PERINDOPRIL 2MG, 4MG, 8MG TABLETS
PL 00530/0764-66

UKPAR

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PERINDOPRIL 2MG, 4MG, 8MG TABLETS
PL 00530/0764-66

LAY SUMMARY

The MHRA granted Norton Healthcare Ltd Marketing Authorisations (licenses) for the medicinal products Perindopril 2mg, 4mg, and 8mg Tablets (PL 00530/0764-66). These are prescription only medicines (POM) for the treatment of hypertension and symptomatic heart failure.

Perindopril 2mg, 4mg, and 8mg Tablets contain the active ingredient perindopril as the perindopril erbumine. 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)

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, 4MG, 8MG TABLETS
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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Perindopril 2mg, 4mg, and 8mg Tablets to Norton Healthcare Ltd on 11th of December 2006. The products are prescription only medicines.

These applications comprise of a complex and two standard abridged National Marketing Application for Perindopril 2mg, 4mg, and 8mg Tablets made under EC Article 10.1 (a) (iii), first paragraph. The proposed legal status is Prescription Only Medicine.

The products contain the active ingredient perindopril and are indicated for the treatment of hypertensionand symptomatic heart failure.

Perindopril 2mg, 4mg, and 8mg Tablets contain the active ingredient perindopril as the perindopril erbumine. 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)

These applications for Perindopril 2mg, 4mg, and 8mg Tablets were submitted at the same time. The bioequivalence study using the 8 mg strength products, together with the comparative in vitro dissolution studies provided should be sufficient to confirm the bioequivalence of both the 2 mg and 4 mg strength tablets.

PHARMACEUTICAL ASSESSMENT

PL NUMBER: **00530/0764-66**

PRODUCT: **Perindopril 2 mg Tablets**

Perindopril 4 mg Tablets

Perindopril 8 mg Tablets

ACTIVE: **Perindopril erbumine (tert-butylamine)**

COMPANY: **Norton Healthcare Ltd.**

LEGAL STATUS: **POM**

I. INTRODUCTION

These are national, abridged applications (1 x complex and 2 x standard), under Directive 2001/83/EC, Article 10.1 (a) (iii) first paragraph. The applications are for tablets containing 2 mg, 4 mg & 8 mg of perindopril erbumine.

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

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

DRUG SUBSTANCE

III.3 Characterisation

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).

III.4 Control of Drug Substance

III.4.1 Specification

The drug substance specification used by the FPM is the same as that used by the DSM and in line with the current Ph. Eur. monograph. Additional in-house tests are also performed to further control the quality of the drug substance. This is acceptable.

III.4.2 Analytical Procedures

Analytical procedures are the same as those used by the DSM.

III.4.3 Validation of Analytical Procedures

Validation has been performed by both the DSM and the FPM. The methods are essentially those described in the Ph. Eur. monograph for perindopril tert-butylamine and are acceptable.

III.4.4 Batch Analyses

Certificates of analysis for batches of drug substance from the FPM and DSM are provided. All batches comply with the specifications.

III.4.5 Justification of Specification

Appropriate justification has been provided

III.5 Reference Standards or Materials

The finished product manufacturer uses certified reference standards or working standards qualified against the reference standard and obtained from the DSM. This is acceptable.

IV. DRUG PRODUCT

IV.1 Description and Composition of the Drug Product

Composition

Component				**Function**	
Perindopril tert-butylamine				Active substance	
Excipients:					
Lactose anhydrous				Diluent	
Microcrystalline cellulose				Diluent	
Maize starch				Disintegrant	
Silica, colloidal anhydrous				Glidant	
Magnesium stearate				Lubricant	

2 mg: white, round, uncoated, biconvex tablets with ‘P2’ embossed on one side.
4 mg: white, capsule shaped, uncoated tablets with ‘P4’ embossed on one side.
8 mg: white, round, uncoated, biconvex tablets with ‘P8’ embossed on one side.

IV.2 Pharmaceutical Development

IV.2.1 Components of the Drug product

IV.2.1.1 Drug Substance

All development and submission batches were produced using drug substance manufactured by the proposed DSM.

IV.2.1.2 Excipients

All the excipients are common to pharmaceutical manufacture and comply with the requirements of the Ph. Eur.

IV.2.2 Drug Product

IV.2.2.1 Formulation development

The objective of the development was to produce stable, excipient proportional, generic formulations essentially similar to the reference product (UK: Coversyl tablets). The final formulation follows a logical development sequence.

IV.2.2.2 Overages

Not applicable.

IV.2.2.3 Physicochemical and biological properties

Details of the batches used for stability and bioequivalence have been provided. Comparative in vitro dissolution and impurity profiles have been provided and demonstrate the similarity of the test and innovator products. The in vivo bioequivalence study was performed using perindopril 8 mg tablets and UK Coversyl® 8 mg tablets.

IV.2.3 Manufacturing Process Development

Appropriate details of the manufacturing process development have been provided.

IV.2.4 Container Closure System

The applicant indicates that the innovator product is packaged in PVC/Al blisters. In line with this PVC/Al blisters were used for the test product although these are additionally packed into aluminium pouches containing a silica gel canister prior to final carton packaging.

IV.2.5 Microbiological Attributes

Not applicable.

IV.2.6 Compatibility

Not applicable.

