PERINDOPRIL 2 MG, 4 MG AND 8 MG FILM-COATED TABLETS

PL 33410/0049-51, 0128-30

UKPAR

TABLE OF CONTENTS

Lay Summary Page 2
Scientific discussion Page 3
Steps taken for assessment Page 12
Summary of Product Characteristics Page 13
Product Information Leaflet Page 49
Labelling Page 51
PERINDOPRIL 2 MG, 4 MG AND 8 MG FILM-COATED TABLETS

PL 33410/0049-51, 0128-30

LAY SUMMARY

On the 14th May 2012, the MHRA granted APSLA Limited Marketing Authorisations (licences) for the medicinal products Perindopril 2, 4 and 8 mg Film-coated Tablets. These medicines are only available on prescription from your doctor.

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

Perindopril 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 further heart attacks in patients with previous heart attacks or those who have had a bypass operation.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Perindopril 2, 4 and 8 mg Film-coated Tablets outweigh the risks. Hence, Marketing Authorisations have been granted.
PERINDOPRIL 2 MG, 4 MG AND 8 MG FILM-COATED TABLETS

PL 33410/0049-51, 0128-30

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>4</td>
</tr>
<tr>
<td>Pharmaceutical assessment</td>
<td>5</td>
</tr>
<tr>
<td>Non-clinical assessment</td>
<td>8</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>9</td>
</tr>
<tr>
<td>Overall conclusions and risk benefit assessment</td>
<td>11</td>
</tr>
</tbody>
</table>
INTRODUCTION

The MHRA granted Marketing Authorisations for the medicinal products Perindopril 2, 4 and 8 mg Film-coated Tablets (PL 33410/0049-51, 0128-30) on the 14th May 2012. These prescription only medicines are used for the treatment of hypertension, symptomatic heart failure and stable coronary artery disease (for reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation).

These are national abridged applications for Perindopril 2, 4 and 8 mg Film-coated Tablets submitted under Article 10(1) of Directive 2001/83/EC, as amended. These products are generic versions of Coversyl 2 mg, 4 mg and 8 mg tablets (PL 05815/0001-2 and 05815/0023), authorised on 15th December 1989 (2mg and 4mg) and 12th June 2002 (8mg) to LES Laboratoires Servier.

Perindopril is an inhibitor of the enzyme that converts angiotensin I into angiotensin II (Angiotensin Converting Enzyme ACE). Inhibition of ACE results in a reduction of angiotensin II in the plasma, and reduced secretion of aldosterone. 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).

A pharmacovigilance system has been provided with these applications and is satisfactory. A suitable justification for non-submission of the Risk Management Plan has been provided.
DRUG SUBSTANCE

Nomenclature
rINN: Perindopril erbumine monohydrate

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

Structure:

Molecular Formula: C₂₃H₄₃N₃O₅.H₂O
Molecular Weight: 459.6 g/mol
Appearance: White or almost white, crystalline powder, which is freely soluble in alcohol.

The drug substance is the subject of a European Drug Master File (EDMF).

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification based on the European Pharmacopoeia has been provided.

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

The active substance is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for working standards used by the drug substance manufacturer and finished product manufacturer during validation studies.
Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

**DRUG PRODUCT**

**Other ingredients**

Other ingredients consist of the pharmaceutical excipients mannitol E421, sodium starch glycolate (Type A), sodium carbonate, anhydrous, hypromellose (HPMC E-15), macrogol-6000, siliconised talc 3% (3% simeticone in talc), magnesium stearate making up the tablet core; seal coat consisting of hypromellose 6cps, methylene chloride, and film coat consisting of OPADRY AMB OY-B-28920 white (polyvinyl alcohol, titanium dioxide E171, talc, lecithin (Soya) and xanthan Gum).

All excipients used comply with their respective European Pharmacopoeia monograph with the exception of 3% siliconised talc and OPADRY AMB OY-B-28920 white which comply with an in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has stated that none of the excipients are of animal or human origin, and confirms that the magnesium stearate used is of vegetable origin.

**Pharmaceutical development**

Suitable pharmaceutical development data have been provided for these applications. Comparable dissolution and impurity profile are provided for these products versus the originator products.

**Manufacture**

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial batches have been provided. The results are satisfactory.

**Finished product specification**

The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**

The tablets are packed in 3ply aluminium-aluminium laminated blister foil containing 7, 10, 14, 15, 20, 28, 30, 50, 56, 60, 90, 100, 112, 120 and 500 tablets.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.
Based on the results, a shelf-life of 2 years with storage conditions of “Store below 30°C” and “Store in the original packaging in order to protect from moisture” are set. These are satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are pharmaceutically satisfactory.

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

The proposed artwork complies with the relevant statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

Marketing Authorisation Application (MAA) Forms
The MAA forms are pharmaceutically satisfactory.

Expert Report
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of these products from a pharmaceutical point of view.
NON-CLINICAL ASSESSMENT

The pharmacodynamic, pharmacokinetic and toxicological properties of perindopril erbumine monohydrate are well-known. Thus, the applicant has not provided additional studies and further studies are not required.

A non-clinical overview has been provided, written by an appropriately qualified person. This is satisfactory.

A suitable justification has been provided for non-submission of environmental risk assessment.

There are no objections to the approval of these products from a non-clinical point of view.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

BIOEQUIVALENCE
To support the application, the applicant has submitted a bioequivalence study under fasting condition comparing the test product with the reference product.

Study number: 011/05
This was an open-label, randomised, two-treatment, two-period, two sequences, crossover comparative bioavailability study of Perindopril tert-butylamine (erbumine) 8 mg tablets (test) and Coversyl 8 mg Tablets (reference) in healthy adult human subjects under fasting conditions.

A washout period of 13 days was maintained between the two dosing periods in each group. Serial blood sampling before dosing and at 0.25, 0.50, 0.75, 1, 1.25, 1.50, 2, 2.50, 3, 3.50, 4, 4.50, 5, 6, 8, 12, 24, 48, 72, 96, 120 and 144 hours after drug administration was carried out in each group.

