

PERINDOPRIL 2MG TABLETS

PL 20092/0022

PERINDOPRIL 4MG TABLETS

PL 20092/0023

PERINDOPRIL 8MG TABLETS

PL 20092/0024

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PERINDOPRIL 2MG TABLETS

PL 20092/0022

PERINDOPRIL 4MG TABLETS

PL 20092/0023

PERINDOPRIL 8MG TABLETS

PL 20092/0024

LAY SUMMARY

The MHRA granted Lupin (Europe) Limited Marketing Authorisations (licences) for the medicinal products Perindopril 2mg Tablets (PL 20092/0022), Perindopril 4mg Tablets (PL 20092/0023) and Perindopril 8mg Tablets (PL 20092/0024). These are prescription only medicines (POM) that are used to treat a condition where the heart is unable to pump enough blood to meet the body's needs (heart failure) , a condition where the blood supply to the heart is reduced or blocked (coronary artery disease) and to reduce elevated blood pressure.

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

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Perindopril 2mg, 4mg, and 8mg Tablets outweighs the risks, hence Marketing Authorisations have been granted.

PERINDOPRIL 2MG TABLETS

PL 20092/0022

PERINDOPRIL 4MG TABLETS

PL 20092/0023

PERINDOPRIL 8MG TABLETS

PL 20092/0024

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the MHRA granted marketing authorisations for the medicinal products Perindopril 2mg, 4mg, and 8mg Tablets to Lupin (Europe) Limited on 22nd of July 2008. The products are prescription only medicines.

These applications are submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal products of the original products Coversyl 2mg, 4mg and 8mg Tablets (PL 05815/0001-3 Les Laboratoires Servier). The reference products have been authorised in the UK since December 1989 and so the 10-year period of data exclusivity has expired.

These products contain the active ingredient perindopril and are indicated for the treatment of hypertension, symptomatic heart failure and stable coronary artery disease.

Perindopril is an inhibitor of the enzyme that converts angiotensin I into angiotensin II (Angiotensin Converting Enzyme ACE). 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).

PHARMACEUTICAL ASSESSMENT

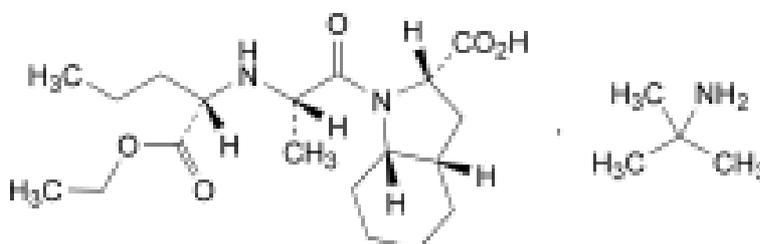
DRUG SUBSTANCE

INN: Perindopril Erbumine

Ph Eur: Perindopril *tert*-butylamine

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

Structure



Molecular formula: C₂₃H₄₃N₃O₅.

Molecular Mass: 441.6

White or almost white, crystalline powder which is freely soluble in alcohol.

This is subject to DMF. A valid letter of access has been provided.

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

Satisfactory characterisation of the drug substance has been provided in the Drug Master File from the Drug Substance Manufacturer (DSM) and by the Finished Product Manufacturer (FPM).

No materials of animal or human origin are used in the production of the active substance.

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

All potential known impurities have been identified and characterised.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Active perindopril tert-butylamine is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

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

Stability data have been provided in accordance with regulatory requirements and support the declared retest interval.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, microcrystalline cellulose, magnesium stearate and silica hydrophobic colloidal.

All excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory specifications and Certificates of Analysis have been provided for all excipients.

The application has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

The current TSE certificate for Magnesium Stearate has been provided.

Dissolution

Dissolution and impurity profiles for all strengths of the drug product were found to be equivalent to those of the reference products.

Manufacturer(s)

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure system

Perindopril tablets are packed in aluminium blister foil and a transparent PVC/Aclar film. Specifications and Certificates of Analysis for all packaging used have been provided. This is satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf life of 2 years with Storage conditions of “Store below 25 degrees C” and “Store in the original package” have been set and these are satisfactory.

Bioequivalence/bioavailability

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

SPC, PIL, Labels

The SPC, PIL and Labels are pharmaceutically acceptable.

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

Conclusion

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

The proposed products are considered to be a generic medicinal product to the reference products with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

1. INTRODUCTION

This is a generic application for perindopril, an ACE inhibitor, under article 10.1, first Paragraph. 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. Coversyl 4mg and 8mg Tablets were used in the bioequivalence study.

2. BACKGROUND

The perindopril has been widely used in clinical practice for the proposed indications of hypertension and symptomatic heart failure. Its safety and efficacy are proven. The clinical overview has briefly described the clinical use and safety profile of perindopril from published sources.

3. 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. DOSE & DOSE SCHEDULE

This is consistent with originator product and is satisfactory.

5. TOXICOLOGY

This is already an authorised product. No new data has been submitted. A non-clinical overview concludes that there are no safety issues.