IV.3 Manufacture

IV.3.1 Manufacturer(s)

The finished product manufacturers are listed.

IV.3.2 Batch Formula

Satisfactory details of the batch formula have been provided.

IV.3.3 Description of Manufacturing Process and Process Controls

The manufacturing process has been adequately described including in-process controls and a flow diagram. The applicant also states that manufacturing is carried out under controlled conditions of temperature and humidity (25 ºC/45 % RH).

IV.3.4 Control of Critical Steps and Intermediates

The in-process controls and intermediates are outlined by the applicant satisfactorily.

IV.3.5 Process Validation and/or Evaluation

Process validation has been carried out on the pilot scale and commercial scale batches. The protocols and reports are presented and provide a detailed investigation of the process.

The manufacturing process appears robust and will consistently produce a product of acceptable quality. The applicant has also confirmed that process validation studies will also be undertaken on the first commercial scale batches manufactured

IV.4 Control of Excipients

IV.4.1 Specifications

Comply with the requirements of the Ph. Eur. Additional in-house tests including microbial contamination and extraneous matter (visual) are also performed. Test specifications and certificates of analysis have been provided by the finished product manufacturer (and suppliers) and are in line with the monograph.

IV.4.2 Analytical Procedures

Tests are performed according to the current version of the monograph. In-house testing methods are also described.

IV.4.3 Validation of Analytical Procedure

Not applicable.

IV.4.4 Justification of Specification

Not applicable.

IV.4.5 Excipients of Human or Animal Origin

The supplier of lactose has provided a general statement regarding their compliance with EMEA/410/01 Rev. 02.
BSE/TSE statements have been provided from the suppliers of the other excipients indicating that they are not manufactured from materials of animal origin.

IV.4.6 Novel Excipients

Not applicable.

IV.5 Control of Drug Product

IV.5.1 Specification(s)

A satisfactory specification has been provided.

IV.5.2 Analytical Procedures

The analytical methods are adequately described.

IV.5.3 Validation of Analytical Procedures

The applicant has provided detailed validation data for the in-house methods.
These methods bear great similarity to the pharmacopoeia methods for perindopril.
Suitable validation data is provided to demonstrate the applicability of the methods to the finished product.

IV.5.4 Batch Analyses

Batch analytical data have been provided for the pilot and commercial-scale batches of each strength. All batches comply with the proposed finished product specifications.

IV.5.5 Characterisation of Impurities

This is acceptable and all impurities detected in the drug substance are tested for in the finished product.

IV.5.6 Justification of Specification(s)

In general the finished product specifications are extensive and suitable for a dosage form of this type.

The release specifications for related substances are controlled in accordance with Ph. Eur. requirements for the drug substance. Widening of the specification limits at shelf-life is acceptable and does not provide a safety concern.

IV.6 Reference Standards or Materials

Certificates of analysis of the working standards have been provided.

IV.7 Container Closure System

Perindopril tablets are blister packed employing a VMCH coated aluminium foil and a transparent PVC film. These are standard packaging materials. The blisters are then packed into aluminium pouches, containing a silica desiccant, which are heat sealed before being placed into cartons.

Specifications and certificates of analysis for the packaging materials are provided. Further information demonstrates that the immediate packaging is suitable for use with pharmaceutical products.

IV.8 Stability

IV.8.1 Stability Summary and Conclusion

Stability studies have been performed on the pilot scale batches. All batches are packaged in the proposed commercial packaging (Al/PVC blisters, Al pouches and cartons). Stability studies were also performed on a batch of each strength of the UK brand leader product (Coversyl tablets).

Stability testing is performed according to the relevant ICH guidelines. Samples are stored under long term (25 ± 2 °C, RH 60 ± 5 %), intermediate (30 ± 2 °C, RH 65 ± 5 %) and accelerated (40 ± 2 °C, RH 75 ± 5 %) conditions for the duration of the protocol.

IV.8.2 Post-approval Stability Protocol and Stability Commitment

The applicant confirms that the first production batches will be placed on stability and that the ongoing study will continue to the proposed 36 month end point.

IV.8.3 Stability Data

Satisfactory stability data in line with relevant guidance is provided to support the shelf life and storage conditions proposed for each container closure system.

V. APPENDICES

Not applicable.

VI. REGIONAL INFORMATION

Not applicable.

VII ASSESSOR'S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET

The SPC, PIL and labels are satisfactory

VII.1 Other information

VII.1.2 Bio-analytical methods

This is satisfactory.

VII.1.3 Bioavailability, bioequivalence

A bioequivalence study was performed on healthy volunteers so as to compare the pharmacokinetic behaviour of IVAX Perindopril 8 mg Tablets with the reference product Coversyl® 8 mg Tablets. The formulation of the Perindopril 8 mg Tablets used in the study are identical to the proposed commercial formulation. The reference product is licensed in UK (Servier Laboratories Ltd).

A single dose, fasting, randomised, 2-way crossover study on the bioavailability of Perindopril 8 mg Tablets compared with the reference product Coversyl® 8 mg Tablets is provided. Plasma levels of both perindopril and its active metabolite perindoprilat are reported. For further details see the medical assessment.

Study Design: A single centre, open-label, single dose, randomized, 2-way crossover, bioavailability study in healthy volunteers under fasted conditions.