Results

Table1. Perindopril pharmacokinetic parameters (n=28)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Least square mean</th>
<th>T/R</th>
<th>90% Confidence Interval for In-transformed data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test (T)</td>
<td>Reference (R)</td>
<td></td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>101.304</td>
<td>112.057</td>
<td>90.404</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>82.60 - 98.95</td>
</tr>
<tr>
<td>AUC0-4 (h,ng/mL)</td>
<td>128.153</td>
<td>123.424</td>
<td>103.831</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>98.02 - 109.98</td>
</tr>
<tr>
<td>AUC0-∞ (h,ng/mL)</td>
<td>134.726</td>
<td>130.358</td>
<td>103.351</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>98.11 - 108.87</td>
</tr>
</tbody>
</table>

Table2. Perindoprilat pharmacokinetic parameters (n=28)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Least square mean</th>
<th>T/R</th>
<th>90% Confidence Interval for In-transformed data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test (T)</td>
<td>Reference (R)</td>
<td></td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>11.333</td>
<td>10.104</td>
<td>112.165</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>103.84 - 121.16</td>
</tr>
<tr>
<td>AUC0-4 (h,ng/mL)</td>
<td>250.250</td>
<td>232.305</td>
<td>107.725</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>103.54 - 112.08</td>
</tr>
<tr>
<td>AUC0-∞ (h,ng/mL)</td>
<td>282.198</td>
<td>263.263</td>
<td>107.193</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>102.22 - 112.41</td>
</tr>
</tbody>
</table>

The results show that the 90% confidence intervals for AUC ratios (both 0-t and 0-inf) and Cmax all fell within the acceptable range (80-125%) for Perindopril and its active metabolite perindoprilat. Bioequivalence has been demonstrated between the test formulation (Perindopril tert-butylamine (erbumine) 8 mg tablets) and the reference formulation (Coversyl 8 mg Tablets).

As the 2 mg and 4 mg strengths of the product meet the bio-waiver criteria specified in the “Note for Guidance on the Investigation of Bioavailability and Bioequivalence” (CHMP/EWP/QWP/1401/98 Rev.1), the results and conclusions of the
bioequivalence study on the 8 mg strength can be extrapolated to the 2 mg and 4 mg strengths.

EFFICACY
No new efficacy data have been submitted and none are required for these applications.

SAFETY
No new safety data have been submitted and none are required for these applications.

EXPERT REPORT
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

SUMMARY OF PRODUCT CHARACTERISTICS
These are satisfactory.

PATIENT INFORMATION LEAFLET
This is satisfactory.

LABELLING
These are satisfactory.

MAA FORMS
These are satisfactory.

CONCLUSIONS
There are no objections to the approval of these products from a clinical point of view.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

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

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
No new data have been submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s Perindopril tert-butylamine (erbumine) 8 mg tablets and the reference product, (Coversyl 8 mg Tablets). As the 2 mg and 4 mg strengths of the product meet the bio-waiver criteria specified in the “Note for Guidance on the Investigation of Bioavailability and Bioequivalence” (CHMP/EWP/QWP/1401/98 Rev.1), the results and conclusions of the bioequivalence study on 8 mg strength can be extrapolated to the 2 mg and 4 mg strengths.

No new or unexpected safety concerns arise from these applications.

The SmPCs and PIL are satisfactory and consistent with those for the reference products. Satisfactory labelling has also been submitted.

RISK BENEFIT ASSESSMENT
The quality of the product 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 erbumine monohydrate is considered to have demonstrated the therapeutic value of the compound. The benefit risk is, therefore, considered to be positive.
PERINDOPRIL 2 MG, 4 MG AND 8 MG FILM-COATED TABLETS

PL 33410/0049-51, 0128-30

STEPS TAKEN FOR ASSESSMENT

1  The MHRA received the marketing authorisation applications on 8th February 2010

2  Following standard checks and communication with the applicant the MHRA considered the applications valid on 17th February 2010.

3  Following assessment of the applications the MHRA requested further information relating to the quality dossier on 8th July 2010, 25th March 2011, 20th July 2011, 17th November 2011, and on the clinical section on 19th May 2010.

4  The applicant responded to the MHRA’s requests, providing further information to the quality section on 12th July 2010, 9th June 2011, 19th October 2011 and 14th February 2012 and on clinical section 18th June 2010.

5  The applications were determined on 14th May 2012.
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Perindopril 2 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 2 mg Perindopril Erbumine (as monohydrate) equivalent to 1.669 mg of Perindopril.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet

Perindopril 2 mg film-coated tablets are white to off white circular, biconvex film coated tablets plain on both sides.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Hypertension:
Treatment of hypertension

Heart failure:
Treatment of symptomatic heart failure

Stable Coronary Artery Disease:
Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation

4.2 Posology and method of administration
For oral use.
It is recommended that Perindopril is taken once daily in the morning before a meal.
The dose should be individualised according to the patient profile (see section 4.4) and blood pressure response.

Hypertension
Perindopril may be used in monotherapy or in combination with other classes of antihypertensive therapy.
The recommended starting dose is 4 mg given once daily in the morning.
Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and/or volume depletion, cardiac decompensation or severe hypertension) may experience an excessive drop in blood pressure following the initial dose.
A starting dose of 2 mg is recommended in such patients and the initiation of treatment should take place under medical supervision.
The dose may be increased to 8 mg once daily after one month of treatment.
Symptomatic hypotension may occur following initiation of therapy with Perindopril; this is more likely in patients who are being treated concurrently with diuretics. Caution is therefore recommended since these patients may be volume and/or salt depleted.
If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with Perindopril (see section 4.4).
In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Perindopril should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Perindopril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.
In elderly patients treatment should be initiated at a dose of 2 mg which may be progressively increased to 4 mg after one month then to 8 mg if necessary depending on renal function (see table below).
Symptomatic heart failure
It is recommended that Perindopril, generally associated with a non-potassium-sparing diuretic and/or digoxin and/or a beta blocker, be introduced under close medical supervision with a recommended starting dose of 2 mg taken in the morning. This dose may be increased by increments of 2 mg at intervals of no less than 2 weeks to 4 mg once daily if tolerated. The dose adjustment should be based on the clinical response of the individual patient.
In severe heart failure and in other patients considered to be at high risk (patients with impaired renal function and a tendency to have electrolyte disturbances, patients receiving simultaneous treatment with diuretics and/or treatment with vasodilating agents), treatment should be initiated under careful supervision (see 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. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with Perindopril (see section 4.4).

Stable coronary artery disease
Perindopril should be introduced at a dose of 4 mg once daily for two weeks, then increased to 8 mg once daily, depending on renal function and provided that the 4 mg dose is well tolerated.
Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily for the next week, before increasing the dose up to 8 mg once daily depending on renal function (see Table 1 “Dosage adjustment in renal impairment”). The dose should be increased only if the previous lower dose is well tolerated.

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

Table 1: Dosage adjustment in renal impairment

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

4.3 Contraindications
- Hypersensitivity to perindopril, to any of the excipients or to any other ACE inhibitor.
- History of angioedema associated with previous ACE inhibitor therapy.
- Hereditary or idiopathic angioedema.
- Second and third trimesters of pregnancy (see 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 section 4.2 and 4.8). Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

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

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Perindopril. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of Perindopril may be necessary.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy
As with other ACE inhibitors, Perindopril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Renal impairment
In cases of renal impairment (creatinine clearance < 60 ml/min) the initial Perindopril dosage should be adjusted according to the patient's creatinine clearance (see 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 bilatral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of Perindopril therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when perindopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or Perindopril may be required.