6. CLINICAL PHARMACOLOGY

Single bioequivalence study has been submitted to support essential similarity with the reference product.

6.1 BIOEQUIVALENCE

The BE study submitted was a randomised, open-label, 2-way crossover design. Perindopril 4 mg tablet (Lupin, India) was compared with Coversyl 4 mg tablet (Les Laboratories Servier, France) in healthy subjects under fasting conditions. This single dose study was conducted in accordance with GCP GLP. A total of 30 subjects (18 males & 12 post-menopausal or surgically sterile females) were recruited and completed the study. The washout period was 28 days and blood samples were collected up to 72 hours post-dose. Plasma samples were analysed by LC MS method.

The data were analysed from 28 subjects.

Perindopril – PK parameters

| Parameters | Test (Perindopril Tert-Butylamine Salt (A)) Mean ± SD | Reference (Coversyl (B)) Mean ± SC |
|---------------------------------|--|---------------------------------------|
| AUC _{0-t} (pg.h/mL) | 54726.61 ± 18851.78 | 54294.78 ± 16737.20 |
| AUC _{0-∞} (pg.h/mL) | 55612.86 ± 18949.05 | 55130.48 ± 16837.78 |
| C _{max} (pg/mL) | 46546.18 ± 17248.74 | 45876.48 ± 14631.08 |
| T _{max} * (h) | 0.667 ± 0.221 | 0.667 ± 0.375 |
| T _{½ cl} (h) | 0.84 ± 0.21 | 0.84 ± 0.19 |

*Medians and interquartile ranges are presented

Perindopril Tert-Butylamine Salt (A) vs Coversyl (B)

| | AUC _{0-t} | AUC _{0-∞} | C _{max} |
|---------------------------------|--------------------|--------------------|-------------------|
| Ratio ¹ | 100.17% | 100.28% | 99.64% |
| 90% Geometric C.I. ² | 95.93% to 104.61% | 96.09% to 104.65% | 91.75% to 108.20% |
| Intra-Subject CV | 9.52% | 9.39% | 18.23% |

¹Calculated using least-square means

²90% confidence Interval using in-transformed data

Perindoprilat – PK parameters

| Parameters | Test (Perindopril Tert-Butylamine Salt (A)) Mean ± SD | Reference (Coversyl (B)) Mean ± SC |
|--------------------------------------|--|---------------------------------------|
| AUC _{0-72h} ** (pg.h/mL) | 121114.33 ± 27300.82 | 119615.57 ± 28125.35 |
| C _{max} (pg/mL) | 5595.53 ± 3226.80 | 5275.06 ± 2830.26 |
| T _{max} (h) | 5.74 ± 1.89 | 6.07 ± 1.78 |
| T _{max} (h)* | 5.00 ± 2.50 | 6.00 ± 2.13 |

*Medians and interquartile ranges are presented

** For this parameter, N=27

Perindopril Tert-Butylamine Salt (A) vs Coversyl (B)

| | AUC _{0-72h} ** | C _{max} |
|---------------------------------|-------------------------|---------------------|
| Ratio ¹ | 101.03% | 104.52% |
| 90% Geometric C.I. ² | 97.24 % to 104.97 % | 93.79 % to 116.47 % |
| Intra-Subject CV | 8.23 % | 24.09 % |

¹Calculated using least-square means

²90% confidence Interval using in-transformed data

On assessors request the company has submitted reanalysis of the data with 30 subjects.

Perindopril – PK parameters (re-analysed)

N = 30

| Parameters | Test (Perindopril Tert-Butylamine Salt (A)) Mean ± SD | Reference (Coversyl (B)) Mean ± SC |
|---------------------------------|--|---|
| AUC _{0-t} (pg.h/mL) | 53990.62 ± 18611.87 | 53572.68 ± 16666.59 |
| AUC _{0-∞} (pg.h/mL) | 54860.58 ± 18715.97 | 54388.02 ± 16771.55 |
| C _{max} (pg/mL) | 46283.63 ± 16958.45 | 45098.43 ± 14458.88 |
| T _{max} * (h) | 0.667 ± 0.179 | 0.667 ± 0.458 |
| T _{½ el} (h) | 0.83 ± 0.21 | 0.82 ± 0.19 |

*Medians and interquartile ranges are presented

Perindopril Tert-Butylamine Salt (A) vs Coversyl (B) (re-analysed)

| | AUC_{0-t} | AUC_{0-∞} | C_{max} |
|---------------------------------|--------------------------|--------------------------|------------------------|
| Ratio ¹ | 100.25% | 100.36% | 100.90% |
| 90% Geometric C.I. ² | 96.29% to 104.36% | 96.45% to 104.42% | 92.61% to 109.94% |
| Intra-Subject CV | 9.18% | 9.05% | 19.71% |

¹Calculated using least-square means

²90% confidence Interval using in-transformed data

Perindoprilat – PK parameters (re-analysed)