The pharmacokinetic parameters for perindopril and perindoprilat were calculated. These included the maximum plasma concentration (C_{max}), time to C_{max} (T_{max}) and AUC. Plasma concentrations were determined following validation of a suitable LC-MS/MS analytical method. For further details, refer to the clinical assessment.

VII.2.1 Administrative

VII.2.2 Comment on Expert report

The expert is suitably qualified and whilst he has provided a non-critical review it is a useful summary of the dossier.

VII.2.3 MAA form

This is acceptable

VII.2.4 GMP

Appropriate proof of GMP has been supplied for the manufacturing and batch release sites.

VII.2.5 Guideline Compliance

The dossier is generally in accordance with current guidelines.

VIII ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

The dossier is generally well presented and the manufacture of both drug substance and finished product appear well controlled.

Pharmaceutical Assessor
08/06/05

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

2. BACKGROUND

ATC Code: CO9A A04, ACE inhibitors, plain
The innovator product Coversyl tablets is marketed throughout Europe by Servier Laboratories.

There is no evidence of a direct relationship between plasma concentrations of perindopril/perindoprilat and haemodynamic response, at therapeutic doses. The dose response to perindopril does appear to be linear over the range of 2-8mg daily in hypertensive patients.

3. INDICATIONS

"Hypertension
Treatment of hypertension.

Heart failure
Treatment of symptomatic heart failure"

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

4. DOSE & DOSE SCHEDULE

"For oral use.
It is recommended that Perindopril Tablets are taken once daily in the morning before a meal. Tablets should be swallowed whole with a glass of water.

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

Hypertension
Perindorpirl tablets may be used in monotherapy or in combination with other classes of antihypertensive therapy.

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

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

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

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

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

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

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

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

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

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

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

Table 1: dosage adjustment in renal impairment

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 per every other day
Haemodialysed patients*, Cl_{CR}	2 mg on the day of dialysis

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

Dosage adjustment in hepatic impairment
No dosage adjustment is necessary in patients with hepatic impairment (see Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties).

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

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

5. TOXICOLOGY

Perindopril has been in clinical use for many years. The applicant has provided a nonclinical overview written by a Consultant in Pharmacology and Toxicology.

6. CLINICAL PHARMACOLOGY

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

Bioequivalence
A single bioequivalence study has been provided.

The study was a single-dose, randomised, two-period, cross-over and open label. This was conducted in healthy volunteers and according to ICH Guidelines for Good Clinical Practice.

A total of 36 subjects (17 males and 19 females) were recruited in the study and received either test product 8mg tablets or the reference product 8mg tablet (Coversyl).

Bioequivalence criteria were based on 80–125% limits for C_{max} and AUC.

The results for both, the parent compound perindopril and the active metabolite perindoprilat are shown in the tables below.

Table 1 A: Summary of PK data for Perindopril (Ivax vs Coversyl 1 × 8 mg tablet): means ± SD, N=34

Parameter	IVAX	Coversyl	Point estimate and 90% CI
C_{max} (ng/ml)	166 ± 38.2	158 ± 36.2	105 (97.2 – 114)
AUC_{0-t} (ng.hr/ml)	251 ± 57.9	256 ± 52.2	98.1 (94.9 – 102)
$AUC_{0-\infty}$ (ng.h/ml)	252 ± 58.0	257 ± 52.3	98.2 (94.9 – 102)
T_{max} (hr)	0.75	0.75	
$t_{½}$ (hr)	1.08	1.07	

Table 1 B: Summary of PK data for Perindoprilat (Ivax vs Coversyl 1 × 8 mg tablet): means ± SD, N=34

Parameter	IVAX	Coversyl	Point estimate and 90% CI
C_{max} (ng/ml)	29.9 ± 8.9	29.8 ± 9.7	100 (96.1 – 104)
AUC_{0-t} (ng.hr/ml)	283 ± 67.4	277 ± 63.4	102 (99.4 – 105)
$AUC_{0-\infty}$ (ng.h/ml)	328 ± 75.1	320 ± 68.0	103 (99.9 – 105)
T_{max} (hr)	1.67	1.67	
$t_{½}$ (hr)	35.9	35.4	

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

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

9. EXPERT REPORT
The clinical overview was written by an independent pharmaceutical consultant and is appropriately qualified. The report is non-critical and has briefly reviewed the efficacy and safety of perindopril.

10. SUMMARY OF PRODUCT CHARACTERISTICS
The Summary of Product Characteristics is identical to the SPC of the reference product.

11. PATIENT INFORMATION LEAFLET
Medically satisfactory

12. LABELLING
Medically satisfactory

13. DISCUSSION
This is an application for generic perindopril. Essential similarity has been claimed with Coversyl tablets. The bioequivalence of the 8mg tablet of the test product has been shown

The clinical efficacy and safety of perindopril is well established through its extensive use in clinical medicine.

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

14. CONCLUSIONS

There is no objection to the grant of a marketing authorisation for these products.

