disorders and administration site conditions

Common: asthenia.
Uncommon: sweating.

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

The recommended treatment of overdosage is intravenous infusion of sodium chloride 9 mg/ml (0.9%) 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 section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: ACE inhibitor, plain, ATC code: C09A A04

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

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

Hypertension

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

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

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

The anti-hypertensive 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 additivetype of synergy. The combination of an ACE inhibitor and a thiazide also decreases the risk of hypokalaemia induced by the diuretic treatment.

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 8 mg perindopril (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 8 mg perindopril 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 is achieved within 1 hour. The plasma half-life of perindopril is equal to 1 hour.

Perindopril is a pro-drug. Twenty seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.

As ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril erbumine should be administered orally in a single daily dose in the morning before a meal.

It has been demonstrated a linear relationship between the dose of perindopril and its plasma exposure.

The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Binding of perindoprilat to plasma proteins is 20%, principally to angiotensin-converting enzyme, but is concentration-dependent.

Perindoprilat is eliminated in the urine and the terminal half-life of the unbound fraction is approximately 17 hours, resulting in steady-state within 4 days.

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 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
Cellulose, microcrystalline,
Sodium hydrogen carbonate,
Lactose anhydrous,
Silica, hydrophobic colloidal,
Magnesium stearate
Aluminium lake of sodium copper chlorophyllin (E141)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25 °C

6.5 Nature and contents of container
Al/OPA/PVC-Al blister packs.
Pack sizes: 14, 30, 60, 90, 100 tablets.
Not all pack sizes and pack types may be marketed

6.6 Special precautions for disposal
No special requirements for disposal

7 MARKETING AUTHORISATION HOLDER
Jenson Pharmaceutical Services Limited
Carradine House,
237 Regents Park Road
London, N3 3LF, UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 17871/0141
PL 17871/0167

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
28/02/2012

10 DATE OF REVISION OF THE TEXT
28/02/2012
Module 3

The following Patient Information Leaflets (PILs) are the approved text for procedure number UK/H/4763/001-3/DC (PL 17871/0165-7) and are included as representative PILs. The text agreed for procedure number UK/H/4521/001-3/DC (PL 17871/0139-41) is consistent with this PIL text. The Marketing Authorisation Holder is required to submit PIL mock-ups to the relevant regulatory authorities for approval before marketing the product in a particular member state.
Package Leaflet: Information For The User

Perindopril Erbumine 2 mg Tablets
Perindopril Erbumine 4 mg Tablets
Perindopril tert-butylamine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet

What is in this leaflet:
1. What Perindopril Erbumine is and what it is used for
2. What you need to know before you take Perindopril Erbumine
3. How to take Perindopril Erbumine
4. Possible side effects
5. How to store Perindopril Erbumine
6. Contents of the pack and other information

1. What Perindopril Erbumine is and what it is used for

Perindopril Erbumine belongs to a group of medicines known as angiotensin converting enzyme (ACE) inhibitors. These work by making your blood vessels wider, which makes it easier for your heart to pump blood through them.

Perindopril Erbumine is 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.

2. What you need to know before you take Perindopril Erbumine

Do not take Perindopril Erbumine

- if you are allergic (hypersensitive) to perindopril, to any other ACE inhibitor or to any of the other ingredients of this medicine (listed in section 6).
- if you are more than 3 months pregnant (it is also better to avoid perindopril in early pregnancy - see pregnancy section).
- if you have experienced symptoms such as wheezing, swelling of the face, tongue or throat, intense itching or severe skin rashes with previous ACE inhibitor treatment or if you or a member of your family have had these symptoms in any other circumstances (a condition called angioedema).
**Warnings and precautions**

Talk to your doctor or pharmacist before taking Perindopril Erbumine if you:

- have aortic stenosis (narrowing of the main blood vessel leading from the heart) or hypertrophic cardiomyopathy (heart muscle disease) or renal artery stenosis (narrowing of the artery supplying the kidney with blood),
- have any other heart problems,
- have liver problems,  
- have kidney problems or if you are receiving dialysis,
- suffer from a collagen vascular disease (disease of the connective tissue) such as systemic lupus erythematosus or scleroderma,
- have diabetes,
- are on a salt restricted diet or use salt substitutes which contain potassium,  
- are to undergo anaesthesia and/or major surgery,  
- are to undergo LDL apheresis (which is removal of cholesterol from your blood by a machine),
- are going to have desensitisation treatment to reduce the effects of an allergy to bee or wasp stings,
- have recently suffered from diarrhoea or vomiting, or are dehydrated

You must tell your doctor if you think that you are (or might become) pregnant. Perindopril Erbumine is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

**Children and adolescents**

Perindopril Erbumine is not recommended for use in children and adolescents.