N = 30

| Parameters | Test (Perindopril Tert-Butylamine Salt (A)) Mean ± SD | Reference (Coversyl (B)) Mean ± SC |
|--------------------------------------|--|---|
| AUC _{0-72h} ** (pg.h/mL) | 120487.48 ± 29312.49 | 119459.12 ± 29173.87 |
| C _{max} (pg/mL) | 5511.02 ± 3242.35 | 5252.57 ± 2885.78 |
| T _{max} (h) | 6.30 ± 3.81 | 6.63 ± 3.71 |
| T _{max} (h)* | 5.00 ± 2.50 | 6.00 ± 2.00 |

*Medians and interquartile ranges are presented

** For this parameter, N=29

Perindopril Tert-Butylamine Salt (A) vs Coversyl (B)(re-analysed)
N = 30

| | AUC_{0-72h}** | C_{max} |
|---------------------------------|------------------------------|------------------------|
| Ratio ¹ | 100.39% | 103.00% |
| 90% Geometric C.I. ² | 96.81% to 104.09% | 92.94% to 114.15% |
| Intra-Subject CV | 8.11% | 23.72% |

¹Calculated using least-square means

²90% confidence Interval using in-transformed data

** For this parameter, N = 29

The total number of subjects for perindoprilat measurement was 29 because the concentration data for subject 26 was missing in period 2. Therefore, the AUC₀₋₇₂ was not performed for this subject.

BE study for Perindopril 8mg tablets

This was a single centre, open-label, single dose, randomised, 2-way crossover study in 30 healthy volunteers (26 males and 4 females). A total of 27 volunteers completed the study. The study was conducted in compliance with the GCP and GLP.

A single dose of perindopril 8mg tablets Lupin Ltd, India was compared with perindopril 8mg tablets, Les Laboratoires Servier, France. The study was performed under fasting conditions. The washout period was 35 days and the sampling period was up to 72 hours post-dose. The analytical method used was LC MS MS. The quantitation limit for perindopril was 1.01 ng/mL and for perindoprilat 0.20 ng/mL.

Perindopril – Pharmacokinetic parameters (N=27)

| Parameters | Test (Perindopril Tert-Butylamin Salt (A)) | | Reference (Coversyl (B)) | |
|--------------------------------|--|--------|--------------------------|--------|
| | Mean ± SD | CV (%) | Mean ± SD | CV (%) |
| AUC _{0-t} (ng.h/mL) | 84.11 ± 21.59 | 25.67 | 84.09 ± 21.89 | 26.03 |
| AUC _{0-inf} (ng.h/mL) | 85.89 ± 21.67 | 25.23 | 85.79 ± 22.10 | 25.76 |
| C _{max} (ng/mL) | 66.50 ± 21.64 | 32.54 | 67.25 ± 21.01 | 31.25 |
| T _{max} (h) | 0.815 ± 0.227 | 27.82 | 0.815 ± 0.324 | 39.74 |
| T _{½ el} (h) | 0.88 ± 0.17 | 18.91 | 0.87 ± 0.14 | 15.95 |

Perindopril Tert-Butylamine Salt (A) vs Coversyl (B)

| | AUC_{0-t} | AUC_{0-inf} | C_{max} |
|--------------------|--------------------------|----------------------------|------------------------|
| Ratio ¹ | 99.44% | 99.56% | 98.20% |

| | | | |
|---------------------------------|----------------------|----------------------|----------------------|
| 90% Geometric C.I. ² | 96.90% to 102.05% | 97.03% to 102.16% | 91.37% to 105.54% |
| Intra-Subject CV | 5.54% | 5.52% | 15.50% |

¹Calculated using least-squares means according to the formulae $\frac{\text{Perindopril Tert-butylamine Salt A} - \text{Coversyl (B)}}{\text{Coversyl (B)}} \times 100$

²90% Geometric Confidence Interval using in-transformed data

Perindoprilat – Pharmacokinetic parameters (N=27)

| Parameters | Test (Perindopril Tert-Butylamine Salt (A)) | | Reference (Coversyl (B)) | |
|-------------------------------------|---|--------|--------------------------|--------|
| | Mean ± SD | CV (%) | Mean ± SD | CV (%) |
| AUC _{0-72h} * (ng.h/mL) | 182.09 ± 63.75 | 35.01 | 188.29 ± 75.74 | 40.22 |
| C _{max} (ng/mL) | 12.39 ± 7.24 | 58.44 | 12.99 ± 9.05 | 69.66 |
| T _{max} | 4.85 ± 1.50 | - | 4.50 ± 1.50 | - |

* For this parameter, N=25

Perindoprilat - Perindopril Tert-Butylamine Salt (A) vs Coversyl (B)

| | AUC _{0-72h} * | C _{max} |
|---------------------------------|------------------------|-------------------|
| Ratio ¹ | 98.13% | 99.52% |
| 90% Geometric C.I. ² | 94.15% to 102.28% | 92.78% to 106.74% |
| Intra-Subject CV | 8.49% | 15.06% |

¹Calculated using least-squares means according to the formulae $\frac{\text{Perindopril Tert-butylamine Salt A} - \text{Coversyl (B)}}{\text{Coversyl (B)}} \times 100$

²90% Geometric Confidence Interval using in-transformed data

*For this parameter, N=25

The data in the tables above clearly establish the bioequivalence of the test product (perindopril 8mg tablets manufactured by Lupin).