Clinical Assessor
29th November 2005

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 and PIL 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, 4MG, 8MG TABLETS
PL 00530/0764-66

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 03/12/2004
2	Following standard checks and communication with the applicant the MHRA considered the application valid on the 11/01/2005
3	Following assessment of the application the MHRA requested further information on the 09/06/2005, 07/12/2005
4	The applicant responded to the MHRA's requests, providing further information on 23/03/2006, 11/04/2006, 23/06/2006, 17/07/2006
5	The application was determined on the 11/12/2006

PERINDOPRIL 2MG, 4MG, 8MG TABLETS
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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

PERINDOPRIL 2MG, 4MG, 8MG TABLETS
PL 00530/0764-66

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Perindopril 2 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains perindopril erbumine 2 mg,(equivalent to 1.669 mg perindopril).

For excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Tablet

White, round, uncoated, biconvex tablets with ‘P2’ engraved on one side of the tablet and the other side plain.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Hypertension

Treatment of hypertension

Heart Failure

Treatment of symptomatic heart failure

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
For oral use.

It is recommended that Perindopril Tablets are taken once daily in the morning before a meal. Tablets should be swallowed whole with a glass of water.

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

Hypertension

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

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

Patients with a strongly activated 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 Special warnings and precautions for use).

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

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

Symptomatic heart failure

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

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

Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy 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 Special warnings and precautions for use).

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 Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties)

Paediatric use

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

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 Pregnancy and lactation).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

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

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Perindopril 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 Posology and method of administration) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients (see Section 4.8 Undesirable effects).

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

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

Hypersensitivity/Angioedema

Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including Perindopril Tablets (see Section 4.8 Undesirable effects). 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 Contraindications).

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

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

Anaphylactic reactions during desensitisation

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

Hepatic failure

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

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia

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

Race

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

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

Cough

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

Surgery/Anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Perindopril 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 Interaction with other medicinal products and other forms of interaction, Antidiabetics.)

Lithium

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

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

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

Lactose

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

Pregnancy and lactation

(See Section 4.3 Contraindications and Section 4.6 Pregnancy and lactation).

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 Special warnings and precautions for use). 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 Special warnings and precautions for use).

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 Special warnings and precautions for use).

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 Preclinical safety data).

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

Lactation

It is not known whether perindopril is excreted into human breast milk. Therefore the use of Perindopril 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, paresthesia

Very rare: confusion

Eye disorders:

Common: vision disturbance

Ear and labyrinth disorders:

Common: tinnitus

Cardio-vascular disorders:

Common: hypotension and effects related to hypotension

Very rare: arrhythmia, angina pectoris, myocardial infarction and stroke, possibly secondary to excessive hypotension in high risk patients (see Section 4.4 Special warnings and precautions for use).

Respiratory, thoracic and mediastinal disorders:

Common: cough, dyspnoea

Uncommon: bronchospasm

Very rare: eosinophilic pneumonia, rhinitis

Gastro-intestinal disorders:

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

Uncommon: dry mouth

Very rare: pancreatitis

Hepato-biliary disorders:

Very rare: hepatitis either cytolytic or cholestatic (see Section 4.4 Special warnings and precautions for use)

Skin and subcutaneous tissue disorders:

Common: rash, pruritus

Uncommon: angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see Section 4.4 Special warnings and precautions for use).

Very rare: erythema multiforme

Musculoskeletal, connective tissue and bone disorders:

Common: muscle cramps

Renal and urinary disorders:

Uncommon: renal insufficiency

Very rare: acute renal failure

Reproductive system and breast disorders:

Uncommon: impotence

General disorders:

Common: asthenia

Uncommon: sweating

Blood and the lymphatic system disorders:

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

Investigations:

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

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 Special warnings and precautions for use, Haemodialysis Patients). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ATC code: 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 reduce 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.

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 Section 4.2 Posology and method of administration and Section 4.4 Special warnings and precautions for use).

5.3 PRECLINICAL SAFETY DATA

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

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose (E460)

Anhydrous lactose

Silica, colloidal anhydrous

Magnesium stearate (E572)

Maize starch

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

21 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25° C

Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER

Perindopril 2 mg Tablets are packed in clear, colourless PVC / VMCH coated aluminium foil coating containing 30 tablets.

The blisters were then packed in Aluminium pouches containing a silica gel cannister (dessicant). The sealed pouches were further packed in cartons.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Not applicable

7 MARKETING AUTHORISATION HOLDER

Norton Healthcare Limited

T/A IVAX Pharmaceuticals UK

Albert Basin

Royal Docks

London

E16 2QJ

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 0530/0764

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/12/2006

10 DATE OF REVISION OF THE TEXT

11/12/2006

1 NAME OF THE MEDICINAL PRODUCT

Perindopril 4 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains perindopril erbumine 4 mg,(equivalent to 3.338 mg perindopril).

For excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, capsule shaped, uncoated, biconvex tablets with 'P4' engraved on one side of the tablet and the other side plain.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hypertension

Treatment of hypertension

Heart Failure

Treatment of symptomatic heart failure

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

For oral use.

It is recommended that Perindopril Tablets are taken once daily in the morning before a meal. Tablets should be swallowed whole with a glass of water.

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

Hypertension

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

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

Patients with a strongly activated 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 Special warnings and precautions for use).

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

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

Symptomatic heart failure

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

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

Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy 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 Special warnings and precautions for use).

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 Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties)

Paediatric use

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

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 Pregnancy and lactation).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

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

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Perindopril 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 Posology and method of administration) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients (see Section 4.8 Undesirable effects).

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

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

Hypersensitivity/Angioedema

Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including Perindopril Tablets (see Section 4.8 Undesirable effects). 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 Contraindications).

