PERINDOPRIL 2 MG TABLETS PL 15922/0070, 74, 81, 84

PERINDOPRIL 4 MG TABLETS PL 15922/0071, 75, 82, 85

PERINDOPRIL 8 MG TABLETS PL 15922/0073, 76, 83, 86

UKPAR

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Labelling Page 69
The MHRA granted Apotex Europe Ltd Marketing Authorisations (licenses) for the medicinal products Perindopril 2mg Tablets (PL 15922/0070, 74, 81, 84), Perindopril 4mg Tablets (PL 15922/0071, 75, 82, 85) and Perindopril 8mg Tablets (PL 15922/0073, 76, 83, 86) on the 24th of July 2006. This prescription only medicine (POM) is used to treat:

**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

Perindopril Tablets contain the active ingredient perindopril tert-butylamine, which is an Angiotensin Converting Enzyme (ACE) Inhibitor, which helps to relax artery walls.

The data presented to the MHRA, pre licensing, demonstrated that Perindopril Tablets are equivalent to the approved products, Coversyl 2mg, 4mg and 8mg tablets. Perindopril Tablets can therefore be used interchangeably with Coversyl tablets.

No new or unexpected safety concerns arose from these applications. It was, therefore, judged that the benefits of taking Perindopril Tablets outweigh the risks. Hence, Marketing Authorisations have been granted.
PERINDOPRIL 2 MG TABLETS PL 15922/0070, 74, 81, 84

PERINDOPRIL 4 MG TABLETS PL 15922/0071, 75, 82, 85

PERINDOPRIL 8 MG TABLETS PL 15922/0073, 76, 83, 86

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Perindopril 2mg Tablets (PL 15922/0070, 74, 81, 84), Perindopril 4mg Tablets (PL 15922/0071, 75, 82, 85) and Perindopril 8mg Tablets (PL 15922/0073, 76, 83, 86) to Apotex Europe Ltd on the 24th of July 2006. The products are prescription only medicines.

These are national, abridged applications, made under Directive 2001/83/EC, Article 10.1 as amended, and have been shown to be generic medicinal products of the original Coversyl tablets.

The products contain the active ingredient perindopril tert-butylamine and are indicated for the treatment of hypertension; treatment of symptomatic heart failure; the treatment of stable coronary artery disease; and the reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation.

Perindopril is an angiotensin-converting enzyme (ACE) inhibitor, used in the treatment of hypertension and heart failure. Perindopril is a prodrug which, following oral absorption, is hydrolysed to its active metabolite, perindoprilat. The beneficial haemodynamic effects resulting from ACE inhibition are a consequence of the reduction in angiotensin II causing dilatation of peripheral vessels and reduction in vascular resistance.
PHARMACEUTICAL ASSESSMENT

I. INTRODUCTION

These are national abridged applications, submitted under article 10.1 of Directive 2001/83/EC. The applicant claims essential similarity to the originator products, Coversyl™ Tablets, first marketed by Servier Laboratories Ltd in France (22/06/1988). The application cross-refers to the UK product Coversyl™ Tablets (PL 05815/0001-02 & 23 held by Servier Laboratories Ltd.) which have been granted market authorisation since 15/12/1989. The legal basis for the 8 mg strength tablet is 10.3 as amended, on the basis that it is a different strength to the so-called original product (Coversyl 2 & 4 mg). The 8 mg Coversyl tablets were added as a line extension in 2002.

Coversyl™ 8 mg Tablets manufactured for the UK market were used in the bioequivalence study.

Three sets of duplicate applications (PL 15922/0074-76 and 0081-86) are included with this application. These are identical to the primary applications.

Perindopril is an angiotensin-converting enzyme (ACE) inhibitor, used in the treatment of hypertension and heart failure. Perindopril is a prodrug which, following oral absorption, is hydrolysed to its active metabolite, perindoprilat.

II. DRUG SUBSTANCE

Information on the suitability of the drug substance has been provided by way of a drug master file (DMF). A suitable letter of access to the confidential data therein has been provided. The drug substance appears well controlled by the drug substance manufacturer (DSM).

This active ingredient is included in the European Pharmacopoeia. All points relating to the DMF have been resolved. The quality of the drug substance is well controlled and suitable for use in this product.

III.1 General information

INN name: Perindopril Erbumine
European Pharmacopoeia: Perindopril tert-butylamine

Molecular formula: C_{23}H_{43}N_{3}O_{5}
Relative molecular mass: 441.6

General Properties
White or almost white, crystalline powder, slightly hygroscopic. Solubility: freely soluble in water and in alcohol, sparingly soluble in methylene chloride.
The drug substance specification is in line with the Ph. Eur. monograph for perindopril. Other tests in line with the general monograph on substances for pharmaceutical use are performed by the DSM.

Methods used to control the drug substance by the finished product manufacturer have been described and evidence of their suitability for control of perindopril from the source has been provided.

Batch analytical data comply with the proposed specifications and stability data support the proposed 1 year re-test period.

III. DRUG PRODUCT

III.1 Description and Composition of the Drug Product

Table 1: Composition of Perindopril Tablets

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Reference to standard</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active ingredient:</strong></td>
<td></td>
</tr>
<tr>
<td>Perindopril</td>
<td>Ph. Eur</td>
</tr>
<tr>
<td>Tert-Butylamine</td>
<td>Ph. Eur</td>
</tr>
<tr>
<td><strong>Excipients:</strong></td>
<td></td>
</tr>
<tr>
<td>Lactose Anhydrous</td>
<td>Ph. Eur.</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>Ph. Eur.</td>
</tr>
</tbody>
</table>

The products are in a tablet form. The 2 mg tablet is a white, round, biconvex tablet engraved ‘APO’ on one side and ‘PE2’ on the other side. The 4 mg tablet is a white, capsule shaped, biconvex tablet engraved ‘APO’ on one side and ‘PE’ bisect ‘4’ on the other side. The 8 mg tablet is a white, capsule shaped, biconvex tablet engraved ‘APO’ on one side and ‘PE’ bisect ‘8’ on the other side.

The tablets are packed into blister pack sizes of 4, 7, 14, 15, 28, 30, 50, 56, 60, 90, 100, 112, 120 and 500 the blisters are made of Aluminum, PVC and PVAC.

Clinical Trial Formulae

The bioequivalence study was performed using Coversyl 8 mg tablets manufactured for the UK market and Perindopril 8 mg tablets. The composition of the test product was the same as that proposed for commercial manufacture. The 2 mg and 4 mg strength tablets are linearly proportional.

III.2 Pharmaceutical Development

The objective of the development trials was, in relation to the innovator product, to develop tablets of similar appearance, comparable dissolution profiles and be bioequivalent.
IV.2.1 Components of the Drug product

IV.2.1.1 Drug Substance

The drug substance appears well controlled by the DSM.

IV.2.1.2 Excipients

Only two excipients, anhydrous lactose and magnesium stearate, are employed in the formulation. These excipients are common to pharmaceutical manufacture and comply with the requirements of the Ph. Eur.