**Other medicines and Perindopril Erbumine**

Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines.

Perindopril Erbumine can affect the way some other medicines work and some medicines can have an effect on Perindopril Erbumine. In particular, tell your doctor if you are using any of the following medicines:

- other medicines for high blood pressure, including diuretics (medicines which increase the amount of urine produced by the kidneys),
- potassium-sparing diuretics (spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes,
- lithium (a medicine for mental health problems)
- non-steroidal anti-inflammatory drugs (e.g. ibuprofen) for pain relief or high dose aspirin,
- medicines to treat diabetes (such as insulin or metformin),
- medicines to treat mental disorders such as depression, anxiety or schizophrenia (e.g. tricyclic antidepressants, antipsychotics),
- immunosuppressants (medicines which reduce the defence mechanism of the body), used for the treatment of auto-immune disorders or following transplant surgery (e.g. ciclosporin),
- medicines for the treatment of gout (e.g. allopurinol),
- medicines for the treatment of an irregular heart beat (e.g. procainamide),
- products that make the blood vessels become wider (i.e. vasodilators, including nitrates),
- medicines used to thin blood (e.g. heparin),
- medicines used for the treatment of low blood pressure, shock or asthma (e.g. ephedrine, noradrenaline or adrenaline).
Taking Perindopril Erbumine with food and drink

It is recommended to take Perindopril Erbumine before a meal.

Pregnancy and breastfeeding

If you are pregnant or breast-feeding, think you maybe pregnant or are planning to have a baby ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy
You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Perindopril Erbumine before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Perindopril Erbumine. Perindopril Erbumine is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breastfeeding
Tell your doctor if you are breastfeeding or about to start breastfeeding. Perindopril Erbumine is not recommended for mothers who are breastfeeding, and your doctor may choose another treatment for you if you wish to breastfeed, especially if your baby is newborn, or was born prematurely.

Driving and using machines

Perindopril Erbumine usually does not affect alertness but dizziness or weakness due to low blood pressure may occur in certain patients. If you are affected in this way, your ability to drive or to operate machinery may be impaired.

Perindopril Erbumine contains Lactose

Perindopril Erbumine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, such as lactose, contact your doctor before taking this medicine.

3. How to take Perindopril Erbumine

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Swallow your tablet with a glass of water, preferably at the same time each day, in the morning and before a meal. Your doctor will decide on the correct dose for you.

The recommended dose for Perindopril Erbumine is:

*High blood pressure:* The recommended starting and maintenance dose is 4 mg once daily. After one month, this can be increased to 8 mg once a day if required. The maximum recommended dose for high blood pressure is 8 mg a day.

If you are 65 years old or older, the recommended starting dose is 2 mg once a day. After a month this can be increased to 4 mg once a day and then, if necessary, to 8 mg once daily.

*Heart failure:* The recommended starting dose is 2 mg once daily. After two weeks, this can be increased to 4 mg once a day, which is the maximum recommended dose for heart failure.

*Stable coronary artery disease:* The recommended starting dose is 4 mg once daily. After two weeks, this can be increased to 8 mg once a day, which is the maximum recommended dose for this indication.
If you are 65 years old or older, the recommended starting dose is 2 mg once a day. After a week this can be increased to 4 mg once a day and after a further week, to 8 mg once daily.

If you take more Perindopril Erbumine than you should

If you take too many tablets, contact your nearest accident and emergency department or tell your doctor immediately. The most likely effect in case of overdose is low blood pressure, which can make you feel dizzy or faint. If this happens, lying down with the legs raised can help.

If you forget to take Perindopril Erbumine

It is important to take your medicine every day as regular treatment works better. However, if you forget to take a dose of Perindopril Erbumine, take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Perindopril Erbumine

As the treatment with Perindopril Erbumine is usually life-long, you should discuss with your doctor before stopping this medicinal product.

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.

If you experience any of the following, stop taking the medicinal product at once and tell your doctor immediately:

- swelling of the face, lips, mouth, tongue or throat, difficulty in breathing,
- severe dizziness or fainting,
- unusual fast or irregular heart beat.