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

Rarely, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid

reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Anaphylactic reactions during desensitisation

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

Hepatic failure

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

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia

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

Race

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

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

Cough

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

Surgery/Anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Perindopril 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 Interaction with other medicinal products and other forms of interaction, Antidiabetics.)

Lithium

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

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

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

Lactose

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

Pregnancy and lactation

(See Section 4.3 Contraindications and Section 4.6 Pregnancy and lactation).

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 Special warnings and precautions for use). 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 Special warnings and precautions for use).

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 Special warnings and precautions for use).

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 Preclinical safety data).

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

Lactation

It is not known whether perindopril is excreted into human breast milk. Therefore the use of Perindopril 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, paresthesia

Very rare: confusion

Eye disorders:

Common: vision disturbance

Ear and labyrinth disorders:

Common: tinnitus

Cardio-vascular disorders:

Common: hypotension and effects related to hypotension

Very rare: arrhythmia, angina pectoris, myocardial infarction and stroke, possibly secondary to excessive hypotension in high risk patients (see Section 4.4 Special warnings and precautions for use).

Respiratory, thoracic and mediastinal disorders:

Common: cough, dyspnoea

Uncommon: bronchospasm

Very rare: eosinophilic pneumonia, rhinitis

Gastro-intestinal disorders:

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

Uncommon: dry mouth

Very rare: pancreatitis

Hepato-biliary disorders:

Very rare: hepatitis either cytolytic or cholestatic (see Section 4.4 Special warnings and precautions for use)

Skin and subcutaneous tissue disorders:

Common: rash, pruritus

Uncommon: angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see Section 4.4 Special warnings and precautions for use).

Very rare: erythema multiforme

Musculoskeletal, connective tissue and bone disorders:

Common: muscle cramps

Renal and urinary disorders:

Uncommon: renal insufficiency

Very rare: acute renal failure

Reproductive system and breast disorders:

Uncommon: impotence

General disorders:

Common: asthenia

Uncommon: sweating

Blood and the lymphatic system disorders:

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

Investigations:

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

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 Special warnings and precautions for use, Haemodialysis Patients). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ATC code: 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 reduce 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.

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 Section 4.2 Posology and method of administration and Section 4.4 Special warnings and precautions for use).

5.3 PRECLINICAL SAFETY DATA

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

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose (E460)

Anhydrous lactose

Silica, colloidal anhydrous

Magnesium stearate (E572)

Maize starch

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
21 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 25° C

Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER
Perindopril 4 mg Tablets are packed in clear, colourless PVC / VMCH coated aluminium foil coating containing 30 tablets.

The blisters were then packed in Aluminium pouches containing a silica gel cannister (dessicant). The sealed pouches were further packed in cartons.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Not applicable

7 MARKETING AUTHORISATION HOLDER
Norton Healthcare Limited

T/A IVAX Pharmaceuticals UK

Albert Basin

Royal Docks

London

E16 2QJ

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 0530/0765

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
11/12/2006

10 DATE OF REVISION OF THE TEXT
11/12/2006

1 NAME OF THE MEDICINAL PRODUCT

Perindopril 8 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains perindopril erbumine 8 mg,(equivalent to 6.876 mg perindopril).

For excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, round, uncoated, biconvex tablets with 'P8' engraved on one side of the tablet and the other side plain.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hypertension

Treatment of hypertension

Heart Failure

Treatment of symptomatic heart failure

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

For oral use.

It is recommended that Perindopril Tablets are taken once daily in the morning before a meal. Tablets should be swallowed whole with a glass of water.

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

Hypertension

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

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

Patients with a strongly activated 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 Special warnings and precautions for use).

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

be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.

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

Symptomatic heart failure

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

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

Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy 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 Special warnings and precautions for use).

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 Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties)

Paediatric use

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

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 Pregnancy and lactation).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

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

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Perindopril 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 Posology and method of administration) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients (see Section 4.8 Undesirable effects).

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

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

Hypersensitivity/Angioedema

Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including Perindopril Tablets (see Section 4.8 Undesirable effects). 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 Contraindications).

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

Rarely, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid

reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Anaphylactic reactions during desensitisation

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

Hepatic failure

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

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia

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

Race

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

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

Cough

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

Surgery/Anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Perindopril 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 Interaction with other medicinal products and other forms of interaction, Antidiabetics.)

Lithium

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

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

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

Lactose

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

Pregnancy and lactation

(See Section 4.3 Contraindications and Section 4.6 Pregnancy and lactation).

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 Special warnings and precautions for use). 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 Special warnings and precautions for use).

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 Special warnings and precautions for use).

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 Preclinical safety data).

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

Lactation

It is not known whether perindopril is excreted into human breast milk. Therefore the use of Perindopril 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, paresthesia

Very rare: confusion

Eye disorders:

Common: vision disturbance

Ear and labyrinth disorders:

Common: tinnitus

Cardio-vascular disorders:

Common: hypotension and effects related to hypotension

Very rare: arrhythmia, angina pectoris, myocardial infarction and stroke, possibly secondary to excessive hypotension in high risk patients (see Section 4.4 Special warnings and precautions for use).