Haemodialysis patients
Anaphylactoid reactions have been reported in patients dialysed with high flux membranes, and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of anti-hypertensive agent.

Kidney transplantation
There is no experience regarding the administration of perindopril in patients with a recent kidney transplantation.
Hypersensitivity/Angioedema
Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including perindopril (see section 4.8). This may occur at any time during therapy. In such cases, Perindopril should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway.

The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

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

Hepatic failure
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see 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/Anaesthesia
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Perindopril may block angiotensin II formation secondary to compensatory renin release. The treatment should be discontinued one day prior to the surgery. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent 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 a significant increase in serum potassium. Hyperkalemia can cause serious, sometimes fatal arrhythmias. If concomitant use of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (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 antihypertensive treatments which have an established safety profile for use in pregnancy.

When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Diuretics
Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating therapy with low and progressive doses of perindopril.

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes
Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with perindopril. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore the combination of perindopril with the above-mentioned drugs is not recommended (see section 4.4). If concomitant use is indicated because of demonstrated hypokalaemia they should be used with caution and with frequent monitoring of serum potassium.
Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE inhibitors. Use of perindopril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin 2-3 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 antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible 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 after initiation of concomitant therapy, and periodically thereafter.

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

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

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

Tricyclic antidepressants/Antipsychotics/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 antihypertensive 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 contraindicated during the second and third trimester 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 antihypertensive 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 foetotoxicity (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 sections 4.3 and 4.4).

Lactation:
Because no information is available regarding the use of Perindopril during breastfeeding, Perindopril 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 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.

As a result the ability to drive or operate machinery may be impaired.

4.8 Undesirable effects
The most commonly (>1/10) reported adverse reactions in clinical studies were nausea, dry mouth, headache and sweating (including night sweats).

Adverse reactions are listed below by system organ class and frequency.
Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data)

<table>
<thead>
<tr>
<th>Frequency Organ System</th>
<th>Very Common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
<th>Rare (≥1/10,000 to &lt;1/1,000)</th>
<th>Very rare (&lt;1/10,000), not known (cannot be estimated from the available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>haemolytic anaemia, decreases in haemoglobin, haematocrit, thrombocytopenia, leucopenia/ neutropenia, and cases of agranulocytosis or pancytopenia and haemolytic anaemia have been reported in patients with a congenital deficiency of G-6PDH (see section 4.4).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>hypo glycaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency/Organ System</td>
<td>Psychiatric disorders</td>
<td>Nervous system disorders</td>
<td>Eye disorders</td>
<td>Ear and labyrinth disorders</td>
<td>Cardiac disorders</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------------------</td>
<td>-------------------------</td>
<td>--------------</td>
<td>-----------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Not known (cannot be estimated from the available data)</td>
<td>mood or sleep disturbances.</td>
<td>headache, dizziness, vertigo, paresthaesia</td>
<td>vision disturbance</td>
<td>tinnitus</td>
<td>hypotension and effects related to hypotension</td>
</tr>
<tr>
<td>Frequency</td>
<td>Common (≥1/100 to &lt;1/10)</td>
<td>Very Common (≥1/100)</td>
<td>Rare (≥1/10,000 to &lt;1/100)</td>
<td>Very rare (&lt;1/10,000)</td>
<td>Not known (cannot be estimated from the available data)</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------------</td>
<td>----------------------</td>
<td>-----------------------------</td>
<td>-----------------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>rash, pruritus</td>
<td>angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see section 4.4).</td>
<td>erythema multiforme</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>muscle cramps</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>renal insufficiency</td>
<td>acute renal failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive and breast disorders</td>
<td>impotence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders</td>
<td>asthenia</td>
<td>sweating</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Investigations:**
Increases in blood urea and plasma creatinine, hyperkalaemia reversible on discontinuation may occur, especially in the presence of renal insufficiency, severe heart failure and renovascular hypertension. Elevation of liver enzymes and serum bilirubin have been reported rarely.

**Clinical trials**
During the randomised period of EUROPA study, only serious adverse events were collected. Few patients experienced serious adverse events: 16 (0.3%) of the 6122 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 antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 87-100 % of peak effects. The decrease in blood pressure occurs rapidly. In responding patients, normalisation is achieved within a month and persists without the occurrence of tachyphylaxis.

Discontinuation of treatment does not lead to a rebound effect.
Perindopril reduces left ventricular hypertrophy.

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

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

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

Studies in patients with heart failure have demonstrated:
- decreased left and right ventricular filling pressures,
- reduced total peripheral vascular resistance,
- increased cardiac output and improved cardiac index.

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

Patients with stable coronary artery disease
The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years.

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

The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure.

Overall, 90% of the patients had a previous myocardial infarction and/or revascularisation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers.

The main efficacy criterion was the composite of cardiovascular mortality, non fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with perindopril 8 mg once daily resulted in a significant absolute reduction in the primary endpoint of 1.9% (relative risk reduction of 20%, 95%CI [9.4; 28.6] – p<0.001).
In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2.2% corresponding to a RRR of 22.4% (95%CI [12.0; 31.6] – p<0.001) in the primary endpoint was observed by comparison to placebo.

5.2 Pharmacokinetic properties
After oral administration, the absorption of perindopril is rapid and the peak concentration complete within 1 hour. Bioavailability is 65 to 70 %. About 20 % of the total quantity of perindopril absorbed is converted into perindoprilat, the active metabolite. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The plasma half-life of perindopril is equal to 1 hour. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.

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

The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Protein binding is slight (binding of perindoprilat to angiotensin converting enzyme is less than 30 %), but is concentration-dependent.

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

After repeated administration, no accumulation of perindopril is observed.

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

Dialysis clearance of perindoprilat is equal to 70 ml/min. Perindopril kinetics are modified in patients with cirrhosis: hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required (see also sections 4.2 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
Dry mix ingredients
Mannitol, E421
Sodium starch glycolate (Type A)
Sodium carbonate, anhydrous
Lubricants
Hypropellose (HPMC E-15)
Macrokol-6000
Siliconised Talc 3% (3% Simeticone in HPCG)
Magnesium stearate
Seal coating
Hypropellose 6cps
Methylene chloride
Film coating
Polyvinyl alcohol
Titanium dioxide E171
Talc
Lecithin (Soya)
Xanthan Gum
6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 30°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container
3 ply Alu-Alu laminated blister foil.
Pack sizes: 7, 10, 14, 15, 20, 28, 30, 50, 56, 60, 90, 100, 112, 120, 500 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
APSLA Limited,
Bayview House,
49 North Strand Road,
Dublin 3, Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 33410/0049 and PL 33410/0128

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
14/05/2012

10 DATE OF REVISION OF THE TEXT
14/05/2012
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Perindopril 4 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 4mg Perindopril Erbumine (as monohydrate) equivalent to 3.338 mg of Perindopril.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Perindopril tablets 4 mg are white to off-white, barrel shaped, biconvex film coated tablets, debossed with ‘PE4’ on one side and a central scoreline on the other.