IV.2.2 Drug Product

IV.2.2.1 Formulation development

A series of experimental trials were performed using various excipients. In vitro dissolution and physical parameters were used to evaluate the suitability of trial formulations. The results of physical parameter testing (hardness, friability, disintegration) are provided for several batches and are satisfactory. The results of dissolution and disintegration testing support the excipients used.

Comparative dissolution

Satisfactory comparative dissolution profiles are provided. The applicant has also conducted comparative dissolution studies of Apotex Perindopril Tablets and reference product from various European markets.

The dissolution profile of the 2 mg and 4 mg strength products are similar to that of the 8 mg batch used in the bioequivalence study.

Dissolution limits are satisfactory.

Comparative Impurities

Aptex has also conducted a comparative degradation compounds survey on Apotex Perindopril 2 mg, 4 mg and 8 mg Tablets and various reference products. This test indicates that there are no signs of high levels of unknown degradation products in the test products on release.

Breakability testing has also been performed on the 4 mg and 8 mg strength tablets the results comply with the Ph.Eur. specifications for uniformity of mass.

Bioequivalence

The bioequivalence study was performed using Coversyl 8 mg tablets manufactured for the UK market and Perindopril 8 mg tablets. The composition of the test product was the same as that proposed for commercial manufacture. The 2 mg and 4 mg strength tablets are linearly proportional.

IV.2.2.2 Overages

Not applicable.

IV.2.2.3 Physicochemical and biological properties

Reference to the general properties section of the drug substance has been made.
Additional data on the development of the in vitro dissolution method have been provided and support the use of the proposed conditions.

IV.2.3 Manufacturing Process Development
The applicant investigated different manufacturing methods and justified the method adopted. Details of the manufacturing process used in the development of nine pilot scale batches are provided.

IV.2.4 Container Closure System
The container closure system is Al/Al cold formable blisters.

IV.2.5 Microbiological Attributes
The applicant indicates that the risk of microbial contamination is minimised via routine GMP and that because the product is a solid oral dosage form non-routine testing will be performed. This is acceptable.

IV.2.6 Compatibility
Not applicable.

III.3 Manufacture

III.3.1 Manufacturer(s)
Manufacture and QC of the finished product are performed at Apotex Inc.

III.3.2 Batch Formula
The batch formula is presented. The batch size varies dependent on the tablet strength. Pilot scale batches were manufactured. The maximum batch size is allowable and scale-up calculations are accurate.

IV.3.3 Description of Manufacturing Process and Process Controls
The manufacturing process has been adequately described including equipment, operational controls and a flow diagram.

IV.3.4 Control of Critical Steps and Intermediates
Satisfactory in-process controls are described and performed.

IV.3.5 Process Validation and/or Evaluation
The results of the process validation conform to the pre-defined acceptance criteria and demonstrate the suitability of the process.

The process validation protocols for the commercial scale-up batches are acceptable.

**IV.4 Control of Excipients**

**IV.4.1 Specifications**

Comply with the requirements of the Ph. Eur. Test specifications. Certificates of analysis have been provided by the finished product manufacturer and are in line with the monograph.

**IV.4.2 Analytical Procedures**

The compendial methods are employed for the tests described in the Ph. Eur. monograph.

**IV.4.3 Validation of Analytical Procedure**

Not applicable.

**IV.4.4 Justification of Specification**

Not applicable.

**IV.4.2 Excipients of Human or Animal Origin**

Both magnesium stearate and anhydrous lactose are excipients of animal origin. The supplier of magnesium stearate has provided a certificate of suitability in relation to the TSE requirements. The supplier of lactose provides a declaration referring to their compliance with the CHMP guideline EMEA/410/01 Rev. 2.

**IV.5 Control of Drug Product**

**IV.5.1 Specification(s)**

Finished Product Specifications have been provided and are acceptable.

**IV.5.2 Analytical Procedures**

The methods have been described in adequate detail.

**IV.5.3 Validation of Analytical Procedures**

Supporting validation data confirm the suitability of the analytical methods proposed.

**IV.5.4 Batch Analyses**

Method references indicate that batches were tested using the validated methods described. All batches comply with the proposed specification.

**IV.5.5 Characterisation of Impurities**
Characterisation and proposed control limits of degradants in the finished product are acceptable. All the named impurities are also controlled by the drug substance specification.

**IV.5.6 Justification of Specification(s)**

The controls included in the specification are appropriate for a product of this nature. The applicant has stated that all batches will be tested in full against the specification.

Control limits are acceptable and are in line with pharmacopoeial and regulatory requirements.

**IV.6 Reference Standards or Materials**

Reference standards used in validation of the analytical methods have been described.

**IV.7 Container Closure System**

Perindopril tablets are blister packed employing an aluminium/PVC cold formable foil and a aluminium PVC/PVAC blister foil. Specifications and a certificate of analysis have been provided. The materials supplier has provided a statement of compliance to EEC directives as confirmation that the packaging is suitable for contact with foodstuffs.

**IV.8 Stability**

**IV.8.1 Stability Summary and Conclusion**

Forced degradation studies indicated that the tablets are susceptible to heat, high humidity and light.

Stability testing is performed according to the relevant ICH guidelines.

The stability data support a shelf-life of 2 years with the storage conditions ‘Store below 25°C. Store in the original package.’

**III.8.2 Post-approval Stability Protocol and Stability Commitments**

A commercial stability protocol has been provided.

**V. APPENDICES**

Not applicable.

**VI. REGIONAL INFORMATION**

Not applicable.

**VII. ASSESSOR’S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET**

The SPC, Labels and Leaflet are acceptable.

**VII.1 Other information**

Not provided.
VII.1.2 Bioanalytical methods

Perindopril and perindoprilat were determined in human plasma using a validated method. The suitability of the method in response to the potential back conversion of glucuronide metabolites has also been established.

V.1.3 Bioavailability, bioequivalence

A bioequivalence study was performed to compare the pharmacokinetic behaviour of Apotex Perindopril 8 mg Tablets with the reference product Coversyl® 8 mg Tablets licensed in the UK (Servier Laboratories Ltd).

The pharmacokinetic parameters for perindopril and perindoprilat were calculated. These included the maximum plasma concentration (C_{max}), time to C_{max} (T_{max}) and AUC. Plasma concentrations were determined using a validated LC-MS/MS analytical method. A summary of the pharmacokinetic results are presented below.