Respiratory, thoracic and mediastinal disorders:

Common: cough, dyspnoea

Uncommon: bronchospasm

Very rare: eosinophilic pneumonia, rhinitis

Gastro-intestinal disorders:

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

Uncommon: dry mouth

Very rare: pancreatitis

Hepato-biliary disorders:

Very rare: hepatitis either cytolytic or cholestatic (see Section 4.4 Special warnings and precautions for use)

Skin and subcutaneous tissue disorders:

Common: rash, pruritus

Uncommon: angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see Section 4.4 Special warnings and precautions for use).

Very rare: erythema multiforme

Musculoskeletal, connective tissue and bone disorders:

Common: muscle cramps

Renal and urinary disorders:

Uncommon: renal insufficiency

Very rare: acute renal failure

Reproductive system and breast disorders:

Uncommon: impotence

General disorders:

Common: asthenia

Uncommon: sweating

Blood and the lymphatic system disorders:

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

Investigations:

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

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 Special warnings and precautions for use, Haemodialysis Patients). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ATC code: 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 reduce 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.

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 Section 4.2 Posology and method of administration and Section 4.4 Special warnings and precautions for use).

5.3 PRECLINICAL SAFETY DATA

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

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose (E460)

Anhydrous lactose

Silica, colloidal anhydrous

Magnesium stearate (E572)

Maize starch

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 25° C

Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER
Perindopril 8 mg Tablets are packed in clear, colourless PVC / VMCH coated aluminium foil coating containing 30 tablets.

The blisters were then packed in Aluminium pouches containing a silica gel cannister (dessicant). The sealed pouches were further packed in cartons.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Not applicable

7 MARKETING AUTHORISATION HOLDER
Norton Healthcare Limited

T/A IVAX Pharmaceuticals UK

Albert Basin

Royal Docks

London

E16 2QJ

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 0530/0766

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
11/12/2006

10 DATE OF REVISION OF THE TEXT
11/12/2006

PERINDOPRIL 2MG, 4MG, 8MG TABLETS
PL 00530/0764-66

IVAX

Perindopril 2mg, 4mg and 8mg Tablets

Patient information leaflet

Please read this leaflet carefully before you start to take your tablets.

It contains important information.

If you are not sure about anything, or you want to know more, ask your doctor or a pharmacist.

Keep this leaflet safe, as you may want to read it again.

About your tablets

Your tablets are called Perindopril Tablets and contain either 2mg, 4mg or 8mg of perindopril erbumine as the active ingredient.

What is in your tablets

Each tablet contains:

- Perindopril erbumine 2mg, 4mg or 8mg (active ingredient);
- Microcrystalline cellulose (E460), anhydrous lactose, silica colloidal anhydrous, magnesium stearate (E572) and maize starch (inactive ingredients).

Perindopril 2mg Tablets are white, round, uncoated, biconvex tablets with 'P2' engraved on one side of the tablet and the other side plain.

Perindopril 4mg Tablets are white, capsule shaped, uncoated, biconvex tablets with 'P4' engraved on one side of the tablet and the other side plain.

Perindopril 8mg Tablets are white, round, uncoated, biconvex tablets with 'P8' engraved on one side of the tablet and the other side plain.

Each strength of Perindopril is available in cartons of 30 tablets.

Your doctor may have given you this medicine before from another company and it may have looked slightly different. Either brand will have the same effect.

Who makes your tablets

The marketing authorisation holder and manufacturer is IVAX Pharmaceuticals UK, Albert Basin, Royal Docks, London, E16 2QJ, UK.

What your tablets do

Perindopril Tablets are used in the treatment of high blood pressure (hypertension). They can also be used to treat heart failure.

Perindopril Tablets belong 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.

Before you take your tablets

Do not take Perindopril Tablets if you:

- are allergic to Perindopril Tablets or any other ACE inhibitor, or to any of the other ingredients in the tablet;
- 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);
- are pregnant, planning to become pregnant or if you suspect you are pregnant;
- are breast-feeding.

Perindopril Tablets should not be given to children.

Please tell your doctor or pharmacist before you start to take Perindopril Tablets if you:

- have aortic or mitral stenosis (Heart valve disease leading to narrowing of the aortic or mitral valves) or hypertrophic cardiomyopathy (cardiac muscle disease) or renal artery stenosis (narrowing of the artery supplying the kidney with blood);
- have any other heart or liver or kidney problems, or if you are receiving dialysis;
- suffer from collagen disease such as systemic lupus erythematosus or scleroderma;
- are on a salt restricted diet or use salt substitutes which contain potassium;
- suffer from diabetes which is not well controlled;
- **have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.**

Please tell your doctor or pharmacist if you are taking any of the following:

- 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) or 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 (eg rheumatoid arthritis) or following transplant surgery;
- procainamide, a treatment for irregular heartbeat;
- non-steroidal anti-inflammatory drugs (NSAIDs) for pain relief, including aspirin;
- medicines used for the treatment of low blood pressure, shock or asthma (eg ephedrine, noradrenaline or adrenaline);
- vasodilators including nitrates (products that make the blood vessels become wider);
- heparin (used to thin the blood).

Please tell your doctor or pharmacist that you are taking Perindopril Tablets if you:

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

Driving and using machines

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.

If you see another doctor or visit a hospital, remember to tell them what medicines you are already taking. If in doubt take your medicines with you.

How to take your tablets

For oral use.

You must take your tablets as your doctor has told you to.