The score line is only to facilitate breaking for ease of swallowing and not to divide 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
For oral use.
It is recommended that Perindopril is taken once daily in the morning before a meal.
The dose should be individualised according to the patient profile (see section 4.4) and blood pressure response.

Hypertension
Perindopril 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; this is more likely in patients who are being treated concurrently with diuretics. Caution is therefore recommended since these patients may be volume and/or salt depleted.
If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with Perindopril (see section 4.4).
In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Perindopril should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Perindopril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.
In elderly patients treatment should be initiated at a dose of 2 mg which may be progressively increased to 4 mg after one month then to 8 mg if necessary depending on renal function (see table below).
**Symptomatic heart failure**
It is recommended that Perindopril, generally associated with a non-potassium-sparing diuretic and/or digoxin and/or a beta blocker, be introduced under close medical supervision with a recommended starting dose of 2 mg taken in the morning. This dose may be increased by increments of 2 mg at intervals of no less than 2 weeks to 4 mg once daily if tolerated. The dose adjustment should be based on the clinical response of the individual patient.
In severe heart failure and in other patients considered to be at high risk (patients with impaired renal function and a tendency to have electrolyte disturbances, patients receiving simultaneous treatment with diuretics and/or treatment with vasodilating agents), treatment should be initiated under careful supervision (see 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. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with Perindopril (see section 4.4).

**Stable coronary artery disease**
Perindopril should be introduced at a dose of 4 mg once daily for two weeks, then increased to 8 mg once daily, depending on renal function and provided that the 4 mg dose is well tolerated.
Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily for the next week, before increasing the dose up to 8 mg once daily depending on renal function (see Table 1 “Dosage adjustment in renal impairment”). The dose should be increased only if the previous lower dose is well tolerated.

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

**Table 1: Dosage adjustment in renal impairment**

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>$ClCR \geq 60$</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 use**
Efficacy and safety of use in children has not been established. Therefore, use in children is not recommended.

**4.3 Contraindications**
- Hypersensitivity to perindopril, to any of the excipients or to any other ACE inhibitor.
- History of angioedema associated with previous ACE inhibitor therapy.
- Hereditary or idiopathic angioedema.
- Second and third trimesters of pregnancy (see 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 section 4.2 and 4.8). Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

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

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Perindopril. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of Perindopril may be necessary.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

As with other ACE inhibitors, Perindopril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Renal impairment

In cases of renal impairment (creatinine clearance < 60 ml/min) the initial Perindopril dosage should be adjusted according to the patient's creatinine clearance (see 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 therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when perindopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or Perindopril may be required.

Haemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes, and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of anti-hypertensive agent.

Kidney transplantation

There is no experience regarding the administration of perindopril in patients with a recent kidney transplantation.
Hypersensitivity/Angioedema
Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including perindopril (see section 4.8). This may occur at any time during therapy. In such cases, Perindopril should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway.

The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

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

Hepatic failure
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see 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/Aneasthesia
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Perindopril may block angiotensin II formation secondary to compensatory renin release. The treatment should be discontinued one day prior to the surgery. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent 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 a significant increase in serum potassium. Hyperkalemia can cause serious, sometimes fatal arrhythmias. If concomitant use of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (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 antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Diuretics
Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating therapy with low and progressive doses of perindopril.

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes
Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with perindopril. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore the combination of perindopril with the above-mentioned drugs is not recommended (see section 4.4). If
concomitant use is indicated because of demonstrated hypokalaemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE inhibitors. Use of perindopril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin

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 antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible 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 after initiation of concomitant therapy, and periodically thereafter.

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

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

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

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

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

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 contraindicated during the second and third trimester 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 antihypertensive 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 foetotoxicity (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 sections 4.3 and 4.4).

**Lactation:**
Because no information is available regarding the use of Perindopril during breastfeeding, Perindopril 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 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. As a result the ability to drive or operate machinery may be impaired.

### 4.8 Undesirable effects
The most commonly (>1/10) reported adverse reactions in clinical studies were nausea, dry mouth, headache and sweating (including night sweats).

Adverse reactions are listed below by system organ class and frequency.

Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data)

<table>
<thead>
<tr>
<th>Frequency Organ System</th>
<th>Very Common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
<th>Rare (≥1/10,000 to &lt;1/1,000)</th>
<th>Very rare (&lt;1/10,000)</th>
<th>Not known (cannot be estimated from the available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
<td>haemolytic anaemia, decreases in haemoglobin, haematocrit, thrombocytopenia, leucopenia/neutropenia, and cases of agranulocytosis or pancytopenia and haemolytic anaemia have been reported in patients with a congenital deficiency of G-6PDH (see section 4.4).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
<td>hypoglycaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency / Organ System</td>
<td>Very Common (\geq 1/10)</td>
<td>Common (\geq 1/100) to &lt;1/10)</td>
<td>Uncommon (\geq 1/1,000) to &lt;1/100)</td>
<td>Rare (\geq 1/10,000) to &lt;1/1,000)</td>
<td>Very rare (&lt;1/10,000), Not known (cannot be estimated from the available data)</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------------</td>
<td>-------------------------------</td>
<td>----------------------------------</td>
<td>---------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td>mood or sleep disturbances.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td>headache, dizziness, vertigo,</td>
<td></td>
<td>confusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td>vision disturbance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
<td>tinnitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>hypotension and effects related to hypotension</td>
<td></td>
<td>arrhythmia, angina pectoris, myocardial infarction and stroke, possibly secondary to excessive hypotension in high risk patients (see section 4.4).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
<td>vasculitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>cough, dyspnoea</td>
<td>bronchospasm</td>
<td></td>
<td>eosinophilic pneumonia, rhinitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastro-intestinal disorders</td>
<td></td>
<td>nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea, constipation</td>
<td>dry mouth</td>
<td>pancreatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td></td>
<td>hepatitis either cytolytic or cholestatic (see section 4.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency Organ System</td>
<td>Very Common (≥1/10)</td>
<td>Common (≥1/100 to &lt;1/10)</td>
<td>Uncommon (≥1/1,000 to &lt;1/100)</td>
<td>Rare (≥1/10,000 to &lt;1/1,000)</td>
<td>Very rare (&lt;1/10,000), Not known (cannot be estimated from the available data)</td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>---------------------</td>
<td>--------------------------</td>
<td>--------------------------------</td>
<td>-------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>rash, pruritus</td>
<td>angioedema of face, extremities, lips, mucous membrane, tongue, glottis and/or larynx, urticaria (see section 4.4).</td>
<td>erythema multiforme</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>muscle cramps</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td>renal insufficiency</td>
<td></td>
<td>acute renal failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive and breast disorders</td>
<td></td>
<td>impotence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders</td>
<td>asthenia</td>
<td>sweating</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Investigations:**
Increases in blood urea and plasma creatinine, hyperkalaemia reversible on discontinuation may occur, especially in the presence of renal insufficiency, severe heart failure and renovascular hypertension. Elevation of liver enzymes and serum bilirubin have been reported rarely.