In decreasing order of frequency, side effects can include:

Common (may affect up to 1 in 10 people):

- headache, dizziness, vertigo, pins and needles,
- vision disturbances,
- tinnitus (sensation of noises in the ears),
- light-headedness due to low blood pressure,
- cough, shortness of breath,
- gastro-intestinal disorders (nausea, vomiting, abdominal pain, taste disturbances, dyspepsia – difficulty of digestion, diarrhoea, constipation),
- allergic reactions (such as skin rashes, itching),
- muscle cramps,
- tiredness.

Uncommon (may affect up to 1 in 100 people):

- mood swings or sleep disturbances,
- tightening of the chest, wheezing and shortness of breath (bronchospasm),
- dry mouth,
- angioedema (symptoms such as wheezing, swelling of the face, tongue or throat, intense itching or severe skin rashes),
- kidney problems,
- impotence,
- sweating.
Very rare (may affect up to 1 in 10,000 people):
- confusion,
- cardiovascular disorders (irregular heart beat, angina, heart attack and stroke),
- eosinophilic pneumonia (a rare type of pneumonia),
- rhinitis (blocked up or runny nose),
- erythema multiforme,
- disorders of the blood, pancreas or liver.

In case of diabetic patients, hypoglycaemia (very low blood sugar level) can occur. Vasculitis (inflammation of blood vessels) has been reported.

If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store Perindopril Erbumine

Keep this medicine out of the sight and reach of children.
Do not store above 25 °C.
Do not use this medicine after the expiry date, which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the Pack and Other Information

What Perindopril Erbumine contains

The active substance is perindopril tert-butylamine.
One 2 mg tablet contains 2 mg of perindopril tert- butylamine, equivalent to 1.669 mg of perindopril.
One 4 mg tablet contains 4 mg of perindopril tert- butylamine, equivalent to 3.338 mg of perindopril.

The other ingredients are:
- Lactose anhydrous,
- magnesium stearate,
- silica,
- hydrophobic colloidal cellulose,
- microcrystalline sodium hydrogen carbonate,
- aluminium lake of sodium copper chlorophyllin E141.

What Perindopril Erbumine looks like and contents of the pack

Perindopril Erbumine 2 mg tablets are green mottled, round, tablets debossed with “PT” over “2” on one side of the tablet and “M” on the other side.

Perindopril Erbumine 4 mg tablets are green mottled, capsule shaped, tablets with side notch, debossed with “PT4” on one side of the tablet and “M” on the other side. The tablet can be divided into equal halves.

Perindopril Erbumine is available in blisters of 14, 30, 60, 90 and 100 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder:

Jenson Pharmaceutical Services Limited
Carradine House,
237 Regents Park Road
London, N3 3LF, UK

Manufacturer:

Gerard Laboratories,
35/36 Baldoyle Industrial Estate, Grange Road, Dublin 13, Ireland.

Generics [UK] Limited,
Station Close, Potters Bar,
Hertfordshire, EN6 1TL, United Kingdom.

This leaflet was last revised in 02/2012.
Package Leaflet: Information For The User

Perindopril Erbumine 8 mg Tablets
Perindopril tert-butylamine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet

What is in this leaflet:
1. What Perindopril Erbumine is and what it is used for
2. What you need to know before you take Perindopril Erbumine
3. How to take Perindopril Erbumine
4. Possible side effects
5. How to store Perindopril Erbumine
6. Contents of the pack and other information

1. What Perindopril Erbumine is and what it is used for

Perindopril Erbumine belongs to a group of medicines known as angiotensin converting enzyme (ACE) inhibitors. These work by making your blood vessels wider, which makes it easier for your heart to pump blood through them.

Perindopril Erbumine is used:
- to treat high blood pressure (hypertension)
- 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.

2. What you need to know before you take Perindopril Erbumine

Do not take Perindopril Erbumine

- if you are allergic (hypersensitive) to perindopril, to any other ACE inhibitor or to any of the other ingredients of this medicine (listed in section 6).
- if you are more than 3 months pregnant (it is also better to avoid perindopril in early pregnancy - see pregnancy section).
- if you have experienced symptoms such as wheezing, swelling of the face, tongue or throat, intense itching or severe skin rashes with previous ACE inhibitor treatment or if you or a member of your family have had these symptoms in any other circumstances (a condition called angioedema).