Table 1A: Summary pharmacokinetic data for perindopril: mean* (%CV)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Apotex Perindopril 8 mg</th>
<th>Coversyl 8 mg</th>
<th>Relative mean** (%)</th>
<th>90% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (ng/ml)</td>
<td>75.5 (25)</td>
<td>73.0 (26)</td>
<td>103.8</td>
<td>97.4 – 110.6</td>
</tr>
<tr>
<td>AUC_{0-4} (ng hr/ml)</td>
<td>89.3 (24)</td>
<td>87.2 (22)</td>
<td>102.1</td>
<td>98.2 – 106.2</td>
</tr>
<tr>
<td>AUC_{0-inf} (ng hr/ml)</td>
<td>91.1 (24)</td>
<td>87.9 (22)</td>
<td>104.4</td>
<td>101.8 – 107.0</td>
</tr>
<tr>
<td>t_{max} (hr)</td>
<td>0.66 (26)</td>
<td>0.66 (21)</td>
<td>113.2</td>
<td>-</td>
</tr>
<tr>
<td>K_{d1} (hr^{-1})</td>
<td>0.88 (20)</td>
<td>0.82 (22)</td>
<td>104.1</td>
<td>-</td>
</tr>
<tr>
<td>t_{d1} (hr)</td>
<td>0.84 (20)</td>
<td>0.89 (22)</td>
<td>95.0</td>
<td>-</td>
</tr>
</tbody>
</table>

* for raw data. For t_{max} these are medians
** based on least squares means (geometric means for C_{max}, AUC_{0-4} and AUC_{0-inf}, arithmetic means for K_{d1} and t_{d1}) t_{max} was calculated by a non-parametric method.

Table 1B: Summary pharmacokinetic data for perindoprilat: mean* (%CV)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Apotex Perindopril 8 mg</th>
<th>Coversyl 8 mg</th>
<th>Relative mean** (%)</th>
<th>90% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (ng/ml)</td>
<td>12.02 (48)</td>
<td>10.54 (46)</td>
<td>113.4</td>
<td>108.2 – 118.9</td>
</tr>
<tr>
<td>AUC_{0-4} (ng hr/ml)</td>
<td>190.1 (31)</td>
<td>184.1 (31)</td>
<td>103.7</td>
<td>100.7 – 106.9</td>
</tr>
<tr>
<td>AUC_{0-inf} (ng hr/ml)</td>
<td>230.0 (31)</td>
<td>225.7 (31)</td>
<td>102.4</td>
<td>99.4 – 105.4</td>
</tr>
<tr>
<td>t_{max} (hr)</td>
<td>4.02 (32)</td>
<td>5.00 (36)</td>
<td>99.4</td>
<td>-</td>
</tr>
<tr>
<td>K_{d1} (hr^{-1})</td>
<td>0.019 (58)</td>
<td>0.018 (69)</td>
<td>106.5</td>
<td>-</td>
</tr>
<tr>
<td>t_{d1} (hr)</td>
<td>48.4 (44)</td>
<td>51.0 (40)</td>
<td>91.1</td>
<td>-</td>
</tr>
</tbody>
</table>

* for raw data. For t_{max} these are medians
** based on least squares means (geometric means for C_{max}, AUC_{0-4} and AUC_{0-inf}, arithmetic means for K_{d1} and t_{d1}) t_{max} was calculated by a non-parametric method.
Bioequivalence for both perindopril and perindoprilat appears to have been demonstrated because the 90% confidence intervals were contained within the 0.80 to 1.25 range for Ln AUC(0-t), Ln AUC(0-∞) and Ln Cmax. For further details, see clinical assessment.

The bioequivalence study using the 8 mg strength products, together with the comparative in vitro dissolution studies provided should be sufficient to confirm the bioequivalence of both the 2 mg and 4 mg strength tablets.

VII.2.1 Administrative

VII.2.2 Comment on Expert report
The expert is suitably qualified and whilst they have provided a non-critical review it is a useful summary of the dossier.

VII.2.3 MAA form
The legal basis for the 2 mg and 4 mg applications is accepted. However, the legal basis for the 8 mg strength tablet is 10.1 (a) (iii) last paragraph on the basis that it is a different strength to the so-called original product. This is because the 8 mg Coversyl tablets were added as a line extension in 2002. The MAA form is satisfactory.

VII.2.4 GMP
The site of finished product manufacture is Apotex Inc. Establishment licences have been provided for this site and an additional site responsible for packaging and QC. These licences are acceptable.

Batch release sites based in the EEA have been stated. Manufacturing licences have been provided.

Details of the bulk product packaging material, stability and holding time have also been provided.

VII.2.5 Guideline Compliance
The dossier is in accordance with current guidelines.

VIII ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

Marketing Authorisations may be granted.

Pharmaceutical Assessor
18/07/06
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

1. INTRODUCTION

This is a generic application for perindopril, an angiotensin converting enzyme inhibitor. Essential similarity is claimed with Coversyl 2mg and 4mg tablets (Les Laboratoires Servier), authorised in France on 22 June 1988. It is marketed in UK as Coversyl tablets (PL – 05815/0001 - 03 Servier Laboratories Ltd).

2. BACKGROUND

ATC Code: CO9A A04, ACE inhibitors, plain
The innovator product Coversyl tablets is marketed throughout Europe by Servier Laboratories. There is no evidence of a direct relationship between plasma concentrations of perindopril/perindoprilat and haemodynamic response, at therapeutic doses. The dose response to perindopril does appear to be linear over the range of 2-8mg daily in hypertensive patients.

3. INDICATIONS

“Hypertension
Treatment of hypertension.

Heart failure
Treatment of symptomatic heart failure”

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

4. DOSE & DOSE SCHEDULE

“It is recommended that Perindopril Tablets are taken once daily in the morning before a meal.

The dose should be individualised according to the patient profile (see section 4.4 Special warnings and precautions for use) and blood pressure response.

Hypertension
Perindopril tablets 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 rennin-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 the 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 Tablets; 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 Tablets (see Section 4.4 Special warnings and precautions for use).

In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Perindopril Tablets should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Perindopril Tablets should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.

In elderly patients treatment should be initiated at a dose of 2 mg which may be progressively increased to 4 mg after one month then to 8 mg if necessary depending on renal function (see table below).

Symptomatic heart failure
It is recommended that Perindopril Tablets, generally associated with a non-potassium-sparing diuretic and/or digoxin and/or a beta blocker, be introduced under close medical supervision with a recommended starting dose of 2 mg taken in the morning. This dose may be increased by increments of 2 mg at intervals of no less than 2 weeks to 4 mg once daily if tolerated. The dose adjustment should be based on the clinical response of the individual patient.

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

Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy with Perindopril Tablets. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with Perindopril Tablets (see Section 4.4 Special warnings and precautions for use).
Dosage 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>$\text{Cl}_{\text{CR}} \geq 60$</td>
<td>4 mg per day</td>
</tr>
<tr>
<td>$30 &lt; \text{Cl}_{\text{CR}} &lt; 60$</td>
<td>2 mg per day</td>
</tr>
<tr>
<td>$15 &lt; \text{Cl}_{\text{CR}} &lt; 30$</td>
<td>2 mg per every other day</td>
</tr>
<tr>
<td>Haemodialysed patients*, $\frac{\text{Cl}<em>{\text{CR}}}{\text{Cl}</em>{\text{R}}}$</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 Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties).

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

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

5. TOXICOLOGY

Perindopril has been in clinical use for many years. The applicant has provided a nonclinical overview.