7. EFFICACY

No new data has been submitted and none is required for this type of application. The efficacy of perindopril is well known in clinical practice.

8. SAFETY

No new data has been submitted and none is required. The safety profile of perindopril is known through its extensive use in clinical practice.

9. EXPERT REPORT

This clinical overview was prepared by medically qualified individual and it is satisfactory.

10. SUMMARY OF PRODUCT CHARACTERISTICS

The SPC is identical to the SPC of the reference product.

11. PATIENT INFORMATION LEAFLET

Satisfactory

12. LABELLING

Medically satisfactory.

13. DISCUSSION

The safety and efficacy of perindopril is well established in the proposed indications. Further reassurance has been provided regarding bioequivalence of perindopril 8mg tablets. Bioequivalence of the test product to the reference formulation has been demonstrated. Marketing authorisation should be granted for these products.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT**QUALITY**

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

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

A bioequivalence study was carried out and the test and reference products shown to be bioequivalent for the appropriate pharmacokinetic criteria.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and Label are satisfactory and consistent with that for the UK reference products.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's product and the reference product are interchangeable. Extensive 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 2MG TABLETS**PL 20092/0022****PERINDOPRIL 4MG TABLETS****PL 20092/0023****PERINDOPRIL 8MG TABLETS****PL 20092/0024****STEPS TAKEN FOR ASSESMENT**

| | |
|---|--|
| 1 | The MHRA received the marketing authorisation applications on 18 th January 2006 |
| 2 | Following standard checks and communication with the applicant the MHRA considered the applications valid on 27 th January 2006 |
| 3 | Following assessment of the application the MHRA requested further information relating to the quality dossier on 7 th June 2006 and 13 th November 2006 and on the clinical dossier 30 th March 2006 and 22 nd September 2006 |
| 4 | The applicant responded to the MHRA's requests, providing further information relating to the quality dossier on 2 nd April 2007 and on the clinical dossier 23 rd August 2006 and 4 th November 2006 |
| 5 | The applications were determined on 22 nd July 2008 |

SUMMARY OF PRODUCT CHARACTERISTICS**1 NAME OF THE MEDICINAL PRODUCT**

Perindopril 2 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

The tablets contain Lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

White, round, biconvex uncoated tablets, plain on both sides.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications*****Hypertension***

Treatment of hypertension

Heart Failure

Treatment of symptomatic heart failure

Stable Coronary Artery Disease

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

4.2 Posology and method of administration

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

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

Hypertension

Perindopril 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 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 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).

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).

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

Stable coronary artery disease

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

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

Dosage adjustment in renal impairment

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

Table 1: dosage adjustment in renal impairment

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

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

Dosage adjustment in hepatic impairment

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

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 section 4.6).

4.4 **Special warnings and precautions for use** **Stable coronary artery disease**

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

Hypotension

ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). In patients with symptomatic heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic

hypotension, initiation of therapy and dose adjustment should be closely monitored (see sections 4.2 and 4.8). Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of 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 Tablets. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of Perindopril Tablets may be necessary.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

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

Renal impairment

In cases of renal impairment (creatinine clearance < 60 ml/min) the initial perindopril dosage should be adjusted according to the patient's creatinine clearance (see section 4.2) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients (see section 4.8).

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

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

Haemodialysis patients

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

Kidney transplantation

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

Hypersensitivity/Angioedema

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

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

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

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

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

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

Anaphylactic reactions during desensitisation

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

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

Hepatic failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism

of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see section 4.8).

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia

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

Race

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

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

Cough

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

Hereditary Disorders

Perindopril Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Surgery/Anaesthesia

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

Hyperkalaemia

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

use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended.

Diabetic patients

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

Lithium

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

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

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

Pregnancy and lactation

(See sections 4.3 and 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Diuretics

Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of therapy with an

ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating therapy with low and progressive doses of perindopril.

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

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

Lithium

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

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

The administration of a non-steroidal anti-inflammatory drug may reduce the antihypertensive effect of ACE inhibitors. Additionally, NSAIDs and ACE

inhibitors exert an additive effect on the increase in serum potassium and may result in a deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function such as those who are elderly or dehydrated.