The label on the pack will tell you how many tablets to take and how often to take them.

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:

IVAX PAGE: 2 of 3	Product: PERINDOPRIL PIL			
	JOB Nº: 4465	SAP Nº: FP1182E	DRAFT Nº: 9	REV DATE: 16/1/06

PERINDOPRIL 2MG, 4MG, 8MG TABLETS
PL 00530/0764-66

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

In the elderly, the usual starting dose is 2mg once a day. After a month, this can be increased to 4mg a day and if necessary to 8mg a day.

Heart failure: treatment should be started under close medical supervision with 2mg once a day. After two weeks, it can be increased to 4mg 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 forget to take a dose at the right time, take it as soon as you remember. Do not take two doses together. If it is almost time to take the next dose, wait until then and then carry on as before.

Do not stop taking Perindopril Tablets unless your doctor tells you so.

What to do if you take too many tablets

It is important not to take too many tablets.

Contact your nearest Accident and Emergency department or a doctor for advice if you have swallowed too many tablets or if you think a child has swallowed any.

Take this leaflet, and any tablets that you still have to show the doctor.

After taking your tablets

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 are reported in between 1 in 10 and 1 in 100 people.

Uncommon side-effects are reported in between 1 in 100 and 1 in 1000 people.

Rare side-effects are reported in between 1 in 1000 and 1 in 10000 people.

Very rare side-effects are reported in less than 1 in 10000 people.

Common

- 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 (eg 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

- changes in mood or sleep;
- bronchospasm (tightening of 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:

Rare

- swelling of the face, lips, mouth, tongue or throat;
- difficulty in breathing;
- dizziness or fainting;
- unusually fast or irregular heartbeat.

This is 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

- 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);
- pancreatis (inflammation of the pancreas);
- hepatitis (inflammation of the liver);
- erythema multiforme (skin reaction like 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.

If you notice any other effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Looking after your tablets

Keep your tablets in a safe place where children cannot see or reach them.

Do not store above 25ºC.

Keep your tablets in the blister strips in which they are packed. Store in the original package. Do not put them into another container.

Do not take the tablets after the expiry date printed on the carton and the blister.

You should take the tablets that are out of date or which you no longer need back to your pharmacist.

These tablets are only for you. Only a doctor can prescribe them for you. Never give them to anyone else, even if they seem to have the same symptoms.

Product Licence Numbers:
Perindopril 2mg Tablets: 00530/0764
Perindopril 4mg Tablets: 00530/0765
Perindopril 8mg Tablets: 00530/0766

This leaflet was written in December 2005

FP1182E

Perindopril 2mg, 4mg and 8mg Tablets

Patient information leaflet

IVAX

IVAX PAGE: 3 of 3 | Product: PERINDOPRIL PIL | JOB Nº: 4465 | SAP Nº: FP1182E | DRAFT Nº: 9 | REV DATE: 16/1/06

PERINDOPRIL 2MG, 4MG, 8MG TABLETS
PL 00530/0764-66

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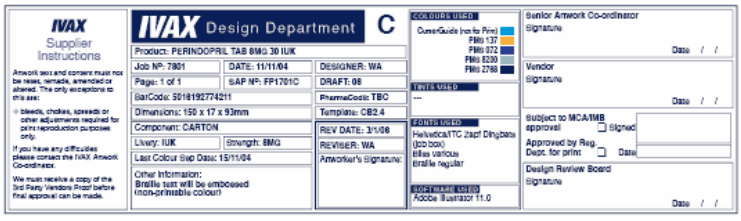
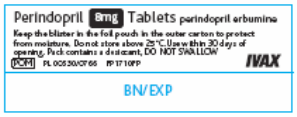
Perindopril (numeral sign) 8mg




Perindopril 8mg Tablets perindopril erbumine
Keep the blister in the foil pouch in the outer carton to protect from moisture. Do not store above 25°C. Use within 30 days of opening. Pack contains a desiccant, DO NOT SWALLOW
PL 00530/0766 FP1710FP
IVAX
BN/EXP


IVAX Supplier Instructions
IVAX Design Department C
Product: PERINDOPRIL TABS 8MG IUK
Job N°: 8753
DATE: 13/10/05
DESIGNER: WA
Page: 1 of 1
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PharmaCode: n/a
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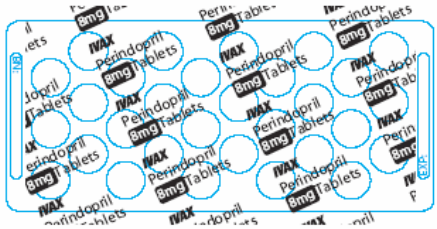
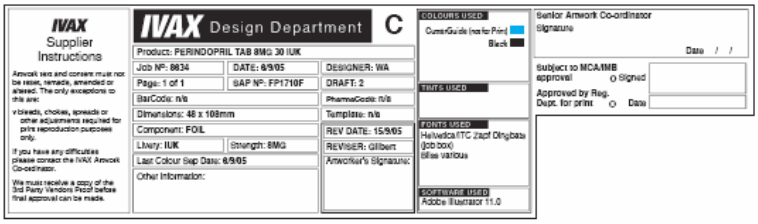