**Clinical trials**
During the randomised period of EUROPA study, only serious adverse events were collected. Few patients experienced serious adverse events: 16 (0.3%) of the 6122 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 kallikreinkinin systems (and thus also activation of the prostaglandin system). It is possible that this mechanism contributes to the blood pressure-lowering action of ACE inhibitors and is partially responsible for certain of their side effects (e.g. cough). Perindopril acts through its active metabolite, perindoprilat. The other metabolites show no inhibition of ACE activity in vitro.

Hypertension

Perindopril is active in all grades of hypertension: mild, moderate, severe; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed. Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate. Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged. The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 87-100% of peak effects. The decrease in blood pressure occurs rapidly. In responding patients, normalisation is achieved within a month and persists without the occurrence of tachyphylaxis. Discontinuation of treatment does not lead to a rebound effect. Perindopril reduces left ventricular hypertrophy. In man, perindopril has been confirmed to demonstrate vasodilatory properties. It improves large artery elasticity and decreases the media: lumen ratio of small arteries. An adjunctive therapy with a thiazide diuretic produces an additive-type of synergy. The combination of an ACE inhibitor and a thiazide also decreases the risk of hypokalaemia induced by the diuretic treatment.

Heart failure

Perindopril reduces cardiac work by a decrease in pre-load and after-load. Studies in patients with heart failure have demonstrated:
- decreased left and right ventricular filling pressures,
- reduced total peripheral vascular resistance,
- increased cardiac output and improved cardiac index.
In comparative studies, the first administration of 2 mg of perindopril to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo. Patients with stable coronary artery disease

The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years. Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to perindopril 8 mg (n=6110) or placebo (n=6108). The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure. Overall, 90% of the patients had a previous myocardial infarction and/or revascularisation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers. The main efficacy criterion was the composite of cardiovascular mortality, non fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with
perindopril 8 mg once daily resulted in a significant absolute reduction in the primary endpoint of 1.9% (relative risk reduction of 20%, 95%CI [9.4; 28.6] – p<0.001).

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

5.2 Pharmacokinetic properties
After oral administration, the absorption of perindopril is rapid and the peak concentration complete within 1 hour. Bioavailability is 65 to 70%.
About 20% of the total quantity of perindopril absorbed is converted into perindoprilat, the active metabolite. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The plasma half-life of perindopril is equal to 1 hour. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.

As ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril should be administered orally in a single daily dose in the morning before a meal.
The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Protein binding is slight (binding of perindoprilat to angiotensin converting enzyme is less than 30%), but is concentration-dependent.
Perindoprilat is eliminated in the urine and the half-life of the unbound fraction is approximately 3 to 5 hours. Dissociation of perindoprilat bound to angiotensin converting enzyme leads to an “effective” elimination half-life of 25 hours, resulting in steady-state within 4 days.

After repeated administration, no accumulation of perindopril is observed.
Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure. Dosage adjustment in renal insufficiency is desirable depending on the degree of impairment (creatinine clearance).
Dialysis clearance of perindoprilat is equal to 70 ml/min.
Perindopril kinetics are modified in patients with cirrhosis: hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required (see also sections 4.2 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
Dry mix ingredients
Mannitol, E421
Sodium starch glycolate (Type A)
Sodium carbonate, anhydrous
Lubricants
Hypromellose (HPMC E-15)
Macrogol-6000
Siliconised Talc 3% (3% Simeticone in talc)
Magnesium stearate
Seal coating
Hypromellose 6cps
Methylene chloride
Film coating
Polyvinyl alcohol
Titanium dioxide E171
Talc
6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
2 years

6.4 **Special precautions for storage**
Store below 30°C. Store in the original package in order to protect from moisture.

6.5 **Nature and contents of container**
3 ply Alu-Alu laminated blister foil.
Pack sizes: 7, 10, 14, 15, 20, 28, 30, 50, 56, 60, 90, 100, 112, 120, 500 tablets
Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 **MARKETING AUTHORISATION HOLDER**
APSLA Limited,
Bayview House,
49 North Strand Road,
Dublin 3, Ireland

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 33410/0050 and PL 33410/0129

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
14/05/2012

10 **DATE OF REVISION OF THE TEXT**
14/05/2012
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Perindopril 8 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 8 mg Perindopril Erbumine (as monohydrate) equivalent to 6.676 mg of Perindopril.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Perindopril 8 mg tablets are white to off-white, barrel shaped, biconvex film coated tablets, debossed with ‘PE8’ on one side and a central scoreline on the other.
The score line is only to facilitate breaking for ease of swallowing and not to divide 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
For oral use.
It is recommended that Perindopril is taken once daily in the morning before a meal.
The dose should be individualised according to the patient profile (see section 4.4) and blood pressure response.

Hypertension
Perindopril 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; this is more likely in patients who are being treated concurrently with diuretics. Caution is therefore recommended since these patients may be volume and/or salt depleted.
If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with Perindopril (see section 4.4).
In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Perindopril should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Perindopril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.
In elderly patients treatment should be initiated at a dose of 2 mg which may be progressively increased to 4 mg after one month then to 8 mg if necessary depending on renal function (see table below).
Symptomatic heart failure
It is recommended that Perindopril, generally associated with a non-potassium-sparing diuretic and/or digoxin and/or a beta blocker, be introduced under close medical supervision with a recommended starting dose of 2 mg taken in the morning. This dose may be increased by increments of 2 mg at intervals of no less than 2 weeks to 4 mg once daily if tolerated. The dose adjustment should be based on the clinical response of the individual patient.
In severe heart failure and in other patients considered to be at high risk (patients with impaired renal function and a tendency to have electrolyte disturbances, patients receiving simultaneous treatment with diuretics and/or treatment with vasodilating agents), treatment should be initiated under careful supervision (see 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. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with Perindopril (see section 4.4).