Antihypertensive agents and vasodilators

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

Antidiabetic agents

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

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates

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

Tricyclic antidepressants/Antipsychotics/Anaesthetics

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

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

4.6 Pregnancy and lactation

Pregnancy

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

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

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

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 Tablets is not recommended in women who are breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

Psychiatric disorders:

Uncommon: mood or sleep disturbances

Nervous system disorders:

Common: headache, dizziness, vertigo, paresthaesia

Very rare: confusion

Eye disorders:

Common: vision disturbance

Ear and labyrinth disorders:

Common: tinnitus

Cardio-vascular disorders: Common: hypotension and effects related to hypotension

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

Respiratory, thoracic and mediastinal disorders:

Common: cough, dyspnoea

Uncommon: bronchospasm

Very rare: eosinophilic pneumonia, rhinitis

Gastro-intestinal disorders:

Common: nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea, constipation

Uncommon: dry mouth

Very rare: pancreatitis

Hepato-biliary disorders:

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

Skin and subcutaneous tissue disorders:

Common: rash, pruritus

Uncommon: angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see section 4.4).

Very rare: erythema multiforme

Musculoskeletal, 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).

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.

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

4.9 Overdose

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

The recommended treatment of overdosage is intravenous infusion of 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 section 4.4, 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: C09A A04

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

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

Hypertension

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

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

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

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

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

Discontinuation of treatment does not lead to a rebound effect.

Perindopril reduces left ventricular hypertrophy.

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

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

Heart failure

Perindopril Tablets 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 Tablets to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo.

Patients with stable coronary artery disease

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

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

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

Overall, 90% of the patients had a previous myocardial infarction and/or revascularisation.

Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers.

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

5.2 Pharmacokinetic properties

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

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

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

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

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

After repeated administration, no accumulation of perindopril is observed.

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

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

Perindopril kinetics are modified in patients with cirrhosis: hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required (see also sections 4.2 and 4.4).

5.3 Preclinical safety data

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

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

Reproduction toxicology studies (rats, mice, rabbits and monkeys) showed no sign of embryotoxicity or teratogenicity. However, angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects on late 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

Microcrystalline cellulose

Lactose monohydrate

Silica, hydrophobic colloidal

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

Clear PVC 250 / Aclar 51/ Aluminium blisters, which is further inserted into an aluminum laminated pouch with desiccant 3g silica gel, further packed in cartons. Packs of 30 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Lupin (Europe) Limited

Victoria Court

Bexton Road

Knutsford

Cheshire WA 16 0PF

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20092/0022

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/07/2008

10 DATE OF REVISION OF THE TEXT

22/07/2008

1 NAME OF THE MEDICINAL PRODUCT

Perindopril 4 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

The tablets contain Lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

White, capsule shaped uncoated tablets, with breakline on both sides.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications*****Hypertension***

Treatment of hypertension

Heart Failure

Treatment of symptomatic heart failure

Stable Coronary Artery Disease

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

4.2 Posology and method of administration

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

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

Hypertension

Perindopril 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 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 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).

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).

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

Stable coronary artery disease

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

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

Dosage adjustment in renal impairment

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

Table 1: dosage adjustment in renal impairment

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

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

Dosage adjustment in hepatic impairment

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

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 section 4.6).

4.4 **Special warnings and precautions for use**

Stable coronary artery disease

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

Hypotension

ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent

hypertension (see sections 4.5 and 4.8). In patients with symptomatic heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored (see sections 4.2 and 4.8). Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of 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 Tablets. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of Perindopril Tablets may be necessary.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

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

Renal impairment

In cases of renal impairment (creatinine clearance < 60 ml/min) the initial perindopril dosage should be adjusted according to the patient's creatinine clearance (see section 4.2) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients (see section 4.8).

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

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum

creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of Perindopril Tablets 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 Tablets 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 Tablets may be required.

Haemodialysis patients

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

Kidney transplantation

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

Hypersensitivity/Angioedema

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

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

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

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

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

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

Anaphylactic reactions during desensitisation

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

Hepatic failure

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

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia

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

Race

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

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

Cough

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

Hereditary Disorders

Perindopril Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Surgery/Anaesthesia

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

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, uncontrolled diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium

supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended.

Diabetic patients

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

Lithium

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

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

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

Pregnancy and lactation

(See sections 4.3 and 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Diuretics

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

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

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

Lithium

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

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

The administration of a non-steroidal anti-inflammatory drug may reduce the antihypertensive effect of ACE inhibitors. Additionally, NSAIDs and ACE

inhibitors exert an additive effect on the increase in serum potassium and may result in a deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function such as those who are elderly or dehydrated.

Antihypertensive agents and vasodilators

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

Antidiabetic agents

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

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates

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

Tricyclic antidepressants/Antipsychotics/Anaesthetics

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

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

4.6 Pregnancy and lactation

Pregnancy

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

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

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

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 Tablets is not recommended in women who are breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

Psychiatric disorders:

Uncommon: mood or sleep disturbances

Nervous system disorders:

Common: headache, dizziness, vertigo, paresthaesia

Very rare: confusion

Eye disorders:

Common: vision disturbance

Ear and labyrinth disorders:

Common: tinnitus

Cardio-vascular disorders:

Common: hypotension and effects related to hypotension

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

Respiratory, thoracic and mediastinal disorders:

Common: cough, dyspnoea

Uncommon: bronchospasm

Very rare: eosinophilic pneumonia, rhinitis

Gastro-intestinal disorders:

Common: nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea, constipation

Uncommon: dry mouth

Very rare: pancreatitis

Hepato-biliary disorders:

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

Skin and subcutaneous tissue disorders:

Common: rash, pruritus

Uncommon: angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see section 4.4).

