

PERINDOPRIL 2MG TABLETS

PL 08137/0208

PERINDOPRIL 4MG TABLETS

PL 08137/0209

PERINDOPRIL 8MG TABLETS

PL 08137/0210

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PERINDOPRIL 2MG TABLETS

PL 08137/0208

PERINDOPRIL 4MG TABLETS

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PERINDOPRIL 8MG TABLETS

PL 08137/0210

LAY SUMMARY

The MHRA today granted Neolab Limited Marketing Authorisations (licences) for the medicinal products Perindopril 2mg Tablets (PL 08137/0208). , Perindopril 4mg Tablets (PL 08137/0209), and Perindopril 8mg Tablets. (PL 08137/0210). These are prescription only medicines (POM) are used to treat a condition where the heart is unable to pump enough blood to meet the body's needs (heart failure) , a condition where the blood supply to the heart is reduced or blocked (coronary artery disease) and to reduce elevated blood pressure.

Perindopril Tablets contain the active substance as the perindopril erbumine as monohydrate.

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

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

PERINDOPRIL 2MG TABLETS

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PERINDOPRIL 4MG TABLETS

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PERINDOPRIL 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 Neolab Limited on 23rd of October 2007. The products are prescription only medicines.

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

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

Perindopril is an inhibitor of the enzyme that converts angiotensin I into angiotensin II (Angiotensin Converting Enzyme ACE). It is possible that this mechanism contributes to the blood pressure-lowering action of ACE inhibitors and is partially responsible for certain of their side effects (e.g. cough).

PHARMACEUTICAL ASSESSMENT

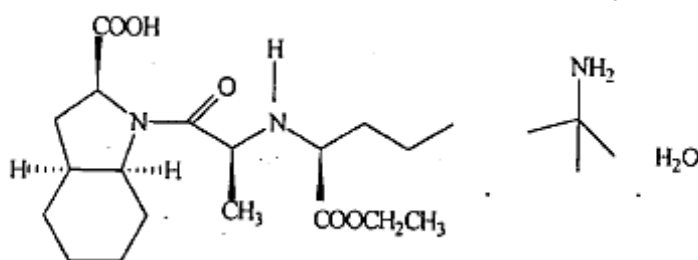
DRUG SUBSTANCE

INN: Perindopril erbumine

Ph Eur: Perindopril *tert*-butylamine

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

Structure



Molecular formula: C₂₃H₄₃N₃O₅·H₂O

Molecular Mass: 459.6 g/mol

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

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

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

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

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

All potential known impurities have been identified and characterised.

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

Active perindopril erbumine monohydrate is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

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

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

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely Mannitol, Sodium starch glycolate (Type A), Anhydrous sodium carbonate, Hypromellose, Macrogol, Purified Talc, Simeticone, Magnesium stearate, Hypromellose, Lecithin, Titanium dioxide E171, Xanthan gum, and Polyvinyl alcohol

All excipients used comply with their respective European Pharmacopoeia monograph with the exception of Lecithin, Titanium dioxide E171, Xanthan gum, and Polyvinyl alcohol which comply with in-house specifications. Satisfactory specifications and Certificates of Analysis have been provided for all excipients.

The current TSE certificate for Magnesium Stearate has been provided.

Dissolution

Dissolution and impurity profiles for all strengths of drug products support the pharmaceutical equivalence of the proposed products with those of the reference products. Relative product composition and dissolution profiles also support extrapolation of conclusions of the bioequivalence study to the 2 and 4mg strength tablets.

Manufacturer(s)

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

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

Finished product specification

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

Container Closure system

Product is packaged in aluminium foil coated with polyamide on one side and PVC on the other side. The proposed package sizes are 28, and 30 Tablets. Specifications and Certificates of Analysis for all packaging used have been provided. This is satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf life of 2 years with Storage conditions of "Protect from moisture", "Store in the original package" and "Do not store above 30 degree C" have been set and these are satisfactory.

Conclusion

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

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

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

1 CLINICAL PHARMACOLOGY

1.1 PHARMACOKINETICS

1.1.1 Absorption

After oral administration, the absorption of perindopril is rapid and the peak concentration achieved within 1 hour. Bioavailability is 65 to 70 %. The plasma half-life of perindopril is 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.

1.1.2 Distribution

Protein binding is slight (binding of perindoprilat to angiotensin converting enzyme is less than 30%), but is concentration-dependent.

1.1.3 Metabolism

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.

1.1.4 Excretion

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.

1.1.5 Special populations

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). 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

1.2 BIOEQUIVALENCE

1.2.1 Pharmaceutical details

The reference product is Coversyl 8 mg Tablets sourced from the UK and the test product is 8 mg tablet. The test product was from a batch of 100000 tablets which was acceptable given that the maximum production batch size is up to 1000000. The test product is considered to be representative of the product proposed for marketing. Satisfactory Certificates of Analysis for the test and reference products were provided.

A biostudy was only performed using the 8 mg strength and this was acceptable as adequate evidence was provided that all of the criteria in the Note for Guidance (CPMP/EWP/QWP1401/98) were met and the pharmacokinetics of perindopril are linear over the proposed strength tablets (2-8 mg). Bioequivalence has been demonstrated using a pilot-scale batch of perindopril 8 mg.

Perindopril and perindoprilat were analysed using a LC-MS/MS after solid phase extraction.

A validation report for perindopril and perindoprilat was provided and was generally acceptable. The LOQ for perindopril and perindoprilat was 4.8 ng/ml and 0.38 ng/ml, respectively.

1.2.2 Method

A randomised, open label, two-treatment, two-sequence, two-period, two-way crossover, single dose bioequivalence study was performed in 32 (4 standbys, 2 of which were excluded from analysis) healthy, adult, male, human volunteers. The number of volunteers required to detect a difference with a power of 0.8 for $C_{\max}$ and AUC was calculated as 28.

Volunteers were randomised to one of the possible sequences and the randomisation was balanced for sequence.

A single 8 mg tablet of test and reference products was administered with 240 ml of water. Subjects were dosed after an overnight fast which was consistent with the SPC which recommends taking the tablets on an empty stomach.

The washout period was 13 days which was adequate given that only subject 19 had pre-dose levels of perindoprilat.

Samples were taken pre-dose and over 144 hours which was sufficient for adequate estimation of AUC for both perindopril and perindoprilat although perindoprilat levels did not return to baseline.

Samples were taken every 15 minutes from 0-1.5 hour and then every 30 minutes from 1.5 to 5 hours to accurately estimate the $C_{\max}$ for perindopril and its active metabolite (expected $T_{\max}$ for perindopril is 1 hour and 3-4 hours for its active metabolite). This was supported by the concentration-time curves for individual volunteers.

The protocol specified bioequivalence acceptance ranges of 80-125% for AUC and $C_{\max}$, but also stated that if the data for $C_{\max}$ were found to be more variable than anticipated the use of wider acceptance criteria would be considered (75-133%). This approach is not acceptable, but given that all the data within the tighter range this is not a concern.

An adequate statistical plan was provided and the planned statistical methods were conventional. Log-transformed data for $AUC_{(0-t)}$, $AUC_{(0-inf)}$, and $C_{\max}$ were analysed by ANOVA. $T_{\max}$ was analysed using the Wilcoxon-Mann-Whitney two one-sided test.

1.2.3 Study Outcome and Results

The 90% confidence intervals for the test/reference lie within the acceptance criteria specified in the CPMP/EWP/QWP/1401/98 Note for Guidance and with those pre-specified in the study protocol. The results for main pharmacokinetic parameters are reported as follows.

Table 1 Perindopril and perindoprilat pharmacokinetic data

Variable	Cipla 8 mg tablets (test)	Coversyl 8 mg tablets (reference)	Point Estimate (Test/reference) (%)	90 % C.I.
<i>Perindopril (n=28)</i>				
C_{max} (ng/ml)	106.7 ± 34.7	116.7 ± 32.1	90.4	82.6 – 99.0
AUC _(0-t) (ngh/ml)	133.5 ± 38.9	128.2 ± 33.9	103.8	98.0 – 110.0
AUC _(0-inf) (ngh/ml)	139.8 ± 38.6	134.8 ± 33.9	103.4	98.1 – 108.9
T_{max} (h)	1.0 ± 0.6	0.7 ± 0.2	-	-
T_{el} (h)	0.7 ± 0.1	0.7 ± 0.1	-	-
<i>Perindoprilat (n=28)</i>				
C_{max} (ng/ml)	12.6 ± 5.9	11.1 ± 4.8	112.2	103.8 – 121.1
AUC _(0-t) (ngh/ml)	255.0 ± 49.7	235.9 ± 40.2	107.7	103.5 – 112.08
AUC _(0-inf) (ngh/ml)	287.5 ± 56.2	267.9 ± 49.0	107.1	102.2 – 112.4
T_{max} (h)	5.4 ± 1.8	5.4 ± 1.6	-	-
T_{el} (h)	43.7 ± 18.9	43.0 ± 20.6	-	-

Data presented are arithmetic mean ± SD

None of the volunteers had pre-dose levels in period II for perindopril and only one volunteer had a pre-dose level for perindoprilat which was very near the LOQ (0.42 ng/ml). For perindoprilat there were statistically significant treatment effects for C_{max} and AUC (also statistically different period effects), but given that these were not associated with statistically significant sequence effects these were of no consequence.

Assessor's Conclusion on Bioequivalence

Bioequivalence of the test product to the reference formulation has been demonstrated in accordance with CHMP criteria.

The multiple dose waiver criteria are met and hence this study is accepted as demonstrating bioequivalence for the other product strengths.

The expert is medically qualified and the expert non-clinical and clinical reports were adequate.

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 TABLETS**PL 08137/0208****PERINDOPRIL 4MG TABLETS****PL 08137/0209****PERINDOPRIL 8MG TABLETS****PL 08137/0210****STEPS TAKEN FOR ASSESMENT**

1	The MHRA received the marketing authorisation applications on 11 th August 2006
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 31 st January 2007
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 15th March 2007 and 30 th August 2007
4	The applicant responded to the MHRA's requests, providing further information relating to the quality dossier on 18 th July 2007 and 14 th September 2007
5	The applications were determined on 23 rd October 2007

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

Perindopril 2 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg perindopril erbumine (as perindopril erbumine monohydrate), equivalent to 1.669 mg perindopril.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (Tablet).

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

4 CLINICAL PARTICULARS**4.1 THERAPEUTIC INDICATIONS**Hypertension

Treatment of hypertension.

Heart Failure

Treatment of symptomatic heart failure.

Stable Coronary Artery Disease

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

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

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

The dose should be individualised according to the patient profile (see 4.4 “Special warnings and special 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 special 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 4.4 “Special warnings and special precautions for use”).

Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with Perindopril 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 special precautions for use”).

Stable coronary artery disease

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

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

Dosage adjustment in renal impairment

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

Table 1: dosage adjustment in renal impairment

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

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

Dosage adjustment in hepatic impairment

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

Paediatric use (under the age of 18 years)

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

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USEStable coronary artery disease

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

Hypotension

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

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

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Perindopril 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 4.2 “Posology and method of administration”) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients (see 4.8 “Undesirable effects”).

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

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these

patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of Perindopril Tablets therapy.

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

Haemodialysis patients

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

Kidney transplantation

There is no experience regarding the administration of Perindopril Tablets in patients with 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 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 4.3 Contraindications).

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

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

Anaphylactic reactions during desensitisation

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

Hepatic failure

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

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia

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

Race

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

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

Cough

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is 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 4.5 Interaction with other medicinal products and other forms of interaction, Antidiabetics.)

Lithium

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

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

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

Pregnancy and lactation

(See section 4.3 “Contraindications” and section 4.6 “Pregnancy and lactation”).

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Diuretics

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

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

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

Lithium

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

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

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

Antihypertensive agents and vasodilators

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

Antidiabetic agents

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

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates

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

Tricyclic antidepressants/Antipsychotics/Anaesthetics

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

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

4.6 PREGNANCY AND LACTATION

Pregnancy

Perindopril Tablets should not be used during the first trimester of pregnancy. When a pregnancy is planned or confirmed, the switch to an alternative treatment should be initiated as soon as possible. Controlled studies with ACE inhibitors have not been done in humans, but in

a limited number of cases with first trimester exposure there do not appear to have been any malformations consistent with human foetotoxicity as described below.

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

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

Very rare: confusion.

Eye disorders:

Common: vision disturbance.

Ear and labyrinth disorders:

Common: tinnitus.

Cardio-vascular disorders:

Common: hypotension and effects related to hypotension

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

Respiratory, thoracic and mediastinal disorders:

Common: cough, dyspnoea.

Uncommon: bronchospasm.

Very rare: eosinophilic pneumonia, rhinitis.

Gastro-intestinal disorders:

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

Uncommon: dry mouth.

Very rare: pancreatitis.

Hepato-biliary disorders:

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

Skin and subcutaneous tissue disorders:

Common: rash, pruritus.

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

Very rare: erythema multiforme.

Musculoskeletal, connective tissue and bone disorders:

Common: muscle cramps.

Renal and urinary disorders:

Uncommon: renal insufficiency.

Very rare: acute renal failure.

Reproductive system and breast disorders:

Uncommon: impotence.

General disorders:

Common: asthenia.

Uncommon: sweating.

Blood and the lymphatic system disorders:

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

Investigations:

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

Clinical trials

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

4.9 OVERDOSE

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

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis. (See 4.4 Special warnings and special precautions for use, Haemodialysis Patients.) Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES**5.1 PHARMACODYNAMIC PROPERTIES**

ATC code: C09A A04.

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

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

Hypertension

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

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

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

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

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

Discontinuation of treatment does not lead to a rebound effect.

Perindopril reduces left ventricular hypertrophy.

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

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

Heart failure

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

Studies in patients with heart failure have demonstrated:

- decreased left and right ventricular filling pressures,
- reduced total peripheral vascular resistance,
- increased cardiac output and improved cardiac index.

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

Patients with stable coronary artery disease

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

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

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

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

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

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

5.2 PHARMACOKINETIC PROPERTIES

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

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

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

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

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

After repeated administration, no accumulation of perindopril is observed.

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

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

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

5.3 PRECLINICAL SAFETY DATA

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

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

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

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

6 PHARMACEUTICAL PARTICULARS**6.1 LIST OF EXCIPIENTS**Tablet core:

Mannitol

Sodium starch glycolate (Type A)

Anhydrous sodium carbonate

Hypromellose

Macrogol

Purified Talc

Simeticone

Magnesium stearate

Tablet coat:

Hypromellose

Lecithin

Purified Talc

Titanium dioxide E171

Xanthan gum

Polyvinyl alcohol

6.2 INCOMPATIBILITIES

None.

6.3 SHELF LIFE

2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30° C. Store in the original package to protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Blister strips comprising OPA/Aluminium/PVC foil and Aluminium foil in an outer carton.
Pack sizes of 28 or 30 tablets (not all packs may be marketed).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Neolab Limited

57 High Street

Odiham

Hants

RG29 1LF

8 MARKETING AUTHORISATION NUMBER(S)

PL 08137/0208

- 9** **DATE OF FIRST AUTHORISATION/RENEWAL OF THE** **AUTHORISATION**
23/10/2007
- 10** **DATE OF REVISION OF THE TEXT**
23/10/2007

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

Perindopril 4 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (Tablet).

Perindopril 4 mg Tablets are white to off white, barrel shaped, biconvex film coated tablets, one side debossed with 'PR' and '4' on either side of a central score line and with a central score line on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS**4.1 THERAPEUTIC INDICATIONS**Hypertension

Treatment of hypertension.

Heart Failure

Treatment of symptomatic heart failure.

Stable Coronary Artery Disease

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

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

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

The dose should be individualised according to the patient profile (see 4.4 "Special warnings and special 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 special 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 4.4 “Special warnings and special precautions for use”).

Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with Perindopril 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 special precautions for use”).

Stable coronary artery disease

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

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

Dosage adjustment in renal impairment

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

Table 1: dosage adjustment in renal impairment

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

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

Dosage adjustment in hepatic impairment

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

Paediatric use (under the age of 18 years)

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

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USEStable coronary artery disease

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

Hypotension

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

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

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Perindopril 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 4.2 “Posology and method of administration”) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients (see 4.8 “Undesirable effects”).

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

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

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

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

Haemodialysis patients

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

Kidney transplantation

There is no experience regarding the administration of Perindopril Tablets in patients with 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 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 4.3 Contraindications).

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

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

Anaphylactic reactions during desensitisation

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

Hepatic failure

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

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia

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

Race

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

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

Cough

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is 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 4.5 Interaction with other medicinal products and other forms of interaction, Antidiabetics.)

Lithium

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

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

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

Pregnancy and lactation

(See section 4.3 “Contraindications” and section 4.6 “Pregnancy and lactation”).

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Diuretics

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

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

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

Lithium

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

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

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

Antihypertensive agents and vasodilators

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

Antidiabetic agents

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

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates

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

Tricyclic antidepressants/Antipsychotics/Anaesthetics

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

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

4.6 PREGNANCY AND LACTATION

Pregnancy

Perindopril Tablets should not be used during the first trimester of pregnancy. When a pregnancy is planned or confirmed, the switch to an alternative treatment should be initiated as soon as possible. Controlled studies with ACE inhibitors have not been done in humans, but in

a limited number of cases with first trimester exposure there do not appear to have been any malformations consistent with human foetotoxicity as described below.

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

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

Very rare: confusion.

Eye disorders:

Common: vision disturbance.

Ear and labyrinth disorders:

Common: tinnitus.

Cardio-vascular disorders:

Common: hypotension and effects related to hypotension

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

Respiratory, thoracic and mediastinal disorders:

Common: cough, dyspnoea.

Uncommon: bronchospasm.

Very rare: eosinophilic pneumonia, rhinitis.

Gastro-intestinal disorders:

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

Uncommon: dry mouth.

Very rare: pancreatitis.

Hepato-biliary disorders:

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

Skin and subcutaneous tissue disorders:

Common: rash, pruritus.

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

Very rare: erythema multiforme.

Musculoskeletal, connective tissue and bone disorders:

Common: muscle cramps.

Renal and urinary disorders:

Uncommon: renal insufficiency.

Very rare: acute renal failure.

Reproductive system and breast disorders:

Uncommon: impotence.

General disorders:

Common: asthenia.

Uncommon: sweating.

Blood and the lymphatic system disorders:

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

Investigations:

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

Clinical trials

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

4.9 OVERDOSE

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

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis. (See 4.4 Special warnings and special precautions for use, Haemodialysis Patients.) Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES**5.1 PHARMACODYNAMIC PROPERTIES**

ATC code: C09A A04.

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

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

Hypertension

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

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

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

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

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

Discontinuation of treatment does not lead to a rebound effect.

Perindopril reduces left ventricular hypertrophy.

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

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

Heart failure

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

Studies in patients with heart failure have demonstrated:

- decreased left and right ventricular filling pressures,
- reduced total peripheral vascular resistance,
- increased cardiac output and improved cardiac index.

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

Patients with stable coronary artery disease

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

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

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

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

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

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

5.2 PHARMACOKINETIC PROPERTIES

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

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

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

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

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

After repeated administration, no accumulation of perindopril is observed.

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

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

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

5.3 PRECLINICAL SAFETY DATA

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

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

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

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

6 PHARMACEUTICAL PARTICULARS**6.1 LIST OF EXCIPIENTS**Tablet core:

Mannitol

Sodium starch glycolate (Type A)

Anhydrous sodium carbonate

Hypromellose

Macrogol

Purified Talc

Simeticone

Magnesium stearate

Tablet coat:

Hypromellose

Lecithin

Purified Talc

Titanium dioxide E171

Xanthan gum

Polyvinyl alcohol

6.2 INCOMPATIBILITIES

None.

6.3 SHELF LIFE

2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30° C. Store in the original package to protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Blister strips comprising OPA/Aluminium/PVC foil and Aluminium foil in an outer carton.
Pack sizes of 28 or 30 tablets (not all packs may be marketed).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Neolab Limited

57 High Street

Odiham

Hants

RG29 1LF

8 MARKETING AUTHORISATION NUMBER(S)

PL 08137/0209

- 9** **DATE OF FIRST AUTHORISATION/RENEWAL OF THE** **AUTHORISATION**
23/10/2007
- 10** **DATE OF REVISION OF THE TEXT**
23/10/2007

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

Perindopril 8 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 8 mg perindopril erbumine (as perindopril erbumine monohydrate), equivalent to 6.676 mg perindopril.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (Tablet)

Perindopril 8 mg Tablets are white to off white, barrel shaped, biconvex film coated tablets, one side debossed with 'PR' and '8' on either side of a central score line and with a central score line on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS**4.1 THERAPEUTIC INDICATIONS**Hypertension

Treatment of hypertension.

Heart Failure

Treatment of symptomatic heart failure.

Stable Coronary Artery Disease

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

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

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

The dose should be individualised according to the patient profile (see 4.4 "Special warnings and special 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 special 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 4.4 “Special warnings and special precautions for use”).

Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with Perindopril 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 special precautions for use”).

Stable coronary artery disease

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

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

Dosage adjustment in renal impairment

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

Table 1: dosage adjustment in renal impairment

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

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

Dosage adjustment in hepatic impairment

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

Paediatric use (under the age of 18 years)

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

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**Stable coronary artery disease**

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

Hypotension

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

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

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Perindopril 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 4.2 “Posology and method of administration”) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients (see 4.8 “Undesirable effects”).

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

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these

patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of Perindopril Tablets therapy.

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

Haemodialysis patients

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

Kidney transplantation

There is no experience regarding the administration of Perindopril Tablets in patients with 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 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 4.3 Contraindications).

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

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

Anaphylactic reactions during desensitisation

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

Hepatic failure

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

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia

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

Race

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

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

Cough

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is 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 4.5 Interaction with other medicinal products and other forms of interaction, Antidiabetics.)

Lithium

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

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

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

Pregnancy and lactation

(See section 4.3 “Contraindications” and section 4.6 “Pregnancy and lactation”).

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Diuretics

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

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

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

Lithium

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

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

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

Antihypertensive agents and vasodilators

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

Antidiabetic agents

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

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates

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

Tricyclic antidepressants/Antipsychotics/Anaesthetics

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

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

4.6 PREGNANCY AND LACTATION

Pregnancy

Perindopril Tablets should not be used during the first trimester of pregnancy. When a pregnancy is planned or confirmed, the switch to an alternative treatment should be initiated as soon as possible. Controlled studies with ACE inhibitors have not been done in humans, but in

a limited number of cases with first trimester exposure there do not appear to have been any malformations consistent with human foetotoxicity as described below.

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

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

Very rare: confusion.

Eye disorders:

Common: vision disturbance.

Ear and labyrinth disorders:

Common: tinnitus.

Cardio-vascular disorders:

Common: hypotension and effects related to hypotension

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

Respiratory, thoracic and mediastinal disorders:

Common: cough, dyspnoea.

Uncommon: bronchospasm.

Very rare: eosinophilic pneumonia, rhinitis.

Gastro-intestinal disorders:

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

Uncommon: dry mouth.

Very rare: pancreatitis.

Hepato-biliary disorders:

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

Skin and subcutaneous tissue disorders:

Common: rash, pruritus.

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

Very rare: erythema multiforme.

Musculoskeletal, connective tissue and bone disorders:

Common: muscle cramps.

Renal and urinary disorders:

Uncommon: renal insufficiency.

Very rare: acute renal failure.

Reproductive system and breast disorders:

Uncommon: impotence.

General disorders:

Common: asthenia.

Uncommon: sweating.

Blood and the lymphatic system disorders:

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

Investigations:

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

Clinical trials

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

4.9 OVERDOSE

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

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis. (See 4.4 Special warnings and special precautions for use, Haemodialysis Patients.) Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES**5.1 PHARMACODYNAMIC PROPERTIES**

ATC code: C09A A04.

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

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

Hypertension

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

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

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

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

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

Discontinuation of treatment does not lead to a rebound effect.

Perindopril reduces left ventricular hypertrophy.

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

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

Heart failure

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

Studies in patients with heart failure have demonstrated:

- decreased left and right ventricular filling pressures,
- reduced total peripheral vascular resistance,
- increased cardiac output and improved cardiac index.

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

Patients with stable coronary artery disease

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

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

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

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

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

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

5.2 PHARMACOKINETIC PROPERTIES

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

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

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

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

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

After repeated administration, no accumulation of perindopril is observed.

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

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

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

5.3 PRECLINICAL SAFETY DATA

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

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

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

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

6 PHARMACEUTICAL PARTICULARS**6.1 LIST OF EXCIPIENTS**Tablet core:

Mannitol

Sodium starch glycolate (Type A)

Anhydrous sodium carbonate

Hypromellose

Macrogol

Purified Talc

Simeticone

Magnesium stearate

Tablet coat:

Hypromellose

Lecithin

Purified Talc

Titanium dioxide E171

Xanthan gum

Polyvinyl alcohol

6.2 INCOMPATIBILITIES

None.

6.3 SHELF LIFE

2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30° C. Store in the original package to protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Blister strips comprising OPA/Aluminium/PVC foil and Aluminium foil in an outer carton.
Pack sizes of 28 or 30 tablets (not all packs may be marketed).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Neolab Limited

57 High Street

Odiham

Hants

RG29 1LF

8 MARKETING AUTHORISATION NUMBER(S)

PL 08137/0210

- 9** **DATE OF FIRST AUTHORISATION/RENEWAL OF THE** **AUTHORISATION**
23/10/2007
- 10** **DATE OF REVISION OF THE TEXT**
23/10/2007

PATIENT INFORMATION LEAFLET
PERINDOPRIL 2, 4 & 8 mg TABLETS
(Perindopril erbumine)



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

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

In this leaflet:

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

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

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

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

2. BEFORE YOU TAKE PERINDOPRIL TABLETS

Do not take Perindopril Tablets if:

- you are **allergic (hypersensitive)** to perindopril, other ACE inhibitors, or to any of the other ingredients in the tablets (these are listed in Section 6, Further Information)
- you have had symptoms such as **wheezing, swelling of the face, tongue or throat, intense itching, skin rashes, fainting or dizziness** with previous ACE inhibitor treatment or have had these symptoms in any other circumstances (this is a condition called angioedema)
- you are **pregnant**, planning to become pregnant or you suspect you are pregnant
- you are **breast-feeding**

Take special care with Perindopril Tablets

Before you take Perindopril Tablets you should tell your doctor:

- if you have **aortic stenosis** (narrowing of the main blood vessel leading from the heart) or **hypertrophic cardiomyopathy** (cardiac muscle disease) or **renal artery stenosis** (narrowing of the artery supplying the kidney with blood)
- if you have any other **heart or liver or kidney problems**, or if you are **receiving dialysis**
- if you suffer from a **collagen disease** such as systemic lupus erythematosus or scleroderma
- if you are on a **salt restricted diet** or **use salt substitutes which contain potassium**
- if you suffer from **diabetes** which is not well controlled
- if you are to undergo **anaesthesia** and/or surgery
- if you have suffered from **recent diarrhoea or vomiting**
- if you are going to have **desensitisation treatment** to reduce the effects of an allergy to bee or wasp stings
- if you are to undergo **LDL apheresis** (which is removal of cholesterol from your blood by a machine).

Taking other medicines

You should tell your doctor if you are taking or have taken any of the following medicines as they may decrease or increase the effect of your Perindopril Tablets.

- other medicines for treating high blood pressure including diuretics (water tablets)
- potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride); potassium supplements and potassium-containing salt substitutes
- medicines for the treatment of diabetes (insulin or tablets) to lower blood sugar
- lithium for mania or depression
- medicines for the treatment of mental disorders such as depression, anxiety, schizophrenia or other psychoses
- allopurinol used for the treatment of gout (painful joints due to a build up of uric acid)
- immunosuppressants used for the treatment of auto-immune disorders (e.g. 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 (e.g. ephedrine, noradrenaline or adrenals)
- vasodilators including nitrates (products that make the blood vessels become wider)
- heparin (used to thin the blood).

It may still be all right for you to take Perindopril Tablets and your doctor will be able to decide what is suitable for you. Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking your medicine with food and alcohol:

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

Pregnancy and breast-feeding

If you are pregnant, likely to become pregnant or are breast-feeding, you must tell your doctor before taking this medicine and your doctor will decide if this medicine is right for you. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

The tablets may make you feel dizzy or tired. You should not drive or use machinery if affected.

3. HOW TO TAKE PERINDOPRIL TABLETS

Dosage

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

Always take Perindopril Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The label on the carton will tell you how many tablets you should take and when.

Please continue reading the back of this leaflet for the rest of the dosage information and the remainder of the leaflet.

AGS/A

The usual doses for Perindopril Tablets are as follows:

High blood pressure:

- The usual starting and maintenance dose for treatment in adults is 4 mg once a day. After a month, this can be increased to 8 mg a day which is the maximum recommended dose.
- If you are 65 or over, the usual starting dose is 2 mg once a day. After a month, this can be increased to 4 mg a day and if necessary to 8 mg a day. Your doctor may give you a blood test to check that your kidneys are working properly before increasing the dose to 8 mg.

Heart failure:

- Treatment should be started under close medical supervision with 2 mg once a day. After two weeks, it can be increased to 4 mg once a day if required.

Stable coronary artery disease:

- The usual starting dose is 4 mg once daily. After two weeks and if 4 mg is well tolerated, this can be increased to 8 mg once daily.
- If you are 65 or over, the usual starting dose is 2 mg once daily. After one week, this can be increased to 4 mg once daily and after a further week to 8 mg once daily. Your doctor may give you a blood test to check that your kidneys are working properly before increasing the dose to 8 mg.

Treatment for these conditions is usually life-long.

Perindopril Tablets are not suitable for use in children (under the age of 18).

Method of Administration

Take your tablet(s) with a glass of water, preferably at the same time each day, in the morning, before a meal. If you are taking water tablets (diuretics), your doctor may decide to reduce or even discontinue these at the beginning of your treatment with Perindopril Tablets.

If you take more Perindopril Tablets than you should:

If you have accidentally taken more than your prescribed dose, contact your casualty emergency department or tell your doctor or pharmacist **immediately**. Remember to take the pack and any remaining tablets with you. The most common signs and symptoms of overdose are a fall in blood pressure (causing dizziness and light-headedness) and stupor (a state of almost complete lack of consciousness). Other symptoms may include a forceful and rapid heartbeat, rapid pulse, anxiety, cough and rapid breathing.

If you forget to take Perindopril Tablets:

It is important to take your medicine every day. However, if you forget to take one or more doses, take another as soon as you remember and then go on as prescribed. Do not take a double dose to make up for a forgotten dose.

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

4. POSSIBLE SIDE-EFFECTS

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

All medicines can cause allergic reactions although serious allergic reactions are very rare. **If you get any of the following symptoms after taking these tablets, you should stop taking the tablets and contact your doctor immediately:**

- Any sudden wheeziness, difficulty in breathing or dizziness, swelling of the eyelids, face, lips or throat
- Peeling and blistering of the skin, mouth, eyes and genitals
- Rash affecting your whole body.

The following side effects have also been reported:

Common side effects (probably affecting up to 1 in 10 people)

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

Uncommon side effects (probably affecting fewer than 1 in 100 people)

- changes in mood or sleep
- bronchospasm (tightening of the chest, wheezing and shortness of breath)
- dry mouth
- kidney problems
- impotence (inability to achieve or sustain an erection)
- sweating

Very rare side effects (probably affecting fewer than 1 in 10,000 people)

- 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)
- pancreatitis (inflammation of the pancreas)
- hepatitis (inflammation of the liver which can cause a yellowing of the skin and eyes)
- changes in the blood: your doctor may decide to carry out blood tests at intervals to monitor for this
- allergic reactions (described above)

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

5. HOW TO STORE PERINDOPRIL TABLETS

Do not store your tablets above 30°C. Store in the original package to protect the tablets from moisture. Do not take this medicine after the expiry date shown on the carton. The expiry date refers to the last day of that month.

Keep all medicines out of the reach and sight of children.

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

6. FURTHER INFORMATION

What Perindopril Tablets contain:

The active substance is perindopril erbumine (as monohydrate). Each tablet contains 2, 4 or 8 mg of perindopril erbumine.

The other ingredients are mannitol, sodium starch glycolate, sodium carbonate, hypromellose, macrogol, talc, simeticone, magnesium stearate, lecithin, titanium dioxide (E171), xanthan gum and polyvinyl alcohol.

What Perindopril Erbumine Tablets look like and the contents of the pack:

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

Perindopril 4 mg Tablets are white to off white, barrel shaped, biconvex film coated tablets, one side debossed with 'PR' and '4' on either side of a central score line and with a central score line on the other side. The score line is only to enable a tablet to be broken in half for ease of swallowing and not to divide into equal doses.

Perindopril 8 mg Tablets are white to off white, barrel shaped, biconvex film coated tablets, one side debossed with 'PR' and '8' on either side of a central score line and with a central score line on the other side. The score line is only to enable a tablet to be broken in half for ease of swallowing and not to divide into equal doses.

Your medicine is available in blister packs of 28 or 30 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer:

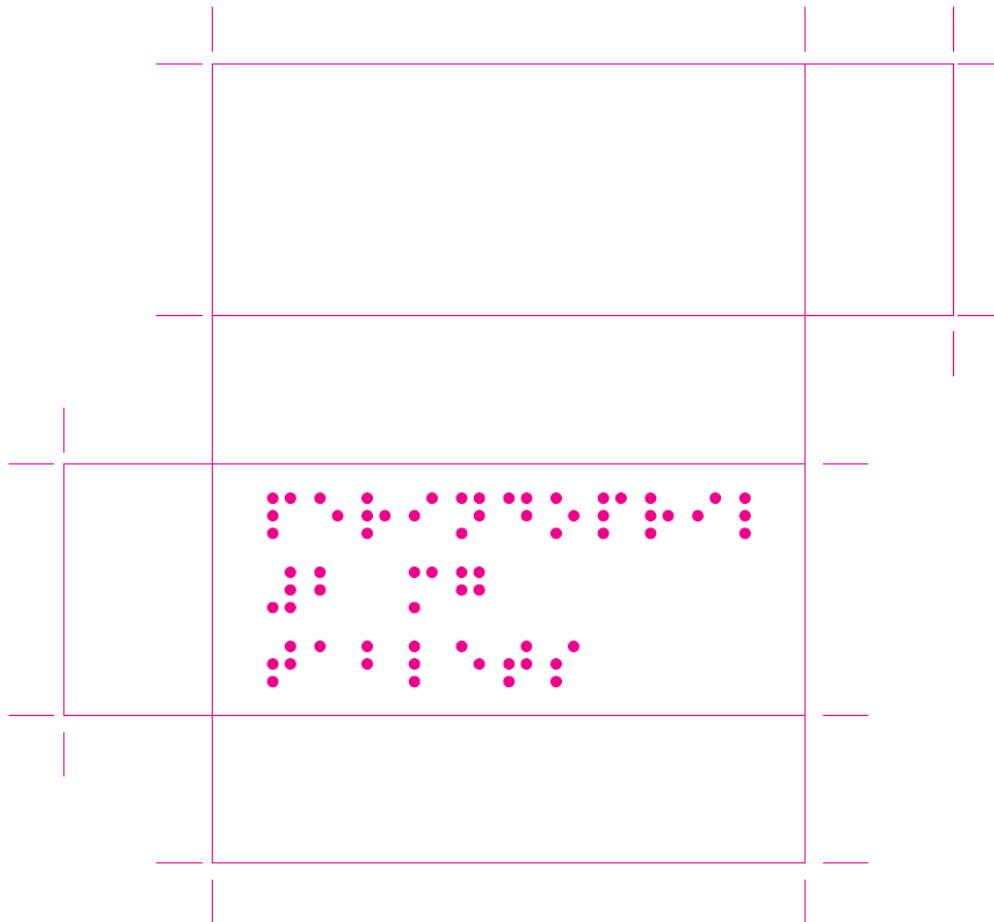
The Product Licence Holder and manufacturer responsible for batch release is Neolab Ltd, 57 High Street, Odiham, Hants, RG29 1LF.

This leaflet was last approved in August 2007.

N/PR-1-L

AG05A





perindopril

Number sign → 2 mg

tablets

Perindopril 2 mg Tablets

For oral use.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Do not store above 30°C.
Store in the original package to protect from moisture.

5060003785606

For dispensing label

30 Film-coated Tablets

Perindopril 2 mg Tablets

PERINDOPRIL ERBUMINE

Each tablet contains 2 mg perindopril erbumine (as monohydrate).

30 Film-coated Tablets

neolab

PL 08137/0208
MA Holder: Neolab Limited
57 High Street, Odiham, Hants, RG29 1LF

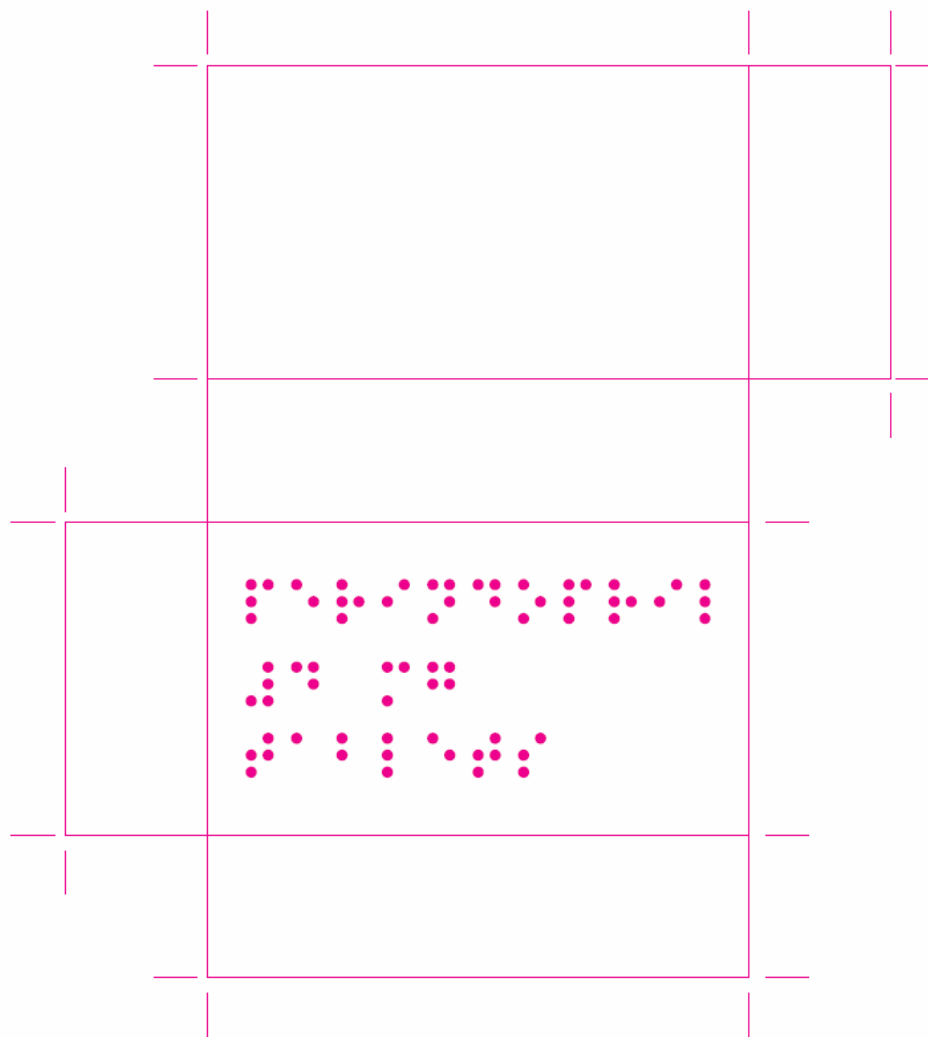
POM

Code No., BN & EXP. will be inkjet printed at the time of packing

Perindopril 2 mg Tablets PERINDOPRIL ERBUMINE MA Holder Neolab Limited	Code No.: GO/DRUGS/536
Perindopril 2 mg Tablets PERINDOPRIL ERBUMINE MA Holder Neolab Limited	XXXXX
Perindopril 2 mg Tablets PERINDOPRIL ERBUMINE MA Holder Neolab Limited	Code No.: GO/DRUGS/536
Perindopril 2 mg Tablets PERINDOPRIL ERBUMINE MA Holder Neolab Limited	XXXXX

Page 1 of 3

Perindopril 4 mg Tablets For oral use. Read the package leaflet before use. Keep out of the reach and sight of children. Do not store above 30°C. Store in the original package to protect from moisture. 510600317856131 For dispensing label	
Perindopril 4 mg Tablets 30 Film-coated Tablets	N/PRO4-1-C
Perindopril 4 mg Tablets PERINDOPRIL ERBUMINE Each tablet contains 4 mg perindopril erbumine (as monohydrate). 30 Film-coated Tablets	Code No., BN & EXP. will be inkjet printed at the time of packing
Perindopril 4 mg Tablets PL 08137/0209 MA Holder: Neolab Limited 57 High Street, Odiham, Hants, RG29 1LF POM	XXXXX



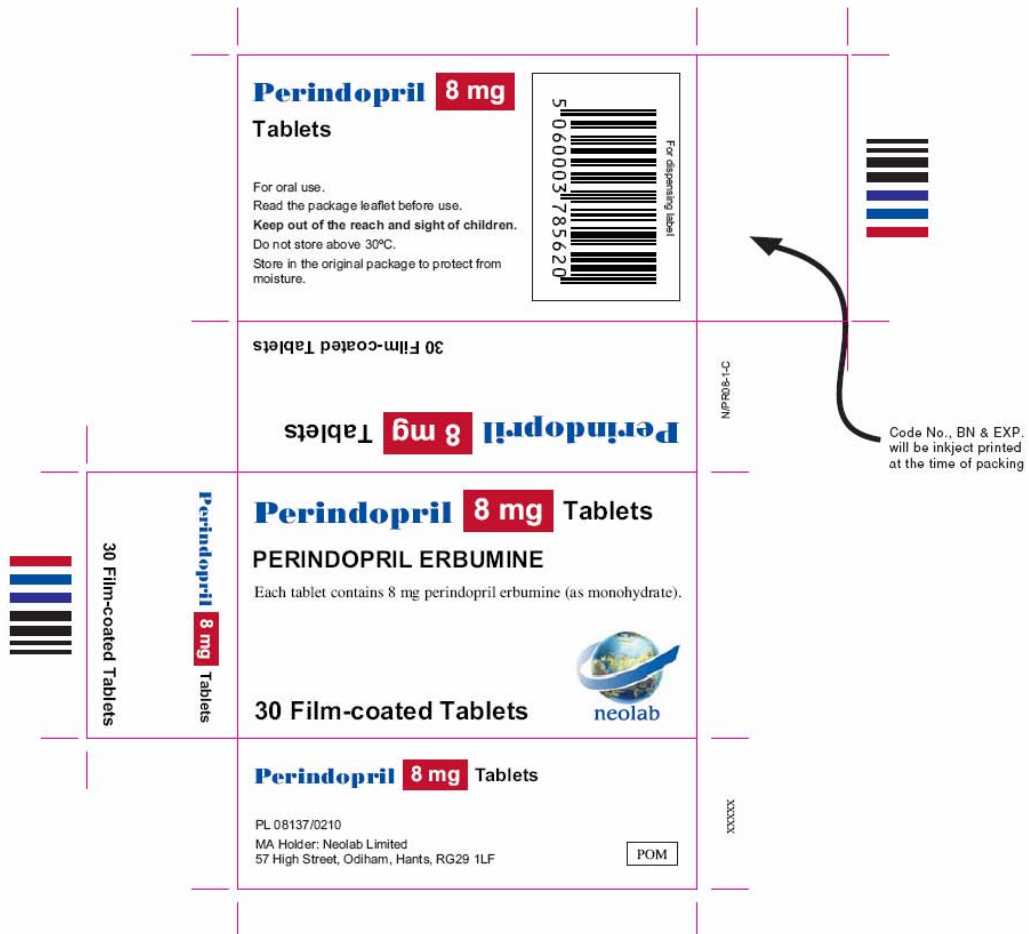
perindopril

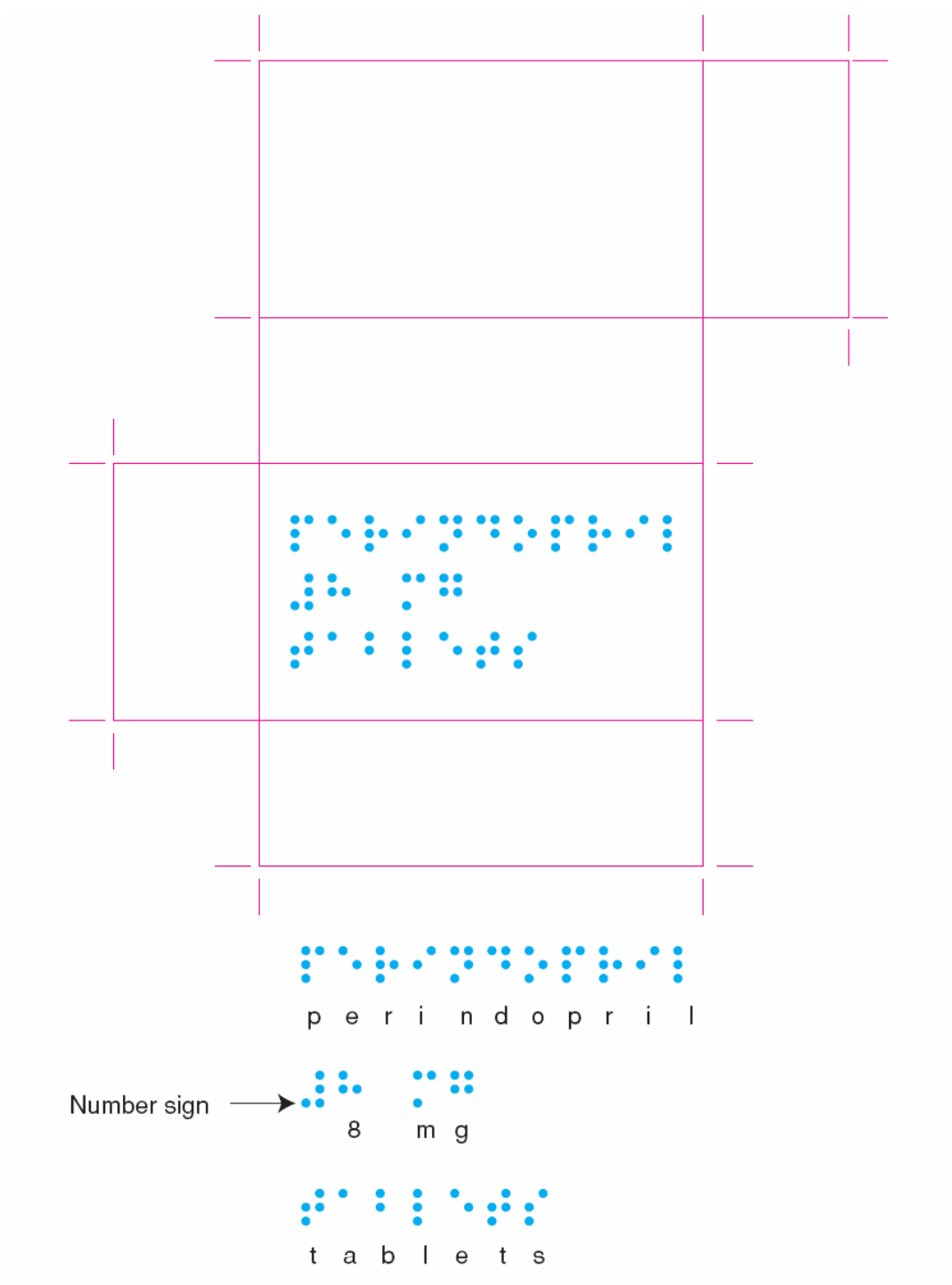
Number sign → 4 mg

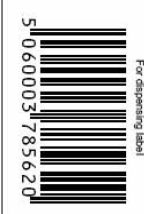
tablets

 30 Film-coated Tablets	Perindopril 4 mg Tablets For oral use. Read the package leaflet before use. Keep out of the reach and sight of children. Do not store above 30°C. Store in the original package to protect from moisture.  For dispensing label 5 060003 1785613	
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 30 Film-coated Tablets Perindopril 4 mg Tablets	Perindopril 4 mg Tablets PERINDOPRIL ERBUMINE Each tablet contains 4 mg perindopril erbumine (as monohydrate).  30 Film-coated Tablets 	Code No., BN & EXP. will be inkjet printed at the time of packing
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	Perindopril 4 mg Tablets PERINDOPRIL ERBUMINE MA Holder Neolab Limited	Code No.: 00DRUGS/536
	Perindopril 4 mg Tablets PERINDOPRIL ERBUMINE MA Holder Neolab Limited	XXXXX
	Perindopril 4 mg Tablets PERINDOPRIL ERBUMINE MA Holder Neolab Limited	XXXXX
	Perindopril 4 mg Tablets PERINDOPRIL ERBUMINE MA Holder Neolab Limited	Code No.: 00DRUGS/536
	Perindopril 4 mg Tablets PERINDOPRIL ERBUMINE MA Holder Neolab Limited	XXXXX
	Perindopril 4 mg Tablets PERINDOPRIL ERBUMINE MA Holder Neolab Limited	XXXXX





 For dispensing label 5 060003 785620	Perindopril 8 mg Tablets For oral use. Read the package leaflet before use. Keep out of the reach and sight of children. Do not store above 30°C. Store in the original package to protect from moisture.	
30 Film-coated Tablets	Perindopril 8 mg Tablets	NPR08-1C
30 Film-coated Tablets Perindopril 8 mg Tablets	Perindopril 8 mg Tablets PERINDOPRIL ERBUMINE Each tablet contains 8 mg Perindopril erbumine (as monohydrate). 30 Film-coated Tablets 	Code No., BN & EXP. will be inkjet printed at the time of packing
30 Film-coated Tablets	Perindopril 8 mg Tablets PL 08137/0210 MA Holder: Neolab Limited 57 High Street, Odiham, Hants, RG29 1LF POM	XXXXXX