Stable coronary artery disease
Perindopril should be introduced at a dose of 4 mg once daily for two weeks, then increased to 8 mg once daily, depending on renal function and provided that the 4 mg dose is well tolerated.
Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily for the next week, before increasing the dose up to 8 mg once daily depending on renal function (see Table 1 “Dosage adjustment in renal impairment”). The dose should be increased only if the previous lower dose is well tolerated.

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

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl&lt;sub&gt;Cr&lt;/sub&gt; ≥ 60</td>
<td>4 mg per day</td>
</tr>
<tr>
<td>30 &lt; Cl&lt;sub&gt;Cr&lt;/sub&gt; &lt; 60</td>
<td>2 mg per day</td>
</tr>
<tr>
<td>15 &lt; Cl&lt;sub&gt;Cr&lt;/sub&gt; &lt; 30</td>
<td>2 mg every other day</td>
</tr>
<tr>
<td>Haemodialysed patients *,</td>
<td></td>
</tr>
<tr>
<td>Cl&lt;sub&gt;Cr&lt;/sub&gt; &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 use
Efficacy and safety of use in children has not been established. Therefore, use in children is not recommended.

4.3 Contraindications
- Hypersensitivity to perindopril, to any of the excipients or to any other ACE inhibitor.
- History of angioedema associated with previous ACE inhibitor therapy.
- Hereditary or idiopathic angioedema.
- Second and third trimesters of pregnancy (see 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 section 4.2 and 4.8). Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

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

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Perindopril. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of Perindopril may be necessary.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy
As with other ACE inhibitors, Perindopril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Renal impairment
In cases of renal impairment (creatinine clearance < 60 ml/min) the initial Perindopril dosage should be adjusted according to the patient's creatinine clearance (see 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 therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when perindopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or Perindopril may be required.

Haemodialysis patients
Anaphylactoid reactions have been reported in patients dialysed with high flux membranes, and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of anti-hypertensive agent.

Kidney transplantation
There is no experience regarding the administration of perindopril in patients with a recent kidney transplantation.
Hypersensitivity/Angioedema
Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including perindopril (see section 4.8). This may occur at any time during therapy. In such cases, Perindopril should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

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 C1 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 receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In the same patients, these reactions have been avoided when the ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Hepatic failure
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see 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/Anaesthesia
In patients undergoing major surgery or during anaesthesia with agents that produce
hypotension, Perindopril may block angiotensin II formation secondary to compensatory renin
release. The treatment should be discontinued one day prior to the surgery. If hypotension
occurs and is considered to be due to this mechanism, it can be corrected by volume
expansion.

Hyperkalaemia
Elevations in serum potassium have been observed in some patients treated with ACE
inhibitors, including perindopril. Patients at risk for the development of hyperkalaemia include
those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus,
intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic
acidosis and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone,
triamterene, or amiloride) or, 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 a
significant increase in serum potassium. Hyperkalemia can cause serious, sometimes fatal
arrhythmia. If concomitant use of the above-mentioned agents is deemed appropriate, they
should be used with caution and with frequent monitoring of serum potassium (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
antihypertensive treatments which have an established safety profile for use in pregnancy.
When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately,
and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

4.5 Interaction with other medicinal products and other forms of interaction
Diuretics
Patients on diuretics, and especially those who are volume and/or salt depleted, may
experience excessive reduction in blood pressure after initiation of therapy with an ACE
inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the
diuretic, by increasing volume or salt intake prior to initiating therapy with low and
progressive doses of perindopril.
Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes
Although serum potassium usually remains within normal limits, hyperkalaemia may occur in
some patients treated with perindopril. Potassium sparing diuretics (e.g. spironolactone,
triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes
may lead to significant increases in serum potassium. Therefore the combination of
perindopril with the above-mentioned drugs is not recommended (see section 4.4). If
concomitant use is indicated because of demonstrated hypokalaemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE inhibitors. Use of perindopril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin
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 antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible 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 after initiation of concomitant therapy, and periodically thereafter.

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

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

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

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

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

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 contraindicated during the second and third trimester 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 antihypertensive
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 foetotoxicity (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 sections 4.3 and 4.4).

Lactation:
Because no information is available regarding the use of Perindopril during breastfeeding, Perindopril 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 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. As a result the ability to drive or operate machinery may be impaired.

4.8 Undesirable effects
The most commonly (>1/10) reported adverse reactions in clinical studies were nausea, dry mouth, headache and sweating (including night sweats).

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data)

<table>
<thead>
<tr>
<th>Frequency Organ System</th>
<th>Very Common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
<th>Rare (≥1/10,000 to &lt;1/1,000)</th>
<th>Very rare (&lt;1/10,000)</th>
<th>Not known (cannot be estimated from the available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>haemolytic anaemia, decreases in haemoglobin, haematocrit, thrombocytopenia, leucopenia/ neutropenia, and cases of agranulocytosis or pancytopenia and haemolytic anaemia have been reported in patients with a congenital deficiency of G-6PDH (see section 4.4).</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>hypoglycaemia</td>
</tr>
<tr>
<td>Frequency</td>
<td>Very Common (≥1/10)</td>
<td>Common (≥1/100 to &lt;1/10)</td>
<td>Uncommon (≥1/1,000 to &lt;1/100)</td>
<td>Rare (≥1/10,000 to &lt;1/1,000)</td>
<td>Very rare (&lt;1/10,000)</td>
<td>Not known (cannot be estimated from the available data)</td>
</tr>
<tr>
<td>------------------</td>
<td>---------------------</td>
<td>---------------------------</td>
<td>-------------------------------</td>
<td>-------------------------------</td>
<td>-----------------------</td>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>mood or sleep disturbances</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>headache, dizziness, vertigo, paresthaesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>confusion</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>vision disturbance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>tinnitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>hypotension and effects related to hypotension</td>
<td></td>
<td></td>
<td>arrhythmia, angina pectoris, myocardial infarction and stroke, possibly secondary to excessive hypotension in high risk patients (see section 4.4).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>vasculitis</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>cough, dyspnoea</td>
<td>bronchospasm</td>
<td></td>
<td>eosinophilic pneumonia, rhinitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastro-intestinal disorders</td>
<td>nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea, constipation</td>
<td>dry mouth</td>
<td></td>
<td>pancreatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td></td>
<td>hepatitis either cytolytic or cholestatic (see section 4.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>Organ System</td>
<td>Very Common (≥1/10)</td>
<td>Common (≥1/100 to &lt;1/10)</td>
<td>Uncommon (≥1/1,000 to &lt;1/100)</td>
<td>Rare (≥1/10,000 to &lt;1/100)</td>
<td>Very rare (&lt;1/10,000)</td>
</tr>
<tr>
<td>--------------------</td>
<td>------------------------------</td>
<td>--------------------</td>
<td>--------------------------</td>
<td>-------------------------------</td>
<td>---------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>rash, pruritus</td>
<td>angioedema of face, extremities, lips, mucous membrane, tongue, glottis and/or larynx, urticaria (see section 4.4).</td>
<td>erythema multiforme</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>muscle cramps</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>renal insufficiency</td>
<td>acute renal failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive and breast disorders</td>
<td>impotence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders</td>
<td>asthenia</td>
<td>sweating</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Investigations:**
Increases in blood urea and plasma creatinine, hyperkalaemia reversible on discontinuation may occur, especially in the presence of renal insufficiency, severe heart failure and renovascular hypertension. Elevation of liver enzymes and serum bilirubin have been reported rarely.