Very rare: erythema multiforme

Musculoskeletal, 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).

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.

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

4.9 Overdose

Limited data are available for overdose 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 overdose is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis. (See section 4.4, 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: C09A A04

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

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

Hypertension

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

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

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

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

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

Discontinuation of treatment does not lead to a rebound effect.

Perindopril reduces left ventricular hypertrophy.

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

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

Heart failure

Perindopril Tablets 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 Tablets to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo.

Patients with stable coronary artery disease

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

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

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

Overall, 90% of the patients had a previous myocardial infarction and/or revascularisation.

Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers.

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

5.2 Pharmacokinetic properties

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

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

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

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

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

After repeated administration, no accumulation of perindopril is observed.

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

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

Perindopril kinetics are modified in patients with cirrhosis: hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required (see also sections 4.2 and 4.4).

5.3 Preclinical safety data

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

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

Reproduction toxicology studies (rats, mice, rabbits and monkeys) showed no sign of embryotoxicity or teratogenicity. However, angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects on late 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**

Microcrystalline cellulose

Lactose monohydrate

Silica, hydrophobic colloidal

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

Clear PVC 250 / Aclar 51/ Aluminium blisters, which is further inserted into an aluminum laminated pouch with desiccant 3g silica gel, further packed in cartons. Packs of 30 tablets.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Lupin (Europe) Limited

Victoria Court

Bexton Road

Knutsford

Cheshire WA 16 0PF

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20092/0023

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/07/2008

10 DATE OF REVISION OF THE TEXT

22/07/2008

1 NAME OF THE MEDICINAL PRODUCT

Perindopril 8 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

The tablets contain Lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

White, round shaped, uncoated tablets, plain on both sides.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications*****Hypertension***

Treatment of hypertension

Heart Failure

Treatment of symptomatic heart failure

Stable Coronary Artery Disease

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

4.2 Posology and method of administration

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

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

Hypertension

Perindopril 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 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 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).

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).

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

Stable coronary artery disease

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

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

Dosage adjustment in renal impairment

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

Table 1: dosage adjustment in renal impairment

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

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

Dosage adjustment in hepatic impairment

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

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 section 4.6).

4.4 Special warnings and precautions for use

Stable coronary artery disease

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

Hypotension

ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). In patients with symptomatic heart failure,

with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored (see sections 4.2 and 4.8). Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of 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 Tablets. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of Perindopril Tablets may be necessary.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

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

Renal impairment

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

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

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

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is

especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of Perindopril Tablets 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 Tablets 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 Tablets may be required.

Haemodialysis patients

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

Kidney transplantation

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

Hypersensitivity/Angioedema

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

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

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

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

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

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

Anaphylactic reactions during desensitisation

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

Hepatic failure

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

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia

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

Race

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

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

Cough

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

Hereditary Disorders

Perindopril Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Surgery/Anaesthesia

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

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, uncontrolled diabetes

mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended.

Diabetic patients

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

Lithium

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

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

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

Pregnancy and lactation

(See sections 4.3 and 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Diuretics

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

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

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

Lithium

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

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

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

Antihypertensive agents and vasodilators

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

Antidiabetic agents

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

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates

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

Tricyclic antidepressants/Antipsychotics/Anaesthetics

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

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

4.6 **Pregnancy and lactation**

Pregnancy

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

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

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

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 Tablets is not recommended in women who are breast-feeding.

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

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

4.8 **Undesirable effects**

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

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

Psychiatric disorders:

Uncommon: mood or sleep disturbances

Nervous system disorders:

Common: headache, dizziness, vertigo, paresthaesia

Very rare: confusion

Eye disorders:

Common: vision disturbance

Ear and labyrinth disorders:

Common: tinnitus

Cardio-vascular disorders: Common: hypotension and effects related to hypotension

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

Respiratory, thoracic and mediastinal disorders:

Common: cough, dyspnoea

Uncommon: bronchospasm

Very rare: eosinophilic pneumonia, rhinitis

Gastro-intestinal disorders:

Common: nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea, constipation

Uncommon: dry mouth

Very rare: pancreatitis

Hepato-biliary disorders:

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

Skin and subcutaneous tissue disorders:

Common: rash, pruritus

Uncommon: angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see section 4.4).

Very rare: erythema multiforme

Musculoskeletal, 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).

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.

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

4.9 Overdose

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

The recommended treatment of overdosage is intravenous infusion of 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 section 4.4, 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: C09A A04

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

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

Hypertension

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

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

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

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

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

Discontinuation of treatment does not lead to a rebound effect.

Perindopril reduces left ventricular hypertrophy.

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

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

Heart failure

Perindopril Tablets 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 Tablets to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo.