6. CLINICAL PHARMACOLOGY

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

Bioequivalence study
A single dose bioequivalence study was conducted comparing 8mg tablet (Apotheses) with the brand leader Coversyl 8 mg tablet. The study was randomised, comparative and two-way crossover design. A total of 28 healthy male subjects (18 – 55 years of age) were recruited in this study which was conducted by the Biomedical Division of Apotex Inc, Toronto, Canada. The study was conducted according to GCP guidelines and according to the Health Canada Food and Drug Regulations.
The subjects received a single 8mg tablets of either the test or the reference product, on two separate occasions, following an overnight fast. The sampling period was 120 hours. There was a washout period of 3 weeks between each treatment.

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

Twenty six subjects competed both periods of the study. One subject was withdrawn prior to period 2 due to elevated GGT levels and another subject allegedly did not return for period 2. The results were as follows:

### Summary pharmacokinetic data for perindopril: mean* (%CV)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Apotex Perindopril 8 mg</th>
<th>Coversyl 8 mg</th>
<th>Relative mean** (%)</th>
<th>90% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>75.5 (25)</td>
<td>73.0 (26)</td>
<td>103.8</td>
<td>97.4 – 110.6</td>
</tr>
<tr>
<td>AUC0-t (ng.hr/ml)</td>
<td>89.3 (24)</td>
<td>87.2 (22)</td>
<td>102.1</td>
<td>98.2 – 106.2</td>
</tr>
<tr>
<td>AUC0-∞ (ng.hr/ml)</td>
<td>91.1 (24)</td>
<td>87.9 (22)</td>
<td>104.4</td>
<td>101.8 – 107.0</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>0.66 (26)</td>
<td>0.66 (21)</td>
<td>113.2</td>
<td></td>
</tr>
</tbody>
</table>

* for raw data. For Tmax these are medians

** based on least square means (geometric means for Cmax, AUC0-t and AUC0-∞; tmax was calculated by a non-parametric method.

### Summary pharmacokinetic data for perindoprilat: mean* (%CV)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Apotex Perindopril 8 mg</th>
<th>Coversyl 8 mg</th>
<th>Relative mean** (%)</th>
<th>90% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>12.02 (48)</td>
<td>10.54 (46)</td>
<td>113.4</td>
<td>108.2 – 118.9</td>
</tr>
<tr>
<td>AUC0-t (ng.hr/ml)</td>
<td>190.1 (31)</td>
<td>184.1 (31)</td>
<td>103.7</td>
<td>100.7 – 106.9</td>
</tr>
<tr>
<td>AUC0-∞ (ng.hr/ml)</td>
<td>230.0 (31)</td>
<td>225.7 (31)</td>
<td>102.4</td>
<td>99.4 – 105.4</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>4.02 (32)</td>
<td>5.00 (36)</td>
<td>99.4</td>
<td></td>
</tr>
</tbody>
</table>

* for raw data. For Tmax these are medians

** based on least square means (geometric means for Cmax, AUC0-t and AUC0-∞; tmax was calculated by a non-parametric method.

**Assessor’s comments on bioequivalence**

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

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

8. **SAFETY**

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

9. **EXPERT REPORT**

The expert report has adequately addressed the issue of efficacy and safety and has discussed the bioequivalence study.

10. **SUMMARY OF PRODUCT CHARACTERISTICS**

The SPC is similar to the SPC of the reference product (Coversyl Tablets).

11. **PATIENT INFORMATION LEAFLET**

The patient information leaflet is satisfactory.

12. **LABELLING**

Medically satisfactory

13. **DISCUSSION**

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

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

The SPC and PIL are satisfactory.

14. **CONCLUSIONS**

There is no clinical objection to the grant of marketing authorisations for these products.

**Clinical Assessor**

**January 2006**

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Perindopril Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data have been supplied with these applications and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant’s Perindopril Tablets and the originator products Coversyl Tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that of the reference product.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s products and the innovator products are interchangeable. Clinical experience with perindopril is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.
PERINDOPRIL 2 MG TABLETS PL 15922/0070, 74, 81, 84

PERINDOPRIL 4 MG TABLETS PL 15922/0071, 75, 82, 85

PERINDOPRIL 8 MG TABLETS PL 15922/0073, 76, 83, 86

**STEPS TAKEN FOR ASSESSMENT**

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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 02/02/2005</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 30/08/2005</td>
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<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information relating to the dossier on and 12/10/2005, 08/03/2006, 27/03/2006</td>
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<td>4</td>
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PERINDOPRIL 2 MG TABLETS PL 15922/0070, 74, 81, 84
PERINDOPRIL 4 MG TABLETS PL 15922/0071, 75, 82, 85
PERINDOPRIL 8 MG TABLETS PL 15922/0073, 76, 83, 86

**STEPS TAKEN AFTER ASSESSMENT**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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PERINDOPRIL 2 MG TABLETS PL 15922/0070, 74, 81, 84

PERINDOPRIL 4 MG TABLETS PL 15922/0071, 75, 82, 85

PERINDOPRIL 8 MG TABLETS PL 15922/0073, 76, 83, 86

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Perindopril 2 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Tablet
White, round, biconvex tablets, engraved "APO" on one side and "PE2" on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension
Treatment of hypertension
Heart Failure
Treatment of symptomatic heart failure
Stable coronary artery disease
Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation

4.2 Posology and method of administration

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

**Hypertension**

Perindopril may be used in monotherapy or in combination with other classes of antihypertensive therapy.

The recommended starting dose is 4 mg given once daily in the morning.

Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and/or volume depletion, cardiac decompensation or severe hypertension) may experience an excessive drop in blood pressure following the initial dose. A starting dose of 2 mg is recommended in such patients and the initiation of treatment should take place under medical supervision.

The dose may be increased to 8 mg once daily after one month of treatment.

Symptomatic hypotension may occur following initiation of therapy with perindopril; this is more likely in patients who are being treated concurrently with diuretics. Caution is therefore recommended since these patients may be volume and/or salt depleted.

If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with Perindopril (see section 4.4 "Special warnings and special precautions for use").

In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Perindopril should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Perindopril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.

In elderly patients treatment should be initiated at a dose of 2 mg which may be progressively increased to 4 mg after one month then to 8 mg if necessary depending on renal function (see table below).

**Symptomatic heart failure**

It is recommended that Perindopril generally associated with a non-potassium-sparing diuretic and/or digoxin and/or a beta-blocker, be introduced under close medical supervision with a recommended starting dose of 2 mg taken in the morning. This dose may be increased by increments of 2 mg at intervals of no less than 2 weeks to 4 mg once daily if tolerated. The dose adjustment should be based on the clinical response of the individual patient.

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

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

**Stable coronary artery disease:**

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

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

**Dosage adjustment in renal impairment**

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

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

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

**Dosage adjustment in hepatic impairment**

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

**Paediatric use**

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

**4.3 Contraindications**

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

4.4 Special warnings and precautions for use

Stable coronary artery disease

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

Hypotension

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

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

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

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

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

Renal impairment
In cases of renal impairment (creatinine clearance < 60 ml/min) the initial perindopril dosage should be adjusted according to the patient's creatinine clearance (see 4.2 "Posology and method of administration") and then as a function of the patient's response to treatment.

Routine monitoring of potassium and creatinine are part of normal medical practice for these patients (see 4.8 "Undesirable effects").