Warnings and precautions

Talk to your doctor or pharmacist before taking Perindopril Erbumine if you:
- have aortic stenosis (narrowing of the main blood vessel leading from the heart) or
hypertrophic cardiomyopathy (heart muscle disease) or renal artery stenosis (narrowing of the artery supplying the kidney with blood),
- have any other heart problems,
- have liver problems,
- have kidney problems or if you are receiving dialysis,
- suffer from a collagen vascular disease (disease of the connective tissue) such as systemic lupus erythematosus or scleroderma,
- have diabetes,
- are on a salt restricted diet or use salt substitutes which contain potassium,
- are to undergo anaesthesia and/or major surgery,
- are to undergo LDL apheresis (which is removal of cholesterol from your blood by a machine),
- are going to have desensitisation treatment to reduce the effects of an allergy to bee or wasp stings, or are dehydrated

You must tell your doctor if you think that you are (or might become) pregnant. Perindopril Erbumine is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

Children and adolescents
Perindopril Erbumine is not recommended for use in children and adolescents.

Other medicines and Perindopril Erbumine

Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines.

Perindopril Erbumine can affect the way some other medicines work and some medicines can have an effect on Perindopril Erbumine. In particular, tell your doctor if you are using any of the following medicines:

- other medicines for high blood pressure, including diuretics (medicines which increase the amount of urine produced by the kidneys),
- potassium-sparing diuretics (spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes,
- lithium (a medicine for mental health problems)
- non-steroidal anti-inflammatory drugs (e.g. ibuprofen) for pain relief or high dose aspirin,
- medicines to treat diabetes (such as insulin or metformin),
- medicines to treat mental disorders such as depression, anxiety or schizophrenia (e.g. tricyclic antidepressants, antipsychotics),
- immunosuppressants (medicines which reduce the defence mechanism of the body), used for the treatment of auto-immune disorders or following transplant surgery (e.g. ciclosporin),
- medicines for the treatment of gout (e.g. allopurinol),
- medicines for the treatment of an irregular heart beat (e.g. procainamide),
- products that make the blood vessels become wider (i.e. vasodilators, including nitrates),
- medicines used to thin blood (e.g. heparin),
- medicines used for the treatment of low blood pressure, shock or asthma (e.g. ephedrine, noradrenaline or adrenaline).

Taking Perindopril Erbumine with food and drink

It is recommended to take Perindopril Erbumine before a meal.
Pregnancy and breastfeeding

If you are pregnant or breast-feeding, think you maybe pregnant or are planning to have a baby ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy
You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Perindopril Erbumine before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Perindopril Erbumine. Perindopril Erbumine is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breastfeeding
Tell your doctor if you are breastfeeding or about to start breastfeeding. Perindopril Erbumine is not recommended for mothers who are breastfeeding, and your doctor may choose another treatment for you if you wish to breastfeed, especially if your baby is newborn, or was born prematurely.

Driving and using machines

Perindopril Erbumine usually does not affect alertness but dizziness or weakness due to low blood pressure may occur in certain patients. If you are affected in this way, your ability to drive or to operate machinery may be impaired.

Perindopril Erbumine contains Lactose

Perindopril Erbumine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, such as lactose, contact your doctor before taking this medicine.

3. How to take Perindopril Erbumine

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Swallow your tablet with a glass of water, preferably at the same time each day, in the morning and before a meal. Your doctor will decide on the correct dose for you.

The recommended dose for Perindopril Erbumine is:

*High blood pressure:* The recommended starting and maintenance dose is 4 mg once daily. After one month, this can be increased to 8 mg once a day if required. The maximum recommended dose for high blood pressure is 8 mg a day.

If you are 65 years old or older, the recommended starting dose is 2 mg once a day. After a month this can be increased to 4 mg once a day and then, if necessary, to 8 mg once daily.

*Stable coronary artery disease:* The recommended starting dose is 4 mg once daily. After two weeks, this can be increased to 8 mg once a day, which is the maximum recommended dose for this indication.

If you are 65 years old or older, the recommended starting dose is 2 mg once a day. After a week this can be increased to 4 mg once a day and after a further week, to 8 mg once daily.