Patients with stable coronary artery disease

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

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

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

Overall, 90% of the patients had a previous myocardial infarction and/or revascularisation.

Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers.

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

5.2 Pharmacokinetic properties

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

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

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

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

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

After repeated administration, no accumulation of perindopril is observed.

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

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

Perindopril kinetics are modified in patients with cirrhosis: hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required (see also sections 4.2 and 4.4).

5.3 Preclinical safety data

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

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

Reproduction toxicology studies (rats, mice, rabbits and monkeys) showed no sign of embryotoxicity or teratogenicity. However, angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects on late 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**

Microcrystalline cellulose

Lactose monohydrate

Silica, hydrophobic colloidal

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

Clear PVC 250 / Aclar 51/ Aluminium blisters, which is further inserted into an aluminum laminated pouch with desiccant 3g silica gel, further packed in cartons. Packs of 30 tablets.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Lupin (Europe) Limited

Victoria Court

Bexton Road

Knutsford

Cheshire WA 16 0PF

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20092/0024

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/07/2008

10 DATE OF REVISION OF THE TEXT

22/07/2008

PATIENT INFORMATION LEAFLET

- pancreatitis (inflammation of the pancreas)
- hepatitis (inflammation of the liver)
- erythema multiforme (skin reaction like an allergy)
- changes in the blood; your doctor may decide to carry out blood tests at intervals to monitor for this

If you experience any of the above symptoms and they persist or become troublesome, you should tell your doctor.

5. HOW TO STORE PERINDOPRIL TABLETS

Keep them out of the reach and sight of children.

Do not store the tablets above 25°C. Store in the original container.

If your doctor decides to stop the treatment, return any tablets left over to the pharmacist. Only keep them if your doctor tells you to.

This medicine should not be taken after the expiry date, which is clearly marked on the outside of the packet.

The expiry date refers to the last day of that month.

Disposal

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Perindopril Tablets contain

The active substance is perindopril tert-butylamine.

The other ingredients are:

Lactose monohydrate, cellulose microcrystalline, magnesium stearate and hydrophobic silica.

What Perindopril Tablets look like and the contents of the pack

Perindopril Tablets are available in three strengths.

- The white, round, biconvex uncoated tablets, plain on both the sides contain Perindopril tert-Butylamine 2mg equivalent to 1.660mg of perindopril;
- The white capsule shaped uncoated tablets, with breakline on both sides contain Perindopril tert-Butylamine 4mg equivalent to 3.338mg of perindopril;
- The white, round shaped, uncoated tablets, plain on both sides contains Perindopril tert-Butylamine 8mg equivalent to 6.676mg of perindopril;

The tablets are available in Clear PVC 250 / Actar 51/ Aluminium blisters, which is further inserted into an aluminium laminated pouch with desiccant 3g silica gel, further packed in cartons. The tablets are available in packs of 30 tablets.

Do not swallow the desiccant (drying agent) enclosed in the aluminium pouch

Marketing Authorisation Holder and Manufacturer

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This leaflet was last approved in

How can you obtain more information about Perindopril Tablets?

This leaflet gives you only some of the most important information about Perindopril Tablets. If you have any questions after you have read it, ask your doctor or pharmacist, who will give you further information.

Further information and advice is available from the following organization:
Marketing Authorisation Holder

Date of preparation: June 2008

PATIENT INFORMATION LEAFLET PERINDOPRIL 2mg, 4mg and 8mg TABLETS perindopril tert-butylamine

Read all of this leaflet carefully before you start taking this medicine. It is an important source of information about your medicine and how to take it safely

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- **REMEMBER:** 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. Unless your doctor tells you to, do not keep medicines that you no longer need, give them back to your pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed on this leaflet, please tell your doctor or pharmacist.

In This Leaflet:

1. What Perindopril Tablets are and what they are used for.
2. Before you take Perindopril Tablets.
3. How to take Perindopril Tablets.
4. Possible side effects.
5. How to store Perindopril Tablets.
6. Further information.

1. WHAT PERINDOPRIL TABLETS ARE AND WHAT THEY ARE USED FOR

The active ingredient in Perindopril Tablets is Perindopril tert-Butylamine. This belongs to a class of medicines called ACE inhibitors. These work by widening the blood vessels, which makes it easier for your heart to pump blood through them.
For the other ingredients in Perindopril Tablets (see section 6)

Your doctor has prescribed Perindopril Tablets for the treatment of high blood pressure (hypertension). They can also be used to treat heart failure and to reduce the risk of cardiac events, such as heart attack, in patients with stable coronary artery disease (a condition where the blood supply to the heart is reduced or blocked) and who have already had a heart attack and/or an operation to improve the blood supply to the heart by widening the vessels that supply it.