In patients with symptomatic heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of Perindopril therapy.

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

**Haemodialysis Patients**

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

**Kidney transplantation**

There is no experience regarding the administration of Perindopril in patients with a recent kidney transplantation.

**Hypersensitivity/ Angioedema**

Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including Perindopril (see 4.8 Undesirable effects). This may occur at any time during therapy. In such cases, Perindopril should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally
resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

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

Anaphylactoid reactions during low-density Lipoproteins LDL apheresis

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

Anaphylactic reactions during desensitisation

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

Hepatic failure

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

Neutropenia/Agranulocytosis/Thrombocytopenia/Aenaemia

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

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

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

Surgery / Anaesthesia
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Perindopril may block angiotensin II formation secondary to compensatory rennin release. The treatment should be discontinued one day prior to the surgery. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, uncontrolled diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended.

Diabetic Patients
In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor. (See 4.5 Interaction with other medicinal products and other forms of interaction, Antidiabetics.)

Lithium
The combination of lithium and perindopril is generally not recommended (see 4.5 Interaction with other medicinal products and other forms of interaction).

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes
The combination of perindopril and potassium sparing diuretics, potassium supplements or potassium- containing salt substitutes is generally not recommended (see 4.5 Interaction with other medicinal products and other forms of interaction).

Pregnancy and lactation

(See section 4.3 "Contraindications" and section 4.6 "Pregnancy and lactation").
The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Diuretics

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

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

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

Lithium

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

Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin = 3 g/day

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

**Antihypertensive agents and vasodilators**

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

**Antidiabetic agents**

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

**Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates**

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

**Tricyclic antidepressants/ Antipsychotics/ Anesthetics**

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

**Sympathomimetics**

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

### 4.6 Pregnancy and lactation

**Pregnancy**

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

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

Prolonged ACE inhibitor exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See 5.3 "Preclinical safety data")
Should exposure to perindopril have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Lactation

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1000, <1/100); rare (>1/10000, <1/1000); very rare (<1/10000), including isolated reports.

Psychiatric disorders:
Uncommon: mood or sleep disturbances

Nervous system disorders:
Common: headache, dizziness, vertigo, paresthesia
Very rare: confusion

Eye disorders:
Common: vision disturbance

Ear and labyrinth disorders:
Common: tinnitus

Cardio-vascular disorders:
Common: hypotension and effects related to hypotension
Very rare: arrhythmia, angina pectoris, myocardial infarction and stroke, possibly secondary to excessive hypotension in high-risk patients (see 4.4 Special warnings and special precautions for use).

Respiratory, thoracic and mediastinal disorders:
Common: cough, dyspnoea
Uncommon: bronchospasm
Very rare: eosinophilic pneumonia, rhinitis

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

Hepato-biliary disorders:
Very rare: hepatitis either cytolytic or cholestatic (see section 4.4 Special warnings and special precautions for use)

Skin and subcutaneous tissue disorders:
Common: rash, pruritus
Uncommon: angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see 4.4 Special warnings and special precautions for use).
Very rare: erythema multiforme

Musculoskeletal, connective tissue and bone disorders:
Common: muscle cramps

Renal and urinary disorders:
Uncommon: renal insufficiency
Very rare: acute renal failure

Reproductive system and breast disorders:
Uncommon: impotence

General disorders:
Common: asthenia
Uncommon: sweating

Blood and the lymphatic system disorders:
Decreases in haemoglobin and hematocrit, thrombocytopenia, leucopenia/neutropenia, and cases of agranulocytosis or pancytopenia, have been reported very rarely. In patients with a congenital deficiency of G-6PDH, very rare cases of haemolytic anaemia have been reported (see section 4.4 Special warnings and special precautions for use).

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

Clinical trial
During the randomised period of the EUROPA study, only serious adverse events were controlled. Few patients experienced serious adverse events: 16 (23%) of the 6122 perindopril patients and 10 (0.2%) of the 6017 placebo patients. In perindopril- treated patients, hypotension was observed in 6 patients, angioedema in 3 patients and sudden cardiac arrest in 1 patient. More patients withdrew for cough, hypotension or other intolerance on perindopril than on placebo, 6.0% (n=366) versus 2.1% (n=129) respectively.
4.9 Overdose
Limited data are available for overdosage in humans. Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered.

Perindopril may be removed from the general circulation by haemodialysis. (See 4.4 Special warnings and special precautions for use, Haemodialysis Patients.) Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: CO9A AO4

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

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

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

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

Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged.
The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 87-100 % of peak effects.

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

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

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

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

Heart failure
Perindopril reduces cardiac work by a decrease in pre- load and after- load. Studies in patients with heart failure have demonstrated:

- Decreased left and right ventricular filling pressures, - reduced total peripheral vascular resistance,
- Increased cardiac output and improved cardiac index.
In comparative studies, the first administration of 2 mg of Perindopril to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo.

Patients with stable coronary artery disease
The EUROPA study, a multicenter, international, randomised, double-blind, placebocontrolled clinical trial, lasted 4 years.

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

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

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

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

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

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

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

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

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

After repeated administration, no accumulation of perindopril is observed. Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure. Dosage adjustment in renal insufficiency is desirable depending on the degree of impairment (creatinine clearance).

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

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

5.3 Preclinical safety data

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous Lactose
Magnesium Stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Store below 25°C. Store in the original package.

6.5 Nature and contents of container
Blister packs: 4, 7, 14, 15, 28, 30, 50, 56, 60, 90, 100, 112, 120, 500 tablets.
Aluminum/PVC/PVAC

6.6 Special precautions for disposal
None.

7 MARKETING AUTHORISATION HOLDER
Apothez Europe Ltd
Rowan House,
41 London Street
Reading,
Berkshire, RG1 4PS
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 15922/0070

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

10 DATE OF REVISION OF THE TEXT
MHRA PAR – Perindopril Tablets
PL 15922/0070-1, 73-6, 81-86
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Perindopril 4 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains perindopril tert-butylamine 4 mg (equivalent to 3.338 mg perindopril).
For excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Tablet
White, capsule shaped, biconvex tablets, engraved "APO" on one side and "PE" bisect "4" on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension
Treatment of hypertension
Heart Failure
Treatment of symptomatic heart failure
Stable coronary artery disease
Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation

4.2 Posology and method of administration

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

Hypertension
Perindopril may be used in monotherapy or in combination with other classes of antihypertensive therapy.
The recommended starting dose is 4 mg given once daily in the morning.

Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and/or volume depletion, cardiac decompensation or
severe hypertension) may experience an excessive drop in blood pressure following the initial dose. A starting dose of 2 mg is recommended in such patients and the initiation of treatment should take place under medical supervision.

The dose may be increased to 8 mg once daily after one month of treatment.

Symptomatic hypotension may occur following initiation of therapy with perindopril; this is more likely in patients who are being treated concurrently with diuretics. Caution is therefore recommended since these patients may be volume and/or salt depleted.

If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with Perindopril (see section 4.4 "Special warnings and special precautions for use").