**Clinical trials**
During the randomised period of EUROPA study, only serious adverse events were collected. Few patients experienced serious adverse events: 16 (0.3%) of the 6122 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 kallikreinkinin systems (and thus also activation of the prostaglandin system). It is possible that this mechanism contributes to the blood pressure-lowering action of ACE inhibitors and is partially responsible for certain of their side effects (e.g. cough).

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

Hypertension

Perindopril is active in all grades of hypertension: mild, moderate, severe; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed. Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate. Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged.

The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 87-100 % of peak effects. The decrease in blood pressure occurs rapidly. In responding patients, normalisation is achieved within a month and persists without the occurrence of tachyphylaxis. Discontinuation of treatment does not lead to a rebound effect.

Perindopril reduces left ventricular hypertrophy.

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

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

Heart failure

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

Studies in patients with heart failure have demonstrated:
- decreased left and right ventricular filling pressures,
- reduced total peripheral vascular resistance,
- increased cardiac output and improved cardiac index.

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

Patients with stable coronary artery disease

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

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

The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure.

Overall, 90% of the patients had a previous myocardial infarction and/or revascularisation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers.
The main efficacy criterion was the composite of cardiovascular mortality, non fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with perindopril 8 mg once daily resulted in a significant absolute reduction in the primary endpoint of 1.9% (relative risk reduction of 20%, 95%CI [9.4; 28.6] – p<0.001). In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2.2% corresponding to a RRR of 22.4% (95%CI [12.0; 31.6] – p<0.001) in the primary endpoint was observed by comparison to placebo.

5.2 Pharmacokinetic properties
After oral administration, the absorption of perindopril is rapid and the peak concentration complete within 1 hour. Bioavailability is 65 to 70%. About 20% of the total quantity of perindopril absorbed is converted into perindoprilat, the active metabolite. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The plasma half-life of perindopril is equal to 1 hour. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours. As ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril should be administered orally in a single daily dose in the morning before a meal. The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Protein binding is slight (binding of perindoprilat to angiotensin converting enzyme is less than 30%), but is concentration-dependent. Perindoprilat is eliminated in the urine and the half-life of the unbound fraction is approximately 3 to 5 hours. Dissociation of perindoprilat bound to angiotensin converting enzyme leads to an “effective” elimination half-life of 25 hours, resulting in steady-state within 4 days. After repeated administration, no accumulation of perindopril is observed. Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure. Dosage adjustment in renal insufficiency is desirable depending on the degree of impairment (creatinine clearance). Dialysis clearance of perindoprilat is equal to 70 ml/min. Perindopril kinetics are modified in patients with cirrhosis: hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required (see also sections 4.2 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
Dry mix ingredients
Mannitol, E421
Sodium starch glycolate (Type A)
Sodium carbonate, anhydrous
Lubricants
Hypromellose (HPMC E-15)
Macrogol-6000
Siliconised Talc 3% (3% Simeticone in talc)
Magnesium stearate
Seal coating
Hypromellose 6cps
Methylene chloride
Film coating
Polyvinyl alcohol
Titanium dioxide E171
Talc
Lecithin (Soya)
Xanthan Gum

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 30°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container
3 ply Alu-Alu laminated blister foil.
Pack sizes: 7, 10, 14, 15, 20, 28, 30, 50, 56, 60, 90, 100, 112, 120, 500 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
APSLA Limited,
Bayview House,
49 North Strand Road,
Dublin 3, Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 33410/0051 and PL 33410/0130

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
14/05/2012

10 DATE OF REVISION OF THE TEXT
14/05/2012
UKPAR Perindopril 2, 4 and 8 mg Film-coated Tablets
PL 33410/0049-51, 0128-30

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER
Perindopril 2 mg, 4 mg & 8 mg
Film-coated Tablets
Perindopril Erbumine Monohydrate

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

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

1. WHAT PERINDOPRIL IS AND WHAT IT IS USED FOR

The name of your medicine is Perindopril 2 mg or 4 mg or 8 mg Film-coated Tablets. The tablets are available in these strengths.

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

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

2. BEFORE YOU TAKE PERINDOPRIL

Do not take Perindopril:
- if you are allergic (hypersensitive) to perindopril or any of the other ACE inhibitors or any of the other ingredients in the tablets (see section 4 Further information)
- if you have had symptoms such as swelling, oedema, unusual bruising, bleeding, nose or throat infection, wheezing, sneezing, cough, itching, swelling of the face, tongue or throat, intense itching, skin rash, flushing or dizziness with previous ACE inhibitor treatment or have had symptoms in any other circumstances (a condition called angioedema)
- if you are more than 3 months pregnant (see also note to avoid Perindopril in early pregnancy - see section "Pregnancy and breast-feeding")
- if you are breast-feeding (see section "Pregnancy and breast-feeding")

Perindopril should not be given to children.

If you think any of the above situations apply to you, do not take the tablet. Consult your doctor and take broken advice.

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

You should also inform your doctor or the medical staff that you are taking Perindopril:
- if you are underweight and/or anorexic
- if you have suffered from recent dizziness in standing or are dizzy/dizzy
- if you are going to have discontinuation treatment to reduce the effects of any allergy to bee or wasp stings
- if you are to undergo LDL apheresis (which is removal of cholesterol from your blood by a machine).

You must tell your doctor if you think you are (or might become) pregnant. Perindopril 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).