8mg
IVAX
Perindopril
Tablets
EXP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DESIGNER: WA
Page: 1 of 1
SAP N°: FP1710F
DRAFT: 2
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PharmaCode: n/a
Dimensions: 48 x 108mm
Template: n/a
Component: FOIL
REV DATE: 15/9/05
Livery: IUK
Strength: 8MG
REVISER: Gilbert
Last Colour Sep Date: 6/9/05
Artworker's Signature:
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CureGuide (not for Print)
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Bliss various
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Adobe Illustrator 11.0
Senior Artwork Co-ordinator
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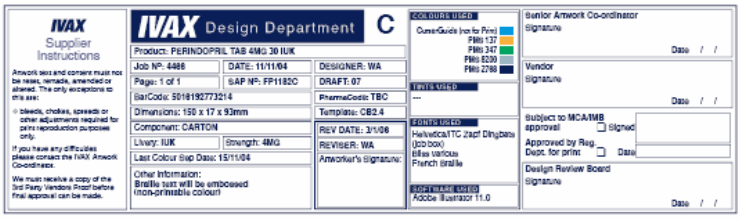
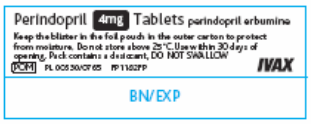
Subject to MCA/MB approval
Signed
Approved by Reg. Dept. for print
Date

Braille text reads:
Perindopril (numeral sign) 4mg




Perindopril 4mg Tablets perindopril erbumine
Keep the blister in the foil pouch in the outer carton to protect from moisture. Do not store above 25°C. Use within 30 days of opening. Pack contains a desiccant, DO NOT SWALLOW
PL 00530/0765 FP1182FP
IVAX
BN/EXP


IVAX Supplier Instructions
IVAX Design Department C
Product: PERINDOPRIL TABS 4MG IUK
Job N°: 8752
DATE: 13/10/05
DESIGNER: WA
Page: 1 of 1
SAP N°: FP1182FP
DRAFT: 8
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PharmaCode: n/a
Dimensions: 73 x 27mm
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Strength: 4MG
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Last Colour Sep Date: 13/10/05
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Other Information: —
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Signature
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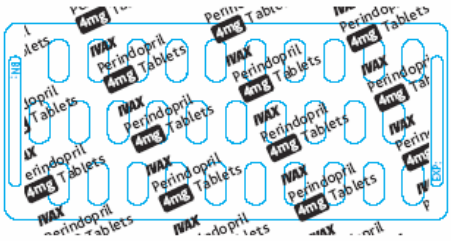
IVAX Perindopril 4mg Tablets
EXP


IVAX Supplier Instructions
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Page: 1 of 1
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REVISER: GC
Last Colour Sep Date: 11/11/04
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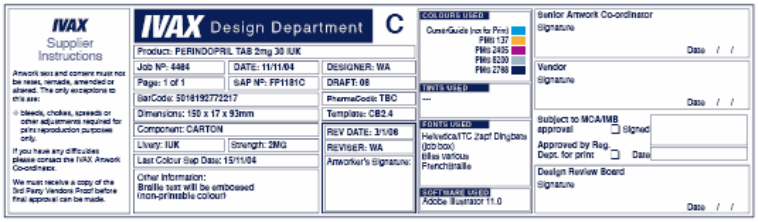

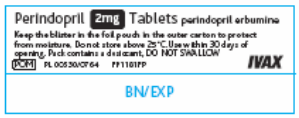
Perindopril 2mg Tablets perindopril erbumine
Keep the blister in the foil pouch in the outer carton to protect from moisture. Do not store above 25°C. Use within 30 days of opening. Pack contains a desiccant, DO NOT SWALLOW
PL 00530/0764 FP1181FP
IVAX
BN/EXP


IVAX Supplier Instructions
IVAX Design Department C
Product: PERINDOPRIL TABS 2MG IUK
Job N°: 8751
DATE: 13/10/05
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Page: 1 of 1
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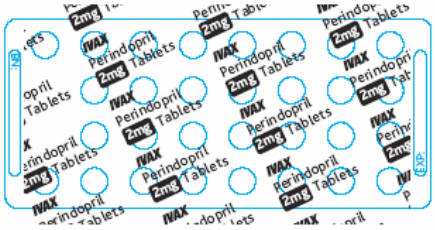
2mg Perindopril Tablets
IVAX
EXP


IVAX Supplier Instructions
IVAX Design Department C
Product: PERINDOPRIL TAB 2MG 30 IUK
Job N°: 4483
DATE: 11/11/04
DESIGNER: WA
Page: 1 of 1
SAP N°: FP1181F
DRAFT: 4
BarCode: n/a
PharmaCode: n/a
Dimensions: 108 x 48mm
Template: n/a
Component: FOIL
REV DATE: 15/5/05
Livery: IUK
Strength: 2MG
REVISER: GC
Last Colour Sep Date: 11/11/04
Artworker's Signature:
Other Information: —
COLOURS USED
CutterGuide (not for Print)
Black
TINTS USED
FONTS USED
Helvetica/ITC Zapf Dingbats (job box)
Bitstream Various
SOFTWARE USED
Adobe Illustrator 11.0
Senior Artwork Co-ordinator Signature
Date
Vendor Signature
Date
Subject to MCA/IMB approval
Signed
Approved by Reg. Dept. for print
Date
Design Review Board Signature
Date