Perindopril/Indapamide 2mg/0.625mg and 4mg/1.25mg Tablets

PL 20092/0058-9

UKPAR

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LAY SUMMARY

On 30th March 2010, the MHRA granted Marketing Authorisations (licences) for the medicinal products Perindopril and Indapamide Tablets.

The tablets are provided in two different strengths, containing either 2mg perindopril together with 0.625mg indapamide or 4mg perindopril together with 1.25mg indapamide.

These are medicines used in the treatment of high blood pressure (also called hypertension). The medicines are only available on prescription from your doctor.

The name of the company approved to sell these medicines is Lupin (UK) Ltd.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Perindopril and Indapamide Tablets outweigh the risks. Hence Marketing Authorisations have been granted.
Perindopril/Indapamide 2mg/0.625mg and 4mg/1.25mg 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/Indapamide 2mg/0.625mg and 4mg/1.25mg Tablets (PL 20092/0058-9) on the 30th March 2010.

The product is for the Treatment of essential hypertension, Perindopril/Indapamide Tablets is indicated in patients whose blood pressure is not adequately controlled on perindopril alone.

The applications are according to Article 10(1) of 2001/83/EC, generic applications, as amended. The applications are for the generic products Perindopril/Indapamide 2mg/0.625mg and 4mg/1.25mg Tablets. The EU reference product is Preterax 2 mg/0.625 mg licensed in France by Les Servier Laboratoires whereas the 4 mg/1.25 mg strengths are licensed as Coversyl Plus by Servier Laboratoires, UK (licensed 23/08/1998) and Biperterax in France.

The reference product used in the bioequivalence study was Biperterax 4 mg/1.25 mg tablets manufactured by Les Laboratoires Servier and sourced from France.

Perindopril/Indapamide Tablets is a combination of perindopril tert-butylamine salt, an angiotensin converting enzyme inhibitor, and indapamide, a chlorosulphamoyl diuretic. Its pharmacological properties are derived from those of each of the components taken separately, in addition to those due to the additive synergic action of the two products when combined.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE – PERINDOPRIL

INN: Perindopril tery-Butylamine

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

Molecular Formula: C₁₉H₃₂N₂O₅ C₄H₁₁N

Chemical Structure:

Molecular Weight: 441.6

Appearance: White to off-white powder, crystalline powder slightly hygroscopic

Properties: Freely soluble in water and alcohol, sparingly soluble in methylene chloride.

The drug substance is the subject of a European Drug Master File (EDMF). A letter of access has been provided by the drug substance manufacturer.

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.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificate of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.
Satisfactory specifications and certificates of analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

Indapamide
INN: Indapamide

Chemical name: 4-chloro-N-(2-methyl-indolinyl)-3-sulphamoylbenzamide

**Structure**

![Structure diagram](image)

Molecular formula: C₁₆H₁₆ClN₃O₃S

Molecular Mass: 365.8 g/mol

Appearance: White to almost white

Properties: Insoluble in water and soluble in ethanol.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines (EDQM) certificate of suitability.

**DRUG PRODUCT**

**Other ingredients**

Other ingredients consist of pharmaceutical excipients Colloidal hydrophobic silica, Lactose monohydrate, Magnesium stearate and Microcrystalline cellulose.

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

**Pharmaceutical development**

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

**Manufacture**
A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results appear satisfactory.

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

**Container Closure System**
Tablets in blisters packed in an aluminium pouch containing desiccant silica gel. The tablets are available in pack sizes of 1, 7, 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98, 100 and 500 tablets.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with current guidelines concerning materials in contact with food.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years with storage conditions ‘Do not store above 30degree C’ and ‘Store in the original package’ have been set.

The applicant has committed to continue stability studies as per protocol and to place the first three commercial batches on long-term and intermediate stability testing in line with ICH guidelines. They also commit to place a batch annually on long-term storage conditions. Any out of specification results will be reported to the Competent Authorities.

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

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**MAA Form**
The MAA form is pharmaceutically satisfactory.

**Expert Report**
The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.
Conclusion
It is recommended that Marketing Authorisations are granted for these applications.
PRECLINICAL ASSESSMENT

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

A preclinical expert report has been provided, written by an appropriately qualified person. This is satisfactory.

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

TOXICOLOGY
No new toxicological data have been submitted or are required for these applications.

CLINICAL PHARMACOLOGY
A biostudy was only performed using the 4 mg/1.25 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 and indapamide are linear over the proposed strength tablets (2-4 mg for perindopril and 0.625-1.25 mg for indapamide).

Study
A randomised, open label, two-treatment, two-sequence, two-period, two-way crossover, single dose bioequivalence study was performed in 32 volunteers. The number of volunteers required to detect a difference with a power of 0.8 for $C_{\text{max}}$ and AUC was calculated as 32; no standbys were dosed.
Volunteers were randomised to one of the possible sequences and the randomisation was balanced for sequence. A single 4 mg/1.25 mg tablet of test and reference products was administered with 240 ml of water. Subjects were dosed after an overnight fast. The washout period was 28 days which was adequate given that only subject one had pre-dose levels of perindoprilat which were <1 % of the maximum seen for that volunteer. Samples were taken pre-dose and over 216 hours which was sufficient for adequate estimation of AUC for perindopril, perindoprilat and indapamide although perindoprilat levels did not return to baseline.

Samples were taken every 10 minutes from 0-1 hour and then every 15 minutes from 1.0 to 2.5 hours to accurately estimate the $C_{\text{max}}$ for perindopril and its active metabolite and indapamide (expected $T_{\text{max}}$ for perindopril and indapamide is 1 hour and 3-4 hours for perindoprilat). This was supported by the concentration-time curves for individual volunteers.

Summary of pharmacokinetic data for perindopril (n=20)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Reference Mean</th>
<th>Reference SD</th>
<th>Test Mean</th>
<th>Test SD</th>
<th>Ratio (B/A) %</th>
<th>90% Geometric CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{\text{ug}}$ (pg.h/ml)</td>
<td>73963.20</td>
<td>13928.42</td>
<td>70601.34</td>
<td>14800.65</td>
<td>95.15</td>
<td>89.97 - 100.62%</td>
</tr>
<tr>
<td>AUC$_{\text{umet}}$ (pg.h/ml)</td>
<td>74901.52</td>
<td>13868.80</td>
<td>71545.79</td>
<td>14796.40</td>
<td>95.21</td>
<td>90.10 - 100.60%</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (pg/ml)</td>
<td>64369.81</td>
<td>13372.01</td>
<td>62100.78</td>
<td>15183.70</td>
<td>96.09</td>
<td>86.16 - 107.16%</td>
</tr>
</tbody>
</table>
Of the 32 volunteers, 22 completed the study as 6 were withdrawn due to adverse reactions that could not directly be linked to the products. 3 Subjects did not present for period II dosing and were excluded and one subject was withdrawn on medical grounds before dosing for period II. Although there were 10 dropouts in total which reduces the sample size to 22 volunteers, the reasons for withdrawal seem appropriate and this has not adversely affected the 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.

**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 strength.

**EFFICACY**
No new efficacy data have been submitted or are required for this submission.

**SAFETY**
No new data are submitted or needed.

**EXPERT REPORT**
The Clinical Expert Report has been written by an appropriately qualified person and is a suitable summary of the clinical aspects of the dossier.

**SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**
These are consistent with the SPC for the reference products and are satisfactory.

**PATIENT INFORMATION LEAFLET (PIL)**
The PIL is an accurate reflection of the SPC and complies with the appropriate guidelines.

**LABELLING**
These are satisfactory.

**MAA FORM**
These are satisfactory.

**CONCLUSIONS**
The proposed products are qualitatively and quantitatively the same to the reference product in terms of the active principle, are the same pharmaceutical form and have been demonstrated to be bioequivalent.. The French reference product is considered to be equivalent to the originator product marketed in the UK. Therefore, grant of Marketing Authorisations are recommended.
OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Perindopril/Indapamide 2mg/0.625mg and 4mg/1.25mg 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
The preclinical data submitted have not revealed any evidence of potential risks to human health from treatment with Perindopril/Indapamide 2mg/0.625mg and 4mg/1.25mg Tablets beyond those already described.

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

The use of the reference product is well-established in the UK. Both products contain the same quantitative and qualitative composition of the active ingredients, perindopril tert-butylamine and indapamide.

The 90% confidence intervals for the test/reference lie within the acceptance criteria specified in the CPMP/EWP/QWP/1401/98 Notes for Guidance on the Investigation of Bioavailability and Bioequivalence. Bioequivalence of the test product to the reference formulation has been satisfactorily demonstrated in accordance with CHMP criteria.

No new safety data are supplied or required for these generic applications. Perindopril/Indapamide have well-established side-effect profiles and are generally well-tolerated.

The SPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s product and the innovator product are interchangeable. Extensive clinical experience with Perindopril/Indapamide is considered to have demonstrated the therapeutic value of the compound. The risk-benefit is, therefore, considered to be positive.
Perindopril/Indapamide 2mg/0.625mg and 4mg/1.25mg Tablets

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**STEPS TAKEN FOR ASSESSMENT**

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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 5th March 2008</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 2nd April 2008</td>
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<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information on 14/08/2008, 26/08/2009 and 26/02/2010 for the quality part of the dossier</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 13/08/2009, 12/02/2010 and 13/03/2010 for the quality sections.</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 30th March 2010</td>
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Perindopril/Indapamide 2mg/0.625mg and 4mg/1.25mg Tablets

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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</table>
1 NAME OF THE MEDICINAL PRODUCT
Perindopril/Indapamide 2mg/0.625mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet of Perindopril/Indapamide 2mg/0.625mg contains:
2.00 mg of perindopril tert-butylamine, equivalent to 1.669 mg perindopril and 0.625mg of indapamide

Excipients: Lactose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet
White to off-white; capsule shaped uncoated tablet, with score line on both sides. The tablets can be divided into equal halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of essential hypertension, Perindopril/Indapamide Tablets is indicated in patients whose blood pressure is not adequately controlled on perindopril alone.

4.2 Posology and method of administration
Oral route
The usual dose of Perindopril/Indapamide 2mg/0.625mg is one tablet per day preferably in the morning and before meals. In cases of failure to control blood pressure after one month of treatment the dose may be doubled.

Elderly
Treatment should be initiated after considering blood pressure response and renal function.

Patients with renal impairment (see section 4.4)
In severe renal impairment (creatinine clearance below 30 mL / min), treatment is contraindicated.

In patients with moderate renal impairment (creatinine clearance 30-60 mL / min), the maximum dose should be Perindopril/Indapamide 2mg/0.625mg one tablet per day.

In patients with creatinine clearance greater than or equal to 60 ml / min, no dosage adjustment is necessary.

Current medical practice includes periodic monitoring of creatinine and plasma potassium.

Patients with hepatic impairment (see sections 4.3, 4.4 and 5.2)
In severe hepatic impairment, treatment is contraindicated.

In patients with moderate hepatic impairment, no dose modification is required.

Children and adolescents less than 18 years of age
Perindopril/Indapamide 2mg/0.625mg should not be used in children and adolescents as the efficacy and tolerability of perindopril in children and adolescents, alone or in combination, have not been established.

4.3 Contraindications
Linked to perindopril
- Hypersensitivity to perindopril or any other ACE inhibitor
- History of angioedema (Quincke's oedema) associated with previous ACE inhibitor therapy
- Hereditary / idiopathic angioedema
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)
Linked to indapamide
- Hypersensitivity to indapamide or sulphonamides
- Severe renal impairment (creatinine clearance below 30 mL / min)
- Hepatic encephalopathy
- Severe hepatic impairment
- Hypokalaemia
- Lactation (see section 4.6)
- As a general rule, this medicine is inadvisable in combination with nonantiarrhythmic agents causing torsades de pointes (see section 4.5).

Linked to Perindopril/Indapamide Tablets
- Hypersensitivity to any of the excipients

Due to the lack of sufficient therapeutic experience, Perindopril/Indapamide Tablets should not be used in:

- Dialysis patients
- Patients with untreated decompensated heart failure.

4.4 Special warnings and precautions for use

Special warnings
Common to perindopril and indapamide:

Lithium:
The combination of lithium and the combination of perindopril and indapamide is usually not recommended (see section 4.5).

Linked to perindopril:
Neutropenia/agranulocytosis:
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 procaainamide, 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, periodical monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (e.g. sore throat, fever).

Hypersensitivity/angioneurotic oedema:
Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with angiotensin converting enzyme inhibitors, including perindopril. This may occur at any time during treatment. In such cases perindopril should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. In those instances where swelling has been confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioneurotic oedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, which may include subcutaneous epinephrine solution 1:1000 (0.3 ml to 0.5 ml) and/or measures to ensure a patent airway, should be administered promptly.

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).
Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Anaphylactoid reactions during desensitisation:
There have been isolated reports of patients experiencing sustained, life-threatening anaphylactoid reactions while receiving ACE inhibitors during desensitisation treatment with hymenoptera (bees, wasps) venom. ACE inhibitors should be used with caution in allergic patients treated with desensitisation, and avoided in those undergoing venom immunotherapy. However these reactions could be prevented by temporary withdrawal of ACE inhibitor for at least 24 hours before treatment in patients who require both ACE inhibitors and desensitisation.

Anaphylactoid reactions during 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.

Haemodialysis patients:
Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g., AN 69®) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Potassium-sparing diuretics, potassium salts:
The combination of perindopril and potassium-sparing diuretics, potassium salts is usually not recommended (see section 4.5).

Pregnancy and lactation
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Linked to indapamide:
When liver function is impaired, thiazide diuretics and thiazide-related diuretics may cause hepatic encephalopathy. Administration of the diuretic should be stopped immediately if this occurs.

Photosensitivity:
Cases of photosensitivity reactions have been reported with thiazides and related thiazides diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Sultopride:
The combination of indapamide and sultopride is usually not recommended (see section 4.5).

Precautions for use
Common to perindopril and indapamide:
Renal impairment:
In cases of severe renal impairment (creatinine clearance < 30 ml/min), treatment is contraindicated.
In certain hypertensive patients without pre-existing apparent renal lesions and for whom renal blood tests show functional renal insufficiency, treatment should be stopped and possibly restarted either at a low dose or with one constituent only. In these patients usual medical
follow-up will include frequent monitoring of potassium and creatinine, after two weeks of
treatment and then every two months during therapeutic stability period. Renal failure has
been reported mainly in patients with severe heart failure or underlying renal failure including
renal artery stenosis.
The drug is usually not recommended in case of bilateral renal artery stenosis or a single
functioning kidney.

**Hypotension and water and electrolyte depletion:**
There is a risk of sudden hypotension in the presence of pre-existing sodium depletion (in
particular in individuals with renal artery stenosis). Therefore systematic testing should be
carried out for clinical signs of water and electrolyte depletion, which may occur with an
intercurrent episode of diarrhoea or vomiting. Regular monitoring of plasma electrolytes
should be carried out in such patients.
Marked hypotension may require the implementation of an intravenous infusion of isotonic
saline.
Transient hypotension is not a contraindication to continuation of treatment. After re-
establishment of a satisfactory blood volume and blood pressure, treatment can be started
again either at a reduced dose or with only one of the constituents.

**Potassium levels:**
The combination of perindopril and indapamide does not prevent the onset of hypokalaemia
particularly in diabetic patients or in patients with renal failure. As with any antihypertensive
agent in combination with a diuretic, regular monitoring of plasma potassium levels should be
carried out.

**Excipients:**
This medicinal product contains lactose monohydrate and patients with rare hereditary
problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose
malabsorption should not take this medicine.

**Linked to perindopril:**
**Cough:**
A dry cough has been reported with the use of angiotensin converting enzyme inhibitors. It is
classified by its persistence and by its disappearance when treatment is withdrawn. An
iatrogenic aetiology should be considered in the event of this symptom. If the prescription of
an angiotensin converting enzyme inhibitor is still preferred, continuation of treatment may be
considered.

**Children and adolescents:**
The efficacy and tolerability of perindopril in children and adolescents, alone or in
combination, have not been established.

**Risk of arterial hypotension and/or renal insufficiency (in cases of cardiac insufficiency, water
and electrolyte depletion, etc...):**
Marked stimulation of the renin-angiotensin-aldosterone system has been observed
particularly during marked water and electrolyte depletions (strict sodium restricted diet or
prolonged diuretic treatment), in patients whose blood pressure was initially low, in cases of
renal artery stenosis, congestive heart failure or cirrhosis with oedema and ascites.
The blocking of this system with an angiotensin converting enzyme inhibitor may therefore
cause, particularly at the time of the first administration and during the first two weeks of
treatment, a sudden drop in blood pressure and/or an increase in plasma levels of creatinine,
showing a functional renal insufficiency. Occasionally this can be acute in onset, although
rare, and with a variable time to onset.
In such cases, the treatment should then be initiated at a lower dose and increased
progressively.

**Elderly:**
Renal function and potassium levels should be tested before the start of treatment. The initial
dose is subsequently adjusted according to blood pressure response, especially in cases of
water and electrolyte depletion, in order to avoid sudden onset of hypotension.
Patients with known atherosclerosis:
The risk of hypotension exists in all patients but particular care should be taken in patients
with ischaemic heart disease or cerebral circulatory insufficiency, with treatment being started
at a low dose.

Renovascular hypertension:
The treatment for renovascular hypertension is revascularisation. Nonetheless, angiotensin
converting enzyme inhibitors can be beneficial in patients presenting with renovascular
hypertension who are awaiting corrective surgery or when such a surgery is not possible.
If these tablets are prescribed to patients with known or suspected renal artery stenosis,
treatment should be started in a hospital setting at a low dose and renal function and potassium
levels should be monitored, since some patients have developed a functional renal
insufficiency which was reversed when treatment was stopped.

Other populations at risk:
In patients with severe cardiac insufficiency (grade IV) or in patients with insulin dependent
diabetes mellitus (spontaneous tendency to increased levels of potassium), treatment should be
started under medical supervision with a reduced initial dose. Treatment with beta-blockers in
hypertensive patients with coronary insufficiency should not be stopped: the ACE inhibitor
should be added to the beta-blocker.

Diabetic patients:
The glycaemia levels should be closely monitored in diabetic patients previously treated with
oral antidiabetic drugs or insulin, namely during the first month of treatment with an ACE
inhibitor.

Ethnic differences:
As with other angiotensin converting enzyme inhibitors, perindopril is apparently 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.

Surgery / anaesthesia:
Angiotensin converting enzyme inhibitors can cause hypotension in cases of anaesthesia,
especially when the anaesthetic administered is an agent with hypotensive potential. It is
therefore recommended that treatment with long-acting angiotensin converting enzyme
inhibitors such as perindopril should be discontinued where possible one day before surgery.

Aortic or mitral valve stenosis / hypertrophic cardiomyopathy:
ACE inhibitors should be used with caution in patient with an obstruction in the outflow tract
of the left ventricle.

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

Hyperkalaemia:
Elevations in serum potassium have been observed in some patients treated with ACE
inhibitors, including perindopril. Risk factors for the development of hyperkalaemia include
those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus,
intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic
acidosis and concomitant use of potassium-sparing diuretics (e.g., spironolactone, eplerenone,
triaterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or
those patients taking other drugs associated with increases in serum potassium (e.g. heparin).
The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt
substitutes particularly in patients with impaired renal function may lead to a significant
increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal arrhythmias.
If concomitant use of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

**Linked to indapamide:**

### Water and electrolyte balance:

#### Sodium levels:

These should be tested before treatment is started, then at regular intervals. All diuretic treatment can cause a reduction in sodium levels, which may have serious consequences. Reduction in sodium levels can be initially asymptomatic and regular testing is therefore essential. Testing should be more frequent in elderly and cirrhotic patients (see sections 4.8 and 4.9).

#### Potassium levels:

Potassium depletion with hypokalaemia is a major risk with thiazide diuretics and thiazide-related diuretics. The risk of onset of lowered potassium levels (<3.4 mmol/l) should be prevented in some high risk populations such as elderly and/or malnourished subjects, whether or not they are taking multiple medications, cirrhotic patients with oedema and ascites, coronary patients and patients with heart failure.

In such cases hypokalaemia increases the cardiac toxicity of cardiac glycosides and the risk of rhythm disorders. Subjects presenting with a long QT interval are also at risk, whether the origin is congenital or iatrogenic. Hypokalaemia, as with bradycardia, acts as a factor which favours the onset of severe rhythm disorders, in particular torsades de pointes, which may be fatal.

In all cases more frequent testing of potassium levels is necessary. The first measurement of plasma potassium levels should be carried out during the first week following the start of treatment. If low potassium levels are detected, correction is required.

#### Calcium levels:

Thiazide diuretics and thiazide-related diuretics may reduce urinary excretion of calcium and cause a mild and transient increase in plasma calcium levels. Markedly raised levels of calcium may be related to undiagnosed hyperparathyroidism. In such cases the treatment should be stopped before investigating the parathyroid function.

#### Blood glucose:

Monitoring of blood glucose is important in diabetic patients, particularly when potassium levels are low.

#### Uric acid:

Tendency to gout attacks may be increased in hyperuricaemic patients.

#### Renal function and diuretics:

Thiazide diuretics and thiazide-related diuretics are only fully effective when renal function is normal or only slightly impaired (creatinine levels lower than approximately 25 mg/l, i.e. 220 µmol/l for an adult).

In the elderly the value of plasma creatinine levels should be adjusted to take account of the age, weight and sex of the patient, according to the Cockroft formula:

$$\text{clcr} = (140 - \text{age}) \times \text{body weight} / 0.814 \times \text{plasma creatinine level}$$

with: age expressed in years

body weight in kg

plasma creatinine level in micromol/l

This formula is suitable for an elderly male and should be adapted for women by multiplying the result by 0.85.

Hypovolaemia, resulting from the loss of water and sodium caused by the diuretic at the start of treatment, causes a reduction in glomerular filtration. It may result in an increase in blood urea and creatinine levels. This transitory functional renal insufficiency is of no adverse consequence in patients with normal renal function but may however worsen a pre-existing renal impairment.

#### Athletes:

Athletes should note that this product contains an active substance which may cause a positive reaction in doping tests.

### 4.5 Interaction with other medicinal products and other forms of interaction

Common to perindopril and indapamide:

Concomitant use not recommended:
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 further increase lithium levels and enhance the risk of lithium toxicity with ACE inhibitors. Use of perindopril combined with indapamide with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Concomitant use which requires special care:
- Baclofen: Potentiation of antihypertensive effect. Monitoring of blood pressure and renal function, and dose adaptation of the antihypertensive if necessary.
- Non-steroidal anti-inflammatory medicinal products (including acetylsalicylic acid at high doses > 3 g): the administration of a non-steroidal anti-inflammatory medicinal product may reduce the diuretic, natriuretic and antihypertensive effects in some patients. In elderly patients and patients who may be dehydrated there is a risk of acute renal failure, therefore monitoring of renal function at the initiation of treatment is recommended. Patients should be well hydrated.

Concomitant use which requires some care:
- Imipramine-like antidepressants (tricyclics), neuroleptics: Increased antihypertensive effect and increased risk of orthostatic hypotension (additive effect).
- Corticosteroids, tetracosactide: Reduction in antihypertensive effect (salt and water retention due to corticosteroids).
- Other antihypertensive agents: use of other antihypertensive medicinal products with perindopril/indapamide could result in additional blood pressure lowering effect.

Linked to perindopril:
Concomitant use not recommended:
- Potassium-sparing diuretics (spironolactone, triamterene, alone or in combination), potassium (salts): ACE inhibitors attenuate diuretic induced potassium loss. Potassium-sparing diuretics e.g. spironolactone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium (potentially lethal). If concomitant use is indicated because of documented hypokalaemia they should be used with caution and with frequent monitoring of serum potassium and by ECG.

Concomitant use which requires some care:
- Antidiabetic agents (insulin, hypoglycaemic sulphonamides): Reported with captopril and enalapril. The use of angiotensin converting enzyme inhibitors may increase the hypoglycaemic effect in diabetics receiving treatment with insulin or with hypoglycaemic sulphonamides. The onset of hypoglycaemic episodes is very rare (improvement in glucose tolerance with a resulting reduction in insulin requirements).

Concomitant use which requires some care:
- Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids or procarainamide: Concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia.
- Anaesthetic drugs: ACE inhibitors may enhance the hypotensive effects of certain anaesthetic drugs.
- Diuretics (thiazide or loop diuretics): Prior treatment with high dose diuretics may result in volume depletion and in a risk of hypotension when initiating therapy with perindopril.

Gold: Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including perindopril.

Linked to indapamide:
Concomitant use which requires special care:
- Torsades de pointes inducing drugs: Due to the risk of hypokalaemia, indapamide should be administered with caution when associated with medicinal products that induced torsades de pointes such as class IA antiarrhythmic agents (quinidine, hydroquinidine, disopyramide); class III antiarrhythmic agents (amiodarone, dofetilide, ibutilide, bretylium, sotalol); some neuroleptics (chlorpromazine, cyamemazine, levomepromazine, thioridazine, triflupromazine), benzamides (amisulpride, sulphiride, sulpuropride, tiapride), butyrophenones (droperidol,
haloperidol), other neuroleptics (pimozide); other substances such as bepridil, cisapride, diphenamid, IV erythromycin, halofantrine, mizolastine, moxifloxacin, pentamidine, sparfloxacin, IV vincamine, methadone, astemizole, terfenadine. Prevention of low potassium levels and correction if necessary: monitoring of the QT interval.
- Potassium-lowering drugs: amphotericin B (IV route), glucocorticoids and mineralocorticoids (systemic route), tetracosactide, stimulant laxatives: Increased risk of low potassium levels (additive effect). Monitoring of potassium levels, and correction if necessary; particular consideration required in cases of treatment with cardiac glycosides. Non stimulant laxatives should be used.
- Cardiac glycosides: Low potassium levels favour the toxic effects of cardiac glycosides. Potassium levels and ECG should be monitored and treatment reconsidered if necessary. Concomitant use which requires some care:
- Metformin: Lactic acidosis due to metformin caused by possible functional renal insufficiency linked to diuretics and in particular to loop diuretics. Do not use metformin when plasma creatinine levels exceed 15 mg/l (135 micromol/l) in men and 12 mg/l (110 micromol/l) in women.
- Iodinated contrast media: In cases of dehydration caused by diuretics, there is an increased risk of acute renal insufficiency, particularly when high doses of iodinated contrast media are used. Rehydration should be carried out before the iodinated compound is administered.
- Calcium (salts): Risk of increased levels of calcium due to reduced elimination of calcium in the urine.
- Ciclosporin: Risk of increased creatinine levels with no change in circulating levels of ciclosporin, even when there is no salt and water depletion.

4.6 Pregnancy and lactation

Linked to perindopril:

Pregnancy

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section 5.3.). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

Lactation

Because no information is available regarding the use of perindopril during breastfeeding, perindopril is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Linked to indapamide:

Pregnancy:

Prolonged exposure to thiazide during the third trimester of pregnancy can reduce maternal plasma volume as well as uteroplacental blood flow, which may cause a feto-placental ischemia and growth retardation. Moreover, rare cases of hypoglycemia and thrombocytopenia in neonates have been reported following exposure near term.
**Lactation:**
Indapamide is excreted in human milk. Indapamide is closely related to thiazide diuretics which have been associated, during breast-feeding, with decrease or even suppression of milk lactation. Hypersensitivity to sulfonamide-derived drugs, hypokalaemia and nuclear icterus might occur.

Linked to Perindopril and indapamide:

**Lactation:**
Perindopril/Indapamide Tablets is contraindicated during lactation. As, with both drugs, serious adverse reactions might occur in nursing infants, a decision should be made whether to discontinue nursing or to discontinue therapy taking account the importance of this therapy for the mother.

**4.7 Effects on ability to drive and use machines**
Neither of the two active substances nor Perindopril/Indapamide Tablets affect alertness but individual reactions related to low blood pressure may occur in some patients, particularly at the start of treatment or in combination with another antihypertensive medication.

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

**4.8 Undesirable effects**
The administration of perindopril inhibits the renin-angiotensin-aldosterone axis and tends to reduce the potassium loss caused by indapamide. Two percent of the patients on treatment with Perindopril/Indapamide 2mg/0.625mg Tablets experience hypokalaemia (potassium level < 3.4 mmol/l).

The following undesirable effects could be observed during treatment 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), not known (cannot be estimated from the available data).

**Blood and the lymphatic system disorders:**
Very rare:
Thrombocytopenia, leucopenia/neutropenia, agranulocytosis, aplastic anaemia, haemolytic anaemia.
Anæmia (see section 4.4) has been reported with angiotensin converting enzyme inhibitors in specific circumstances (patients who have had kidney transplants, patients undergoing haemodialysis).

**Psychiatric disorders:**
Uncommon: mood or sleep disturbances.

**Nervous system disorders:**
Common: Paresthesia, headache, dizziness, vertigo.
Very rare: Confusion.

**Eye disorders:**
Common: Vision disturbance.

**Ear and labyrinth disorders:**
Common: Tinnitus.

**Vascular disorders:**
Common: Hypotension whether orthostatic or not (see section 4.4).

**Cardiac disorders:**
Very rare: Arrhythmia including bradycardia, ventricular tachycardia, atrial fibrillation, angina pectoris and myocardial infarction possibly secondary to excessive hypotension in high-risk patients (see section 4.4).
Respiratory, thoracic and mediastinal disorders:
*Common:* A dry cough has been reported with the use of angiotensin converting enzyme inhibitors. It is characterised by its persistence and by its disappearance when treatment is withdrawn. An iatrogenic aetiology should be considered in the presence of this symptom.
*Dyspnoea.*
*Uncommon:* Bronchospasm.
*Very rare:* Eosinophilic pneumonia, rhinitis.

Gastrointestinal disorders:
*Common:* Constipation, dry mouth, nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea.
*Very rare:* Pancreatitus, intestinal angioedema.

Hepato-biliary disorders:
*Very rare:* Hepatitis either cytolytic or cholestatic (see section 4.4).
*Not known:* In case of hepatic insufficiency, there is a possibility of onset of hepatic encephalopathy (see sections 4.3 and 4.4).

Skin and subcutaneous tissue disorders:
*Common:* Rash, pruritus, maculopapular eruptions.
*Uncommon:* Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see section 4.4).
*Hypersensitivity reactions,* mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions.
*Purpura.*
*Possible aggravation of pre-existing acute disseminated lupus erythematosus.*
*Very rare:* Erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome.
Cases of photosensitivity reactions have been reported (see section 4.4).

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 and administration site conditions:
*Common:* Asthenia.
*Uncommon:* Sweating.

Investigations:
Potassium depletion with particularly serious reduction in levels of potassium in some at risk populations (see section 4.4).
Reduced sodium levels with hypovolaemia causing dehydration and orthostatic hypotension.
Increase in uric acid levels and in blood glucose levels during treatment.
Slight increase in urea and in plasma creatinine levels, reversible when treatment is stopped.
This increase is more frequent in cases of renal artery stenosis, arterial hypertension treated with diuretics, renal insufficiency.
Increased levels of potassium, usually transitory.
*Rare:* Raised plasma calcium levels.

4.9 Overdose
The most likely adverse reaction in cases of overdose is hypotension, sometimes associated with nausea, vomiting, cramps, dizziness, sleepiness, mental confusion, oliguria which may progress to anuria (due to hypovolaemia). Salt and water disturbances (low sodium levels, low potassium levels) may occur.
The first measures to be taken consist of rapidly eliminating the product(s) ingested by gastric lavage and/or administration of activated charcoal, then restoring fluid and electrolyte balance in a specialised centre until they return to normal.

If marked hypotension occurs, this can be treated by placing the patient in a supine position with the head lowered. If necessary an intravenous infusion of isotonic saline may be given, or any other method of volaemic expansion may be used.

Perindoprilat, the active form of perindopril, can be dialysed (see section 5.2).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: perindopril and diuretics, ATC code: C09BA04

Perindopril/Indapamide Tablets is a combination of perindopril tert-butylamine salt, an angiotensin converting enzyme inhibitor, and indapamide, a chlorosulphamoyl diuretic. Its pharmacological properties are derived from those of each of the components taken separately, in addition to those due to the additive synergic action of the two products when combined.

Pharmacological mechanism of action

Linked to Perindopril/Indapamide Tablets:

Perindopril/Indapamide Tablets produce an additive synergy of the antihypertensive effects of the two components.

Linked to perindopril:

Perindopril is an inhibitor of the angiotensin converting enzyme (ACE inhibitor) which converts angiotensin I to angiotensin II, a vasoconstricting substance; in addition the enzyme stimulates the secretion of aldosterone by the adrenal cortex and stimulates the degradation of bradykinin, a vasodilatory substance, into inactive heptapeptides.

This results in:
- a reduction in aldosterone secretion
- an increase in plasma renin activity, since aldosterone no longer exercises negative feedback
- a reduction in total peripheral resistance with a preferential action on the vascular bed in muscle and the kidney, with no accompanying salt and water retention or reflex tachycardia, with chronic treatment.

The antihypertensive action of perindopril also occurs in patients with low or normal renin concentrations.

Perindopril acts through its active metabolite, perindoprilat. The other metabolites are inactive.

Perindopril reduces the work of the heart:
- by a vasodilatory effect on veins, probably caused by changes in the metabolism of prostaglandins: reduction in pre-load
- by reduction of the total peripheral resistance: reduction in afterload

Studies carried out on patients with cardiac insufficiency have shown:
- a reduction in left and right ventricular filling pressures
- a reduction in total peripheral vascular resistance
- an increase in cardiac output and an improvement in the cardiac index
- an increase in regional blood flow in muscle

Exercise test results also showed improvement.

Linked to indapamide:

Indapamide is a sulphonamide derivative with an indole ring, pharmacologically related to the thiazide group of diuretics. Indapamide inhibits the reabsorption of sodium in the cortical dilution segment. It increases the urinary excretion of sodium and chlorides and, to a lesser extent, the excretion of potassium and magnesium, thereby increasing urine output and having an antihypertensive action.

Characteristics of antihypertensive action

Linked to Perindopril/Indapamide Tablets:

In hypertensive patients regardless of age, these tablets exert a dose-dependent antihypertensive effect on diastolic and systolic arterial pressure whilst supine or standing.

This antihypertensive effect lasts for 24 hours. The reduction in blood pressure is obtained in less than one month without tachyphylaxis; stopping treatment has no rebound effect. During
clinical trials, the concomitant administration of perindopril and indapamide produced antihypertensive effects of a synergic nature in relation to each of the products administered alone. The effect of the low dose tablets (2mg/0.625 mg) on cardiovascular morbidity and mortality has not been studied.

**Linked to perindopril:**
Perindopril is active in all grades of hypertension: mild to moderate or severe. A reduction in systolic and diastolic arterial pressure is observed in the lying and standing position. The antihypertensive activity after a single dose is maximal at between 4 and 6 hours and is maintained over 24 hours. There is a high degree of residual blocking of angiotensin converting enzyme at 24 hours, approximately 80%. In patients who respond, normalised blood pressure is reached after one month and is maintained without tachyphylaxis.

**Withdrawal of treatment has no rebound effect on hypertension.**
Perindopril has vasodilatory properties and restores elasticity of the main arterial trunks, corrects histomorphometric changes in resistance arteries and produces a reduction in left ventricular hypertrophy.
If necessary, the addition of a thiazide diuretic leads to an additive synergy. The combination of an angiotensin converting enzyme inhibitor with a thiazide diuretic decreases the hypokalaemia risk associated with the diuretic alone.

**Linked to indapamide:**
Indapamide, as monotherapy, has an antihypertensive effect which lasts for 24 hours. This effect occurs at doses at which the diuretic properties are minimal. Its antihypertensive action is proportional to an improvement in arterial compliance and a reduction in total and arteriolar peripheral vascular resistance. Indapamide reduces left ventricular hypertrophy.
When a dose of thiazide diuretic and thiazide-related diuretics is exceeded, the antihypertensive effect reaches a plateau, whereas the adverse effects continue to increase. If the treatment is ineffective, the dose should not be increased.
Furthermore, it has been shown that in the short-term, mid-term and long-term in hypertensive patients, indapamide:
- has no effect on lipid metabolism: triglycerides, LDL-cholesterol and HDL-cholesterol
- has no effect on carbohydrate metabolism, even in diabetic hypertensive patients

5.2 Pharmacokinetic properties
**Linked to Perindopril/Indapamide Tablets:**
The co-administration of perindopril and indapamide does not change their pharmacokinetic properties by comparison to separate administration.

**Linked to perindopril:**
After oral administration, the absorption of perindopril is rapid and the peak concentration is achieved within 1 hour. The plasma half-life of perindopril is equal to 1 hour. Perindopril is a prodrug. Twenty seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.
As ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril tert-butylamine should be administered orally in a single daily dose in the morning before a meal.
It has been demonstrated a linear relationship between the dose of perindopril and its plasma exposure. The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Protein binding of perindoprilat to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration-dependent. Perindoprilat is eliminated in the urine and the terminal half-life of the unbound fraction is approximately 17 hours, resulting in steady-state within 4 days. 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 sections 4.2 and 4.4).

Linked to indapamide:
Indapamide is rapidly and completely absorbed from the digestive tract. The peak plasma level is reached in humans approximately one hour after oral administration of the product. Plasma protein binding is 79%. The elimination half-life is between 14 and 24 hours (average 18 hours). Repeated administration does not produce accumulation. Elimination is mainly in the urine (70% of the dose) and faeces (22%) in the form of inactive metabolites. The pharmacokinetics are unchanged in patients with renal insufficiency.

5.3 Preclinical safety data
Perindopril/Indapamide Tablets has slightly increased toxicity than that of its components. Renal manifestations do not seem to be potentiated in the rat. However, the combination produces gastro-intestinal toxicity in the dog and the toxic effects on the mother seem to be increased in the rat (compared to perindopril). Nonetheless, these adverse effects are shown at dose levels corresponding to a very marked safety margin by comparison to the therapeutic doses used.

Preclinical studies performed separately with perindopril and indapamide did not show genotoxic, carcinogenic or teratogenic potential.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Colloidal hydrophobic silica
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 30°C. Store in the original package.

6.5 Nature and contents of container
Tablets in blisters packed in an aluminium pouch containing desiccant silica gel. The tablets are available in pack sizes of 1, 7, 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98, 100 and 500 tablets.

Not all pack sizes may be marketed.

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

7 MARKETING AUTHORISATION HOLDER
Lupin (Europe) Limited
Victoria Court
Bexton Road
Knutsford
Cheshire WA16 0PF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 20092/0058
NAME OF THE MEDICINAL PRODUCT
Perindopril/Indapamide 4mg/1.25mg Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet of Perindopril/Indapamide 4mg/1.25mg contains:
4.00 mg of perindopril tert-butylamine, equivalent to 3.338 mg perindopril and 1.25mg of indapamide

Excipients: Lactose

For a full list of excipients, see section 6.1.

PHARMACEUTICAL FORM
Tablet
White to off-white; capsule shaped uncoated tablet, plain on both sides.

CLINICAL PARTICULARS

Therapeutic indications
Treatment of essential hypertension, Perindopril / Indapamide Tablets is indicated in patients whose blood pressure is not adequately controlled on perindopril alone.

Posology and method of administration
Oral route
One tablet per day as a single dose, preferably to be taken in the morning, and before a meal.

When possible, individual dose titration with the components can be recommended. The 4mg/1.25mg tablets should be used when blood pressure is not adequately controlled on the 2mg/0.625mg tablets.

When clinically appropriate, direct change from monotherapy to Perindopril/Indapamide 4mg/1.25mg Tablets may be considered.

Elderly
Treatment should be initiated after considering blood pressure response and renal function.

Patients with renal impairment (see section 4.4)
In severe renal impairment (creatinine clearance below 30 mL / min), treatment is contraindicated.

In patients with creatinine clearance greater than or equal to 30 mL / min and less than 60 mL / min, it is recommended to start treatment with the adequate dosage of the free combination. It is not necessary to change the dose when creatinine clearance is greater than 60 mL / min.

Current medical practice includes periodic monitoring of creatinine and plasma potassium.

Patients with hepatic impairment (see sections 4.3, 4.4 and 5.2)
In severe hepatic impairment, treatment is contraindicated.

In patients with moderate hepatic impairment, no dose modification is required.

Children and adolescents less than 18 years of age
Perindopril/Indapamide 4mg/1.25mg Tablets should not be used in children and adolescents as the efficacy and tolerability of perindopril in children and adolescents, alone or in combination, have not been established.

Contraindications
Linked to perindopril
- Hypersensitivity to perindopril or any other ACE inhibitor
- History of angioedema (Quincke's oedema) associated with previous ACE inhibitor therapy
- Hereditary / idiopathic angioedema
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)
Linked to indapamide
- Hypersensitivity to indapamide or sulphonamides
- Severe renal impairment (creatinine clearance below 30 mL / min)
- Hepatic encephalopathy
- Severe hepatic impairment
- Hypokalaemia
- Lactation (see section 4.6)
- As a general rule, this medicine is inadvisable in combination with nonantiarrhythmic agents causing torsades de pointes (see section 4.5).

Linked to Perindopril/Indapamide Tablets
- Hypersensitivity to any of the excipients

Due to the lack of sufficient therapeutic experience, Perindopril/Indapamide Tablets should not be used in:

- Dialysis patients
- Patients with untreated decompensated heart failure.

4.4 Special warnings and precautions for use

Special warnings
Common to perindopril and indapamide:

Lithium:
The combination of lithium and the combination of perindopril and indapamide is usually not recommended (see section 4.5).

Linked to perindopril:
Neutropenia/agranulocytosis:
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 procaainamide, 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, periodical monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (e.g. sore throat, fever).

Hypersensitivity/angioneurotic oedema:
Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with angiotensin converting enzyme inhibitors, including perindopril. This may occur at any time during treatment. In such cases perindopril should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. In those instances where swelling has been confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioneurotic oedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, which may include subcutaneous epinephrine solution 1:1000 (0.3 ml to 0.5 ml) and/or measures to ensure a patent airway, should be administered promptly.

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).
Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Anaphylactoid reactions during desensitisation:
There have been isolated reports of patients experiencing sustained, life-threatening anaphylactoid reactions while receiving ACE inhibitors during desensitisation treatment with hymenoptera (bees, wasps) venom. ACE inhibitors should be used with caution in allergic patients treated with desensitisation, and avoided in those undergoing venom immunotherapy. However these reactions could be prevented by temporary withdrawal of ACE inhibitor for at least 24 hours before treatment in patients who require both ACE inhibitors and desensitisation.

Anaphylactoid reactions during 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.

Haemodialysis patients:
Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g., AN 69®) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Potassium-sparing diuretics, potassium salts:
The combination of perindopril and potassium-sparing diuretics, potassium salts is usually not recommended (see section 4.5).

Pregnancy and lactation
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Linked to indapamide:
When liver function is impaired, thiazide diuretics and thiazide-related diuretics may cause hepatic encephalopathy. Administration of the diuretic should be stopped immediately if this occurs.

Photosensitivity:
Cases of photosensitivity reactions have been reported with thiazides and related thiazides diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Sultopride:
The combination of indapamide and sultopride is usually not recommended (see section 4.5).

Precautions for use
Common to perindopril and indapamide:
Renal impairment:
In cases of severe renal impairment (creatinine clearance < 30 ml/min), treatment is contraindicated.
In certain hypertensive patients without pre-existing apparent renal lesions and for whom renal blood tests show functional renal insufficiency, treatment should be stopped and possibly restarted either at a low dose or with one constituent only. In these patients usual medical
follow-up will include frequent monitoring of potassium and creatinine, after two weeks of treatment and then every two months during therapeutic stability period. Renal failure has been reported mainly in patients with severe heart failure or underlying renal failure including renal artery stenosis. The drug is usually not recommended in case of bilateral renal artery stenosis or a single functioning kidney.

**Hypotension and water and electrolyte depletion:**
There is a risk of sudden hypotension in the presence of pre-existing sodium depletion (in particular in individuals with renal artery stenosis). Therefore systematic testing should be carried out for clinical signs of water and electrolyte depletion, which may occur with an intercurrent episode of diarrhoea or vomiting. Regular monitoring of plasma electrolytes should be carried out in such patients. Marked hypotension may require the implementation of an intravenous infusion of isotonic saline.

Transient hypotension is not a contraindication to continuation of treatment. After re-establishment of a satisfactory blood volume and blood pressure, treatment can be started again either at a reduced dose or with only one of the constituents.

**Potassium levels:**
The combination of perindopril and indapamide does not prevent the onset of hypokalaemia particularly in diabetic patients or in patients with renal failure. As with any antihypertensive agent in combination with a diuretic, regular monitoring of plasma potassium levels should be carried out.

**Excipients:**
This medicinal product contains lactose monohydrate and patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**Linked to perindopril:**
**Cough:**
A dry cough has been reported with the use of angiotensin converting enzyme inhibitors. It is characterised by its persistence and by its disappearance when treatment is withdrawn. An iatrogenic aetiology should be considered in the event of this symptom. If the prescription of an angiotensin converting enzyme inhibitor is still preferred, continuation of treatment may be considered.

**Children and adolescents:**
The efficacy and tolerability of perindopril in children and adolescents, alone or in combination, have not been established.

**Risk of arterial hypotension and/or renal insufficiency (in cases of cardiac insufficiency, water and electrolyte depletion, etc...):**
Marked stimulation of the renin-angiotensin-aldosterone system has been observed particularly during marked water and electrolyte depletions (strict sodium restricted diet or prolonged diuretic treatment), in patients whose blood pressure was initially low, in cases of renal artery stenosis, congestive heart failure or cirrhosis with oedema and ascites. The blocking of this system with an angiotensin converting enzyme inhibitor may therefore cause, particularly at the time of the first administration and during the first two weeks of treatment, a sudden drop in blood pressure and/or an increase in plasma levels of creatinine, showing a functional renal insufficiency. Occasionally this can be acute in onset, although rare, and with a variable time to onset.
In such cases, the treatment should then be initiated at a lower dose and increased progressively.

**Elderly:**
Renal function and potassium levels should be tested before the start of treatment. The initial dose is subsequently adjusted according to blood pressure response, especially in cases of water and electrolyte depletion, in order to avoid sudden onset of hypotension.
**Patients with known atherosclerosis:**
The risk of hypotension exists in all patients but particular care should be taken in patients with ischaemic heart disease or cerebral circulatory insufficiency, with treatment being started at a low dose.

**Renovascular hypertension:**
The treatment for renovascular hypertension is revascularisation. Nonetheless, angiotensin converting enzyme inhibitors can be beneficial in patients presenting with renovascular hypertensive who are awaiting corrective surgery or when such a surgery is not possible. If these tablets are prescribed to patients with known or suspected renal artery stenosis, treatment should be started in a hospital setting at a low dose and renal function and potassium levels should be monitored, since some patients have developed a functional renal insufficiency which was reversed when treatment was stopped.

**Other populations at risk:**
In patients with severe cardiac insufficiency (grade IV) or in patients with insulin dependent diabetes mellitus (spontaneous tendency to increased levels of potassium), treatment should be started under medical supervision with a reduced initial dose. Treatment with beta-blockers in hypertensive patients with coronary insufficiency should not be stopped: the ACE inhibitor should be added to the beta-blocker.

**Diabetic patients:**
The glycaemia levels should be closely monitored in diabetic patients previously treated with oral antidiabetic drugs or insulin, namely during the first month of treatment with an ACE inhibitor.

**Ethnic differences:**
As with other angiotensin converting enzyme inhibitors, perindopril is apparently 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.

**Surgery / anaesthesia:**
Angiotensin converting enzyme inhibitors can cause