Perindopril is not recommended for use in children and adolescents.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. In particular, you should check with your doctor if you are taking any of the following to be sure that it is safe to take Perindopril at the same time:
- other medicines for treating high blood pressure including diuretics (water tablets)
- potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements and potassium-containing salt substitutes
- medicines for the treatment of diabetes mellitus or tablets such as metformin to lower blood sugar
- medicines for the treatment of manic disorders such as depression, manic, schizophrenia or other psychoses (anti-depressants, antipsychotics)
- serendipital used for the treatment of manic
- immunosuppressants used for the treatment of auto-immune disorders (e.g. rheumatoid arthritis) or following transplant surgery
- prednisolone, a treatment for simple heart disease
- non-steroidal anti-inflammatory drugs (e.g. ibuprofen) for pain relief or arthritis
- medicines used for the treatment of liver, blood pressure, shock, allergies (e.g. salicylic, antihistamine or ophthalmic), cardiovascular (e.g. antibodies that make the blood vessels become wider)
- insulin (used to treat the blood)

Ask your doctor if you are not sure what these medicines are. If you go into hospital, tell the medical staff here you are taking perindopril.

Tablets Perindopril with food and drink.
It is recommended that Perindopril should be taken before a meal.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any 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 before you become pregnant as soon as you know you are pregnant and will advise you to take another medicine instead of Perindopril. Perindopril 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.

Breastfeeding
Tell your doctor if you are breast-feeding or plan to start breast-feeding. Perindopril is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Driving and using machines
Do not drive or use machinery if you experience dizziness or weakness while taking Perindopril. If this occurs you should talk to your doctor.

3. HOW TO TAKE PERINDOPRIL

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

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

Method of administration:
Take your tablet(s) with a glass of water preferably at the same time each day, in the morning, before a meal. If you are taking water tablets (diuretics), your doctor may decide to reduce or reduce the dose before the beginning of your tablets with Perindopril.
UKPAR Perindopril 2, 4 and 8 mg Film-coated Tablets

PL 33410/0049-51, 0128-30

The usual dosages for Perindopril Tablets are as follows:

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

**Heart failure:**
- Adults: the elderly: treatment should be started under medical supervision with 2 mg once a day. After two weeks, it may be increased to 4 mg once a day which is the maximum recommended dose for heart failure.

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

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

**Use in children:**
Perindopril Tablets are not suitable for use in children.

If you take more Perindopril than you should:
If you take too many tablets, contact your nearest hospital accident and emergency department or call your doctor immediately. The most likely effect of an overdose is low blood pressure, which can make you feel faint or dizzy. If this happens, lay down on your back with your legs raised to help.

If you forget to take Perindopril:
It is important to take your medicine as your doctor has told you. However, if you forget to take one or more doses, take the next dose at the usual time and then carry on as normal. Do not take a double dose to make up for a dose which you forgot.

If you stop taking Perindopril:
The taking of perindopril is usually lifelong, you should discuss stopping taking your tablets with your doctor before you stop taking your medications.

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

**POSSIBLE SIDE EFFECTS:**
Like all medicines, perindopril can cause side effects, although not everybody gets them.
Do not be alarmed by the list below, you may not get any of them.

Stop taking your tablets and tell your doctor immediately if you experience any of the following effects of angioedema:
- Swelling of the face, lips, mouth, tongue or throat
- Difficulty in swallowing, breathing or fainting
- Swollen feet or irregular heart beat

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

Other side effects that may occur:
- Common (affects 1 to 10 users in 100):
  - Cough
  - Headache
  - Light-headedness
  - Low blood pressure (particularly after the first few doses, if the dose is increased or when water tablets are taken)
  - Headache, dizziness, vertigo, tiredness, pain and needles, muscle cramps, visual disturbances (e.g. blurred vision, eye pain), sensation of covers in the ear (tinnitus)
  - Bruising, swelling, abdominal pain, changes in your sense of taste, feeling of unbalance, dizziness, constipation
- Rare (affects 1 to 10 users in 2,000):
  - Changes in mood or sleep
  - Tightening of the chest, wheezing and shortness of breath (bronchospasm)
- Very rare (affects less than 1 user in 10,000):
  - Convulsion
  - Intense, aching pain, muscle, heart attack and stroke (these have been reported with ACE inhibitors in association with low blood pressure)
  - Rare type of pneumonia called eosinophilic pneumonia
  - Blurred vision or blurry nose (rhinitis)
  - Inflammation of the pancreas (pancreatitis)
  - Inflammation of the liver (hepatitis)
  - Skin reaction like an allergy called systemic urticaria
  - Kidney failure
  - Changes in the blood: your doctor may decide to carry out blood tests at intervals to monitor for this.
  - In cases of diabetic patients, hypoglycaemia (very low blood sugar levels) can occur.
  - Varicella (inflammation of blood vessels) has been reported.

If any of these side effects get worse, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**HOW TO STORE PERINDOPRIL:**
Keep out of reach of children.
Do not use Perindopril after the expiry date which is stated on the carton after “Exp.” The expiry date refers to the last day of that month.
Store in original package in order to protect from moisture.
Store below 30°C.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

**FURTHER INFORMATION:**
What Perindopril Tablets contain:
- The active substance is Perindopril erbumine monohydrate.
- Each tablet contains 2, 4 or 8 mg Perindopril Erbumine.
- The other ingredients are:
- Tablet core: mannitol (E421), sodium starch glycolate (Type A), sodium carbonate anhydrous, hypromellose (HPC E15), magnesium stearate, talc, leucine (B90), swallowable gum.
- Tablet coating: hypromellose 6pc, polyethylene glycol, titanium dioxide (E171), talc, leucine (290), swallowable gum.

What Perindopril Tablets look like and contents of the pack:
Perindopril 2 mg tablets are white to off-white, circular, bevelled film coated tablets, plain on both sides.
Perindopril 4 mg tablets are white to off-white, rounded shaped, bevelled-film coated tablets, embossed with “PE4” on one side and a central concavity on the other. The concavity is only to enable a tablet to be broken in half for ease of swallowing, and not to divide into equal doses.
Perindopril 8 mg tablets are white to off-white, bevelled shaped, bevelled-film coated tablets, embossed with “PE8” on one side and a central concavity on the other. The concavity is only to enable a tablet to be broken in half for ease of swallowing, and not to divide into equal doses.

The tablets are supplied in blister packs (Aluminium laminated foil) of 7, 10, 14, 15, 20, 28, 30, 50, 60, 60, 90, 90, 112, 120, 500 tablets per pack.
Not all pack sizes may be marketed.

**Marketing Authorisation Holder:**
APSLA Limited,
Boyne House,
40 North Strand Road,
Dublin 3, Ireland.

**Manufacturer:**
APC Pharmaceuticals & Chemicals (Europe) Limited, 9a Floor, CF House, 97-107 Upper Broad Road, Enfield, London W3 5TL.

**Distributor By:**
APC Pharmaceuticals & Chemicals (Europe) Limited, 9a Floor, CF House, 97-107 Upper Broad Road, Enfield, London W3 5TL.

This leaflet was last revised in April 2011.

50