In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Perindopril should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Perindopril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.

In elderly patients treatment should be initiated at a dose of 2 mg which may be progressively increased to 4 mg after one month then to 8 mg if necessary depending on renal function (see table below).

**Symptomatic heart failure**

It is recommended that Perindopril generally associated with a non-potassium-sparing diuretic and/or digoxin and/or a beta-blocker, be introduced under close medical supervision with a recommended starting dose of 2 mg taken in the morning. This dose may be increased by increments of 2 mg at intervals of no less than 2 weeks to 4 mg once daily if tolerated. The dose adjustment should be based on the clinical response of the individual patient.

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

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

**Stable coronary artery disease:**

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

**Dosage adjustment in renal impairment**

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

<table>
<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>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 "Special warnings and special precautions for use" and 5.2 "Pharmacokinetic properties")

**Paediatric use**

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

### 4.3 Contraindications

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

### 4.4 Special warnings and precautions for use

**Stable coronary artery disease**

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

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

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

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

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

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

Renal impairment

In cases of renal impairment (creatinine clearance < 60 ml/min) the initial perindopril dosage should be adjusted according to the patient's creatinine clearance (see 4.2 "Posology and method of administration") and then as a function of the patient's response to treatment.

Routine monitoring of potassium and creatinine are part of normal medical practice for these patients (see 4.8 "Undesirable effects").

In patients with symptomatic heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum
creatine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of Perindopril therapy.

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

Haemodialysis Patients

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

Kidney transplantation

There is no experience regarding the administration of Perindopril in patients with a recent kidney transplantation.

Hypersensitivity/ Angioedema

Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including Perindopril (see 4.8 Undesirable effects). This may occur at any time during therapy. In such cases, Perindopril should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (See 4.3 Contraindications).
Anaphylactoid reactions during low-density Lipoproteins LDL apheresis

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

Anaphylactic reactions during desensitisation

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

Hepatic failure

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

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia

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

Race

ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

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

Cough

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

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Perindopril may block angiotensin II formation secondary to compensatory rennin release. The treatment should be discontinued one day prior to the surgery. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, uncontrolled diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended.

Diabetic Patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor. (See 4.5 Interaction with other medicinal products and other forms of interaction, Antidiabetics.)

Lithium

The combination of lithium and perindopril is generally not recommended (see 4.5 Interaction with other medicinal products and other forms of interaction).

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

The combination of perindopril and potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes is generally not recommended (see 4.5 Interaction with other medicinal products and other forms of interaction).

Pregnancy and lactation

(See section 4.3 "Contraindications" and section 4.6 "Pregnancy and lactation").

The tablets contain lactose.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take this medicine.
4.5 Interaction with other medicinal products and other forms of interaction

Diuretics

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

Potassium sparing diuretics. Potassium supplements or potassium-containing salt substitutes

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

Lithium

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

Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin = 3 g/day

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

Antihypertensive agents and vasodilators

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

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

**Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates**

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

**Tricyclic antidepressants/ Antipsychotics/ Anesthetics**

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

**Sympathomimetics**

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

### 4.6 Pregnancy and lactation

**Pregnancy**

Perindopril should not be used during the first trimester of pregnancy.

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

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

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

**Lactation**

It is not known whether perindopril is excreted into human breast milk. Therefore the use of Perindopril is not recommended in women who are breast-feeding.
4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The following undesirable effects have been observed during treatment with perindopril and ranked under the following frequency:
Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1000, <1/100); rare (>1/10000, <1/1000); very rare (<1/10000), including isolated reports.

Psychiatric disorders:
Uncommon: mood or sleep disturbances

Nervous system disorders:
Common: headache, dizziness, vertigo, paresthesia
Very rare: confusion

Eye disorders:
Common: vision disturbance

Ear and labyrinth disorders:
Common: tinnitus

Cardio-vascular disorders:
Common: hypotension and effects related to hypotension
Very rare: arrhythmia, angina pectoris, myocardial infarction and stroke, possibly secondary to excessive hypotension in high-risk patients (see 4.4 Special warnings and special precautions for use).

Respiratory, thoracic and mediastinal disorders:
Common: cough, dyspnoea
Uncommon: bronchospasm
Very rare: eosinophilic pneumonia, rhinitis

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

Hepato-biliary disorders:
Very rare: hepatitis either cytoytic or cholestatic (see section 4.4 Special warnings and special precautions for use)

Skin and subcutaneous tissue disorders:
Common: rash, pruritus
Uncommon: angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see 4.4 Special warnings and special precautions for use).
Very rare: erythema multiforme

Musculoskeletal, connective tissue and bone disorders:
Common: muscle cramps

Renal and urinary disorders:
Uncommon: renal insufficiency
Very rare: acute renal failure

Reproductive system and breast disorders:
Uncommon: impotence

General disorders:
Common: asthenia
Uncommon: sweating

Blood and the lymphatic system disorders:
Decreases in haemoglobin and haematocrit, thrombocytopenia, leucopenia/neutropenia, and cases of agranulocytosis or pancytopenia, have been reported very rarely. In patients with a congenital deficiency of G-6PDH, very rare cases of haemolytic anaemia have been reported (see section 4.4 Special warnings and special precautions for use).

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

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

4.9 Overdose

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

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If
available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered.

Perindopril may be removed from the general circulation by haemodialysis. (See 4.4 Special warnings and special precautions for use, Haemodialysis Patients.) Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: CO9A AO4

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

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

Hypertension

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

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

In man, perindopril has been confirmed to demonstrate vasodilatory properties. It improves large artery elasticity and decreases the media:lumen ratio of small arteries.
An adjunctive therapy with a thiazide diuretic produces an additive-type of synergy. The combination of an ACE inhibitor and a thiazide also decreases the risk of hypokalaemia induced by the diuretic treatment.

**Heart failure**

Perindopril reduces cardiac work by a decrease in pre-load and after-load. Studies in patients with heart failure have demonstrated:
- Decreased left and right ventricular filling pressures,
- reduced total peripheral vascular resistance,
- Increased cardiac output and improved cardiac index.

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

**Patients with stable coronary artery disease**

The EUROPA study, a multicenter, international, randomised, double-blind, placebo-controlled clinical trial, lasted 4 years.

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

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

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

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

5.2 **Pharmacokinetic properties**

After oral administration, the absorption of perindopril is rapid and the peak concentration complete within 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 perindoprilat is equal to 1 hour. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.

As ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril should be administered orally in a single daily dose in the morning before a meal.
The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Protein binding is slight (binding of perindoprilat to angiotensin converting enzyme is less than 30 %), but is concentration-dependent.

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

After repeated administration, no accumulation of perindopril is observed. Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure. Dosage adjustment in renal insufficiency is desirable depending on the degree of impairment (creatinine clearance).

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

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

5.3 Preclinical safety data

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

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous Lactose
Magnesium Stearate
6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Blister packs: 4, 7, 14, 15, 28, 30, 50, 56, 60, 90, 100, 112, 120, 500 tablets.
Aluminum/PVC/PVAC

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER(S)

PL 15922/0071

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/07/2006

10 DATE OF REVISION OF THE TEXT

24/07/2006
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Perindopril 8 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains perindopril tert-butylamine 8 mg (equivalent to 6.676 mg perindopril).

For excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Tablet
White, capsule shaped, biconvex tablets, engraved "APO" on one side and "PE" bisect "8" on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension
Treatment of hypertension

Heart Failure
Treatment of symptomatic heart failure

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

4.2 Posology and method of administration

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

Hypertension

Perindopril may be used in monotherapy or in combination with other classes of antihyper‐tensive therapy.
The recommended starting dose is 4 mg given once daily in the morning.

Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and/or volume depletion, cardiac decompensation or severe hypertension) may experience an excessive drop in blood pressure following the initial dose. A starting dose of 2 mg is recommended in such patients and the initiation of treatment should take place under medical supervision.

The dose may be increased to 8 mg once daily after one month of treatment.

Symptomatic hypotension may occur following initiation of therapy with perindopril; this is more likely in patients who are being treated concomitantly with diuretics. Caution is therefore recommended since these patients may be volume and/or salt depleted.

If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with Perindopril (see section 4.4 "Special warnings and special precautions for use").

In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Perindopril should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Perindopril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.

In elderly patients treatment should be initiated at a dose of 2 mg which may be progressively increased to 4 mg after one month then to 8 mg if necessary depending on renal function (see table below).

**Symptomatic heart failure**

It is recommended that Perindopril generally associated with a non-potassium-sparing diuretic and/or digoxin and/or a beta-blocker, be introduced under close medical supervision with a recommended starting dose of 2 mg taken in the morning. This dose may be increased by increments of 2 mg at intervals of no less than 2 weeks to 4 mg once daily if tolerated. The dose adjustment should be based on the clinical response of the individual patient.

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

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

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

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

Dosage adjustment in renal impairment

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

Table I: 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 otherday</td>
</tr>
</tbody>
</table>

Haemodialysed patients *

| ClCR < 15                   | 2 mg on the day of dialysis |

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

Dosage adjustment in hepatic impairment

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

Paediatric use

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

4.3 Contraindications

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

Stable coronary artery disease

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

Hypotension

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

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

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

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

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

Renal impairment

In cases of renal impairment (creatinine clearance < 60 ml/min) the initial perindopril dosage should be adjusted according to the patient's creatinine clearance (see 4.2 "Posology and method of administration") and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients (see 4.8 "Undesirable effects").
In patients with symptomatic heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of Perindopril therapy.

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

**Haemodialysis Patients**

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

**Kidney transplantation**

There is no experience regarding the administration of Perindopril in patients with a recent kidney transplantation.

**Hypersensitivity/ Angioedema**

Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including Perindopril (see 4.8 Undesirable effects). This may occur at any time during therapy. In such cases, Perindopril should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.
Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

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

**Anaphylactoid reactions during low-density Lipoproteins LDL apheresis**

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

**Anaphylactic reactions during desensitisation**

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

**Hepatic failure**

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

**Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia**

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

**Race**

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

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

Surgery / Anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Perindopril may block angiotensin II formation secondary to compensatory rennin release. The treatment should be discontinued one day prior to the surgery. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, uncontrolled diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended.

Diabetic Patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor. (See 4.5 Interaction with other medicinal products and other forms of interaction, Antidiabetics.)

Lithium

The combination of lithium and perindopril is generally not recommended (see 4.5 Interaction with other medicinal products and other forms of interaction).

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

The combination of perindopril and potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes is generally not recommended (see 4.5 Interaction with other medicinal products and other forms of interaction).

Pregnancy and lactation

(See section 4.3 "Contraindications" and section 4.6 "Pregnancy and lactation").
The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Diuretics

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

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

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

Lithium

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

Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin = 3 g/day

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

Antihypertensive agents and vasodilators

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

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

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates

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

Tricyclic antidepressants/ Antipsychotics/ Anesthetics

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

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

4.6 Pregnancy and lactation

Pregnancy

Perindopril should not be used during the first trimester of pregnancy.

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

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

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The following undesirable effects have been observed during treatment with perindopril and ranked under the following frequency: Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1000, <1/100); rare (>1/10000, <1/1000); very rare (<1/10000), including isolated reports.

Psychiatric disorders:
Uncommon: mood or sleep disturbances

Nervous system disorders:
Common: headache, dizziness, vertigo, paresthesia
Very rare: confusion

Eye disorders:
Common: vision disturbance

Ear and labyrinth disorders:
Common: tinnitus

Cardio-vascular disorders:
Common: hypotension and effects related to hypotension
Very rare: arrhythmia, angina pectoris, myocardial infarction and stroke, possibly secondary to excessive hypotension in high-risk patients (see 4.4 Special warnings and special precautions for use).

Respiratory, thoracic and mediastinal disorders:
Common: cough, dyspnoea
Uncommon: bronchospasm
Very rare: eosinophilic pneumonia, rhinitis

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

Hepato-biliary disorders:
Very rare: hepatitis either cytolytic or cholestatic (see section 4.4 Special warnings and special precautions for use)

Skin and subcutaneous tissue disorders:
Common: rash, pruritus
Uncommon: angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see 4.4 Special warnings and special precautions for use).
Very rare: erythema multiforme

Musculoskeletal, connective tissue and bone disorders:
Common: muscle cramps

Renal and urinary disorders:
Uncommon: renal insufficiency
Very rare: acute renal failure

Reproductive system and breast disorders:
Uncommon: impotence

General disorders:
Common: asthenia
Uncommon: sweating

Blood and the lymphatic system disorders:
Decreases in haemoglobin and haematocrit, thrombocytopenia, leucopenia/neutropenia, and cases of agranulocytosis or pancytopenia, have been reported very rarely. In patients with a congenital deficiency of G-6PDH, very rare cases of haemolytic anaemia have been reported (see section 4.4 Special warnings and special precautions for use).

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

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

4.9 Overdose

Limited data are available for overdosage in humans. Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough. The recommended treatment of overdosage is intravenous
infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis. (See 4.4 Special warnings and special precautions for use, Haemodialysis Patients.) Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: CO9A AO4

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

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

Hypertension

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

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

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

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

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

Discontinuation of treatment does not lead to a rebound effect. Perindopril reduces left ventricular hypertrophy.
In man, perindopril has been confirmed to demonstrate vasodilatory properties. It improves large artery elasticity and decreases the media:lumen ratio of small arteries.

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

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

Patients with stable coronary artery disease
The EUROPA study, a multicenter, international, randomised, double-blind, placebocontrolled clinical trial, lasted 4 years.

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

The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure. Overall, 90 % of the patients had a previous myocardial infarction and/or a previous coronary revasculariation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers. The main efficacy criterion was the composite of cardiovascular mortality, non fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with perindopril 8 mg once daily resulted in a significant absolute reduction in the primary endpoint of 1.9% (relative risk reduction of 20%, 95%CI [9.4; 28.6] – p<0.001).