2. BEFORE YOU TAKE PERINDOPRIL TABLETS

Do not take Perindopril Tablets:

- if you are allergic (hypersensitive) to the active substance Perindopril tert-Butylamine, or to any of the other ingredients. (See section 6 for a list of these.)
- if you have had symptoms such as wheezing, swelling of the face, tongue or throat, intense itching, skin rashes, fainting or dizziness with previous ACE inhibitor treatment or have had these symptoms in any other circumstances (this is a condition called angioedema)
- if you are pregnant or breast-feeding

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

Take special care with Perindopril Tablets

You should check with your doctor before taking Perindopril Tablets:

- if you have aortic stenosis (narrowing of the main blood vessel leading from the heart) or hypertrophic cardiomyopathy (cardiac muscle disease) or renal artery stenosis (narrowing of the artery supplying the kidney with blood)
- if you have any other heart or liver or kidney problems, or if you are receiving dialysis
- if you suffer from a collagen disease such as systemic lupus erythematosus or scleroderma
- if you are on a salt restricted diet or use salt substitutes which contain potassium
- if you suffer from diabetes, which is not well controlled

You should also inform your doctor or the medical staff that you are taking Perindopril Tablets:

- if you are to undergo anaesthesia and/or surgery
- if you have suffered from recent diarrhoea or vomiting
- if you are going to have desensitisation treatment to reduce the effects of an allergy to bee or wasp stings
- if you are to undergo LDL apheresis (which is removal of cholesterol from your blood by a machine)

Using other medicines

In order to avoid possible interactions between different medicines, you should **always inform** your doctor or your pharmacist of any other medicines that you are taking – **even those bought without a doctor's prescription** – before taking Perindopril Tablets. In particular, you should check with your doctor if you are taking any of the following to be sure that it is safe to take Perindopril Tablets at the same time:

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

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

Using Perindopril Tablets with food and alcohol

It is recommended that Perindopril Tablets should be taken before a meal in order to reduce the influence of food on the way in which the medicine works. Drinking alcohol with Perindopril Tablets may make you feel dizzy or light-headed. You should check with your doctor whether drinking is advisable for you.

Pregnancy and breast-feeding

You should **not** take Perindopril Tablets:

- if you are pregnant, planning to become pregnant or if you suspect you are pregnant
- if you are breast-feeding

Children

Perindopril Tablets should not be given to children.

Driving and using machinery

You may experience **dizziness** or **weariness** while taking Perindopril Tablets. If this occurs do not drive or use machinery. You should talk to your doctor.

(Now please read the rest of this leaflet. It has other important information for your safety.)

Important information about some of the Ingredients of Perindopril Tablets

'If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.'

3. HOW TO TAKE PERINDOPRIL TABLETS

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

The usual dosages for Perindopril Tablets are as follows:

- High blood pressure: the usual starting and maintenance dose for treatment in adults is 4 mg once a day. After a month, this can be increased to 8 mg a day, which is the maximum recommended dose
- In the elderly, the usual starting dose is 2 mg once a day. After a month, this can be increased to 4 mg a day and if necessary to 8 mg a day
- Heart failure: treatment should be started under close medical supervision with 2 mg once a day. After two weeks, it can be increased to 4 mg once a day if required

Take your tablet(s) with a glass of water, preferably at the same time each day, in the morning, before a meal. If you are taking water tablets (diuretics), your doctor may decide to reduce or even discontinue these at the beginning of your treatment with Perindopril Tablets. Treatment for high blood pressure or heart failure is usually life-long. Perindopril Tablets are not suitable for use in children.

If you take more tablets than you should:

If you have taken too many tablets, contact your nearest hospital accident and emergency department or tell your doctor **immediately**.

If you forget to take your tablets:

It is important to take your medicine every day. However, if you forget to take one or more doses, take another as soon as you remember unless it is almost time for your next dose, then go on as prescribed. Do not take a **double** dose.

4. POSSIBLE SIDE EFFECTS

Please remember:

- The expected benefits of your medicine will usually be greater than the risk of suffering any harmful side effects
- If you notice any other effects not mentioned in this leaflet, please inform your doctor or pharmacist

Perindopril Tablets like all medicines can cause side effects in some patients. Do not be alarmed by the list below, you may not get any of them.

Common side effects: reported in between 1 in 10 and 1 in 100 people, included:

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

Uncommon side effects; reported in between 1 in 100 and 1 in 1,000 people, included;

- changes in mood or sleep
- bronchospasm (tightening of the chest, wheezing and shortness of breath)
- dry mouth
- kidney problems
- impotence
- sweating
- angioedema

If you experience any of the following effects, stop taking your tablets at once and TELL YOUR DOCTOR IMMEDIATELY: swelling of the face, lips, mouth, tongue or throat, difficulty in breathing, dizziness or fainting, unusually fast or irregular heart beat.

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

Very rare side effects, reported in less than 1 in 10,000 people, include:

- confusion
- irregular heart beat, angina, heart attack and stroke (these have been reported with ACE inhibitors in association with low blood pressure)
- eosinophilic pneumonia (a rare type of pneumonia)
- rhinitis (blocked up or runny nose)



 Varnish Free Area



Perindopril
#2 mg Tablets



 Varnish Free Area



**Perindopril
#4 mg Tablets**



Varnish Free Area



Perindopril
#8 mg Tablets