If you take more Perindopril Erbumine than you should

If you take too many tablets, contact your nearest accident and emergency department or tell your doctor immediately. The most likely effect in case of overdose is low blood pressure, which can make you feel dizzy or faint. If this happens, lying down with the legs raised can help.
If you forget to take Perindopril Erbumine

It is important to take your medicine every day as regular treatment works better. However, if you forget to take a dose of Perindopril Erbumine, take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Perindopril Erbumine

As the treatment with Perindopril Erbumine is usually life-long, you should discuss with your doctor before stopping this medicinal product.
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.

If you experience any of the following, stop taking the medicinal product at once and tell your doctor immediately:
• swelling of the face, lips, mouth, tongue or throat, difficulty in breathing,
• severe dizziness or fainting,
• unusual fast or irregular heart beat.

In decreasing order of frequency, side effects can include:
Common (may affect up to 1 in 10 people):
• headache, dizziness, vertigo, pins and needles,
• vision disturbances,
• tinnitus (sensation of noises in the ears),
• light-headedness due to low blood pressure,
• cough, shortness of breath,
• gastro-intestinal disorders (nausea, vomiting, abdominal pain, taste disturbances, dyspepsia – difficulty of digestion, diarrhoea, constipation),
• allergic reactions (such as skin rashes, itching),
• muscle cramps,
• tiredness.

Uncommon (may affect up to 1 in 100 people):
• mood swings or sleep disturbances,
• tightening of the chest, wheezing and shortness of breath (bronchospasm),
• dry mouth,
• angioedema (symptoms such as wheezing, swelling of the face, tongue or throat, intense itching or severe skin rashes),
• kidney problems,
• impotence,
• sweating.

Very rare (may affect up to 1 in 10,000 people):
• confusion,
• cardiovascular disorders (irregular heart beat, angina, heart attack and stroke),
• eosinophilic pneumonia (a rare type of pneumonia),
• rhinitis (blocked up or runny nose),
• erythema multiforme,
• disorders of the blood, pancreas or liver,
In case of diabetic patients, hypoglycaemia (very low blood sugar level) can occur. Vasculitis (inflammation of blood vessels) has been reported.

If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store Perindopril Erbumine

Keep this medicine out of the sight and reach of children.
Do not store above 25 °C.
Do not use this medicine after the expiry date, which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the Pack and Other Information

What Perindopril Erbumine contains

The active substance is perindopril tert-butylamine.
One 8 mg tablet contains 8 mg of perindopril tert-butylamine, equivalent to 6.676 mg of perindopril.

The other ingredients are:
Lactose anhydrous, magnesium stearate, silica, hydrophobic colloidal, cellulose, microcrystalline, sodium hydrogen carbonate, aluminium lake of sodium copper chlorophyllin E141.

What Perindopril Erbumine looks like and contents of the pack

Perindopril Erbumine 8 mg tablets are green mottled, round, tablets debossed with “PT8” on one side of the tablet and “M” on the other side.

Perindopril Erbumine is available in blisters of 14, 30, 60, 90 and 100 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder:

Jenson Pharmaceutical Services Limited
Carradine House,
237 Regents Park Road
London, N3 3LF, UK

Manufacturer:

Gerard Laboratories,
35/36 Baldoyle Industrial Estate, Grange Road, Dublin 13, Ireland.

Generics [UK] Limited,
Station Close, Potters Bar,
Hertfordshire, EN6 1TL, United Kingdom.

This leaflet was last revised in 02/2012.
Module 4
Labelling

The following labelling is the approved text for procedure number UK/H/4763/001-3/DC (PL 17871/0165-7) and is included as representative labelling. The text agreed for procedure number UK/H/4521/001-3/DC (PL 17871/0139-41) is consistent with this labelling text. The Marketing Authorisation Holder is required to submit mock-ups of labelling to the relevant regulatory authorities for approval before marketing the product in a particular member state.

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON FOR BLISTERS</th>
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</table>

1. **NAME OF THE MEDICINAL PRODUCT**

Perindopril Erbumine 2 mg tablets

Perindopril tert-butylamine

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

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

3. **LIST OF EXCIPIENTS**

Contains lactose anhydrous. See package leaflet for more information

4. **PHARMACEUTICAL FORM AND CONTENTS**

14 tablets.

30 tablets.

60 tablets.

90 tablets.

100 tablets.

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

For oral use. Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP

9. **SPECIAL STORAGE CONDITIONS**

Do not store above 25 °C

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**
<table>
<thead>
<tr>
<th>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jenson Pharmaceutical Services Limited</td>
</tr>
<tr>
<td>Carradine House,</td>
</tr>
<tr>
<td>237 Regents Park Road</td>
</tr>
<tr>
<td>London, N3 3LF, UK</td>
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<th>12. MARKETING AUTHORISATION NUMBER(S)</th>
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<table>
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<th>13. BATCH NUMBER</th>
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<tr>
<th>14. GENERAL CLASSIFICATION FOR SUPPLY</th>
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<tbody>
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<td>Medicinal product subject to medicinal prescription</td>
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<table>
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<tr>
<th>15. INSTRUCTIONS ON USE</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>16. INFORMATION IN BRAILLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perindopril Erbumine 2 mg tablets</td>
</tr>
<tr>
<td>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</td>
</tr>
<tr>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>BLISTERS</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perindopril Erbumine 2 mg tablets</td>
</tr>
<tr>
<td>Perindopril tert-butylamine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jenson Pharmaceutical Services Limited</td>
</tr>
<tr>
<td>Carradine House,</td>
</tr>
<tr>
<td>237 Regents Park Road</td>
</tr>
<tr>
<td>London, N3 3LF, UK</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
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<tbody>
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<td>EXP</td>
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</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
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<tbody>
<tr>
<td>Batch</td>
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</table>

<table>
<thead>
<tr>
<th>5. OTHER</th>
</tr>
</thead>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARDBOARD CARTON FOR BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Perindopril Erbumine 4 mg tablets
Perindopril tert-butylamine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose anhydrous. See package leaflet for more information

4. PHARMACEUTICAL FORM AND CONTENTS

14 tablets.
30 tablets.
60 tablets.
90 tablets.
100 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Limited
Carradine House,
237 Regents Park Road
London, N3 3LF, UK

12. MARKETING AUTHORISATION NUMBER(S)

PL 17871/0166

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medicinal prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Perindopril Erbumine 4 mg tablets
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLISTERS</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></td>
</tr>
<tr>
<td>Perindopril Erbumine 4 mg tablets</td>
</tr>
<tr>
<td>Perindopril <em>tert</em>-butylamine</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>2. NAME OF THE MARKETING AUTHORISATION HOLDER</strong></td>
</tr>
<tr>
<td>Jenson Pharmaceutical Services Limited</td>
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<tr>
<td>Carradine House,</td>
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<tr>
<td>237 Regents Park Road</td>
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<tr>
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<td><strong>4. BATCH NUMBER</strong></td>
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<td>Batch</td>
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<tr>
<td><strong>5. OTHER</strong></td>
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</tbody>
</table>
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARDBOARD CARTON FOR BLISTERS

1. **NAME OF THE MEDICINAL PRODUCT**

   Perindopril Erbumine 8 mg tablets

   Perindopril tert-butylamine

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

   Each tablet contains 8 mg of perindopril tert-butylamine, equivalent to 6.676 mg of perindopril

3. **LIST OF EXCIPIENTS**

   Contains lactose anhydrous. See package leaflet for more information

4. **PHARMACEUTICAL FORM AND CONTENTS**

   14 tablets.
   30 tablets.
   60 tablets.
   90 tablets.
   100 tablets.

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

   For oral use. Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

   Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

   EXP

9. **SPECIAL STORAGE CONDITIONS**

   Do not store above 25 °C

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**
<table>
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<tr>
<th>12. MARKETING AUTHORISATION NUMBER(S)</th>
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<tr>
<th>15. INSTRUCTIONS ON USE</th>
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<table>
<thead>
<tr>
<th>16. INFORMATION IN BRAILLE</th>
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</thead>
<tbody>
<tr>
<td>Perindopril Erbumine 8 mg tablets</td>
</tr>
</tbody>
</table>
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Perindopril Erbumine 8 mg tablets
Perindopril tert-butylamine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Limited
Carradine House,
237 Regents Park Road
London, N3 3LF, UK

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER
Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Perindopril Erbumine 2 mg, 4 mg and 8 mg Tablets (PL 17871/0139-41 & 0165-7; UK/H/4521/001-3 &4763/001-3/DC) could be approved. These applications were submitted via the decentralised procedure, with the UK as Reference Member State (RMS) and Belgium, Czech Republic, France, Italy, Luxembourg, Netherlands, Poland, Slovakia as Concerned Member State (CMS). These products are prescription-only medicines (POM).

Perindopril Erbumine 2 mg, 4 mg and 8 mg tablets are indicated for the:

- treatment of hypertension.
- reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation (stable coronary artery disease).

In addition, Perindopril 2 mg and 4 mg tablets are indicated for treatment of symptomatic heart failure.

These are abridged applications submitted under Article 10(1) of Directive 2001/83/EC as amended, cross-referring to Coversyl 2mg, 4 mg and 8mg tablets (Les Laboratories Servier, France), which have been authorised in the EEA since 1989.

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

No new non-clinical studies were conducted, which is acceptable given that the products are intended to be generic versions of the originator products that have been licensed for over 10 years.

One bioequivalence study (single dose) was submitted to support these applications, comparing the test product Perindopril Erbumine 8 mg tablets (Jenson Pharmaceutical Services Limited) with the reference product Coversyl 8mg tablets (Les Laboratoires Servier).
With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications were for products that are intended to be generic versions of the originator products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 209) on 08 February 2012. After a subsequent national phase, the licences were granted in the UK on 28 February 2012.
## II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Perindopril Erbumine 2 mg tablets  
Perindopril Erbumine 4 mg tablets  
Perindopril Erbumine 8 mg tablets |
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Perindopril tert-butylamine</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Angiotensin Converting Enzyme (ACE) inhibitor, plain (C09CA06)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>2 mg, 4 mg and 8 mg tablets</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/4521/001-3/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>
| Concerned Member State | UK/H/4521/001/DC: France and the Netherlands  
UK/H/4521/002-3/DC: Belgium, Czech Republic, France, Italy, Luxembourg, Netherlands, Poland |
| Marketing Authorisation Number(s) | PL 17871/0139-41 & 0165-7 |
| Name and address of the authorisation holder | Jenson Pharmaceutical Services Limited, Carradine House, 237 Regents Park Road, London, N3 3LF, UK. |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Perindopril erbumine
Other name: Perindopril tert-butylamine
Chemical name: 2-methylpropan-2-amine (2S, 3aS, 7aS)-1-[(2S)-2-[[1S]-1-(ethoxycarbonyl)butyl]amino]propanoyl]octahydro-1H-indole-2-carboxylate

Structure:

Molecular formula: C_{23}H_{43}N_{3}O_{5}
Molecular mass: 441.6
Appearance: Perindopril tert-butylamine is a white or almost white, slightly hygroscopic, crystalline powder. It is freely soluble in water and ethanol and sparingly soluble in methylene chloride.

Perindopril tert-butylamine is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose, sodium hydrogen carbonate, lactose anhydrous, hydrophobic colloidal silica, magnesium stearate and
Aluminium lake of sodium copper chlorophyllin (E141).

All excipients comply with their respective European Pharmacopoeia monographs with the exception of Aluminium lake of sodium copper chlorophyllin which is compliant with a suitable in-house specification and with current EU directives concerning the use of colouring agents. Satisfactory certificates of analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of lactose anhydrous, none of the excipients contain materials of animal or human origin. The supplier of lactose anhydrous has confirmed that the lactose is sourced from healthy animals under the same conditions as milk for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development
The objective of the development programme was to formulate stable, robust, tablets containing 2 mg, 4 mg and 8 mg perindopril tert-butylamine, which could be considered generic medicinal products of Coversyl 2mg, 4 mg and 8mg tablets (Les Laboratories Servier).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The proposed finished product specifications are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided, which comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container-Closure System
All strengths of the finished product are packaged in aluminium/oriented polyamide (OPA)/polyvinylchloride (PVC) aluminium blister strips in pack sizes of 14, 30, 60, 90 and 100 tablets.

It has been stated that not all pack sizes may be marketed, however, the Marketing Authorisation Holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.
Stability of the product
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years with the storage conditions ‘Do not store above 25°C’.

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PIL and labels are acceptable.

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

Marketing Authorisation Application (MAA) form
The MAA forms are satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
There are no objections to the approval of these products from a pharmaceutical viewpoint.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of perindopril tert-butylamine are well-known, no new non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant pharmacology and toxicology.

Suitable justification has been provided for non-submission of an environmental risk assessment. As these products are intended for generic substitution with other products already on the market, it is not considered to increase the environmental risk. Thus, the applicant’s justification is accepted.

There are no objections to the approval of these products from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS
Pharmacokinetics
In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open label, balanced, randomised, two-period, two-treatment, two-sequence, single-dose, crossover, study to compare the pharmacokinetics of the test product Perindopril
Erbume 8 mg tablets (Jenson Pharmaceutical Services Limited) versus the reference product Coversyl 8mg tablets (LesLaboratories Servier, France) in healthy adult volunteers under fasted conditions.

All volunteers received a single oral dose of either the test or reference product as a 1 x 8 mg tablet administered after an overnight fast of at least 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 72 hours post dose. The washout period between treatment periods was at least 10 days.

The pharmacokinetic results for perindopril are presented below (log-transformed values; geometric least squares mean, ratios and 90% confidence intervals):

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC&lt;sub&gt;0-t&lt;/sub&gt; ng/ml/h</th>
<th>AUC&lt;sub&gt;0-∞&lt;/sub&gt; ng/ml/h</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; ng/ml</th>
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</thead>
<tbody>
<tr>
<td>Test (mean)</td>
<td>136.963</td>
<td>138.355</td>
<td>100.671</td>
</tr>
<tr>
<td>Reference (mean)</td>
<td>133.835</td>
<td>135.558</td>
<td>101.157</td>
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<tr>
<td>Ratio (90% CI)</td>
<td>101.23 (97.75-104.84%)</td>
<td>100.97 (97.48-104.57%)</td>
<td>99.48 (91.18-108.53%)</td>
</tr>
</tbody>
</table>

AUC<sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours
AUC<sub>0-∞</sub> area under the plasma concentration-time curve from time zero to infinity
C<sub>max</sub> maximum plasma concentration

The pharmacokinetic results for perindoprilat (active metabolite) are presented below (log-transformed values; geometric least squares mean, ratios and 90% confidence intervals):

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC&lt;sub&gt;0-t&lt;/sub&gt; ng/ml/h</th>
<th>AUC&lt;sub&gt;0-∞&lt;/sub&gt; ng/ml/h</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; ng/ml</th>
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<tr>
<td>Test (mean)</td>
<td>220.935</td>
<td>258.774</td>
<td>16.272</td>
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<tr>
<td>Reference (mean)</td>
<td>213.980</td>
<td>255.247</td>
<td>16.566</td>
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<tr>
<td>Ratio (90% CI)</td>
<td>102.56 (99.02-106.22%)</td>
<td>100.16 (97.07-103.35%)</td>
<td>99.75 (93.85-106.02%)</td>
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</table>

AUC<sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours
AUC<sub>0-∞</sub> area under the plasma concentration-time curve from time zero to infinity
C<sub>max</sub> maximum plasma concentration

The 90% confidence intervals for AUC and C<sub>max</sub> for test versus reference product for the parent compound perindopril and its active metabolite perindoprilat are within predefined acceptance criteria specified in "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev 1/, Corr). Thus, the data support the claim that the test product is bioequivalent to the reference product.

As the 2 mg, 4 mg and 8 mg strengths of the product meet the criteria specified in "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev 1/, Corr), the results and conclusions of the bioequivalence study on the 8 mg strength can be extrapolated to the 2 mg and 4 mg strength.

**Pharmacodynamics**
No new pharmacodynamic data were submitted and none were required for these applications.

**Efficacy**
No new efficacy data were submitted and none were required for these applications.
Safety
With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were highlighted by the bioequivalence data.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PIL and labels are acceptable. The SmPCs are consistent with that for the originator products. The PIL is consistent with the SmPCs and in line with current guidelines. The labelling is in-line with current guidelines.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for these products.

Conclusion
There are no objections to the approval of these products from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

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

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type. The pharmacodynamic, pharmacokinetic and toxicological properties of perindopril tert-butylamine are well-known.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s Perindopril Erbumine 8 mg tablets and its respective reference product (Coversyl 8mg tablets, LesLaboratories Servier, France). As the 2 mg, 4 mg and 8 mg strengths of the product meet the biowaiver criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/, Corr), the results and conclusions of the bioequivalence studies on the 8 mg strength can be extrapolated to the 2 mg and 4 mg strengths.

SAFETY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type. As the safety profile of perindopril tert-butylamine is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence studies.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with that for the reference products, where appropriate, in line with current guidelines.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the originator products are interchangeable. Extensive clinical experience with perindopril tert-butylamine is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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