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

5.2 Pharmacokinetic properties

After oral administration, the absorption of perindopril is rapid and the peak concentration complete within 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 perindopril to angiotensin converting enzyme is less than 30 %), but is concentration-dependent.

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

After repeated administration, no accumulation of perindopril is observed.

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

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

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

### 5.3 Preclinical safety data

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

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

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

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

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

Anhydrous Lactose
Magnesium Stearate

MHRA PAR – Perindopril Tablets

PL 15922/0070-1, 73-6, 81-86
6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25°C. Store in the original package

6.5 Nature and contents of container

Blister packs: 4, 7, 14, 15, 28, 30, 50, 56, 60, 90, 100, 112, 120, 500 tablets. Aluminum/PVC/PVAC

6.6 Special precautions for disposal

None

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

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Perindopril Patient Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

PERINDOPRIL 2 mg TABLETS
PERINDOPRIL 4 mg TABLETS
PERINDOPRIL 8 mg TABLETS

Perindopril tert-butylamine

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- Ask your doctor or pharmacist if you have any 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

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

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

2. Before you take Perindopril

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

Take special care with Perindopril:

Talk to your doctor before taking Perindopril if:
- you have narrowing of the blood vessels (anterior or posterior ischaemic heart disease) or heart muscle disease (hypertrophic cardiomyopathy) or narrowing of the artery supplying the kidney with blood (renal artery stenosis)
- you have any other heart or liver or kidney problems, or if you are having dialysis
- you have been told to limit the salt in your diet or to use a salt substitute containing potassium
- you have a collagen disease such as systemic lupus erythematosus or scleroderma.

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

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

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. In particular, tell your doctor before taking Perindopril if you are taking:
- medicines for high blood pressure including water tablets (diuretics)
- water tablets (diuretics) which affect potassium, such as spironolactone, triamterene or amiloride
- medicines to increase your level of potassium
- heparin (for thinning the blood) can also affect potassium levels in your blood
- medicines for diabetes (insulin or tablets)
- medicines for mental health problems such as depression, anxiety, schizophrenia or other psychoses
- advacnye for pain
- medicines to treat auto-immune disorders (such as rheumatoid arthritis) or given after transplant surgery. These are called immunosuppressants.
- ibuprofen (for inflammatory conditions such as arthritis)
- non-steroidal anti-inflammatory drugs (NSAIDs such as ibuprofen, diclofenac), including aspirin for pain
- medicines for high blood pressure, shock or asthma
- including bisoprolol, furosemide or metoprolol
- medicines that make the blood vessels wider (vasodilators, such as nitric oxide).

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

Taking Perindopril with food and drink

Drinking alcohol with Perindopril may make you feel dizzy. Check with your doctor whether you can drink alcohol while taking this medicine.

Take your Perindopril tablet in the morning before a meal.

Pregnancy and breast-feeding

You should not take Perindopril if you:
- are pregnant or breast-feeding.

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

Driving and using machines

You may feel dizzy or feel that you are losing your balance. Do not drive or use dangerous machinery.

Information on special patient groups

Perindopril tablets should not be given to children.

3. How to take Perindopril

Your doctor will decide on the amount of perindopril you should take to. This may be increased depending on your condition and other medicines you are taking. Always take Perindopril exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. Do not change the amount of medicine you take unless your doctor tells you. Perindopril may be used on its own, or with other medicines which lower blood pressure.

- Take Perindopril tablets by mouth only.
- Take them in the morning, before a meal.
- It is best to take your tablet(s) with a glass of water at the same time each day.

MHRA PAR – Perindopril Tablets

PL 15922/0070-1, 73-6, 81-86

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The usual dose is:

- High blood pressure:
  - 4 mg each day
  - after a month, this may be raised to 8 mg each day
  - 8 mg each day is the highest amount normally used.

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

If you are taking water tablets (diuretics):
- your doctor may stop you 1 to 3 days before you start taking Perindopril. This is to prevent a fall in your blood pressure.
- if needed, you can start taking water tablets again after you have started Perindopril.

- It is not possible to stop your water tablets, then you can take 2 mg of perindopril as well.
Your doctor or pharmacist will tell you exactly what you should do.

The doctor may start you with 2 mg perindopril if:
- your blood pressure is very high
- you have not enough water in your body (dehydrated)
- you have a low level of sodium in your blood
- you have a heart problem which makes it difficult for the body to pump blood (heart failure, heart attack, stroke)
- you have to take in more sodium than usual (e.g., ascites from liver failure)
- you have high blood pressure due to the kidneys being blocked (constriction of the arteries).

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

Stroke coronary artery disease:
- the usual starting dose is 4 mg once daily
- after 2 weeks, this may be raised to 8 mg each day.

- In older people with stroke coronary artery disease the highest amount is usually:
  - 2 mg each day
  - after 1 week, this may be raised to 4 mg each day
  - after a further week to 8 mg each day which is the highest amount used.

If you take more Perindopril than you should, talk to a doctor or pharmacist straight away.
The following effects may happen:
- Low blood pressure, shock, kidney problems, fast breathing, fast heartbeat, arrhythmias, pain, heart attack, feeling dizzy or faint.

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

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

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

4. Possible side effects
Like all medicines, Perindopril can cause side effects, although not everybody gets them.

- headache, feeling dizzy or tired, feeling dizzy with a spinning sensation (vertigo), pCla and needles, muscle cramps, blurred vision, eye pain, sensation of noises in the ears (tinnitus)
- feeling or being sick, stomach pain or indigestion, changes in your sense of taste, diarrhea, constipation
- skin rash, itching
- Uncommon (affecting less than 1 person in 100)
  - changes in mood or sleep
  - tight feeling in the chest, wheezing and short of breath (bronchospasm)
  - dry mouth
  - kidney problems
  - unable to get an erection
  - sweating
  - swelling
  - mucus in the nose or throat, intense itching, skin rash, itching or feeling dizzy (angioedema)

Very rare (affecting less than 1 person in 10,000)
- feeling confused
- unusual heartbeats, chest pain that happens in heart disease (angina), heart shock and stroke (these have happened with ACE inhibitors in people with high blood pressure)
- chest infection (respiratory tract infections), blocked or runny nose (rhinitis)
- inflamed pancreas (pancreatitis)
  - inflamed liver (hepatitis)
  - skin reaction like an allergy (erythma multiforme)
  - changes in the blood, your doctor may carry out blood tests to check for this.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
Braille Text in accordance with Article 56a of Directive 2001/83/EC as amended name of the medicinal product is as followed expressed in Braille format on the packaging:

Perindopril 2 mg
The Braille conversion is
PERINDOPRIL 2 MG

Perindopril 4 mg
The Braille conversion is
PERINDOPRIL 4 MG

Perindopril 8 mg
The Braille conversion is
PERINDOPRIL 8 MG
Perindopril 2mg Tablets
Perindopril tert-butylamine

For oral use
Each tablet contains 2mg of perindopril tert-butylamine equivalent to 1.669mg perindopril. Also contains lactose, see leaflet for further information. Read the package leaflet before use. Keep out of the reach and sight of children. Store in the original package. Store below 25°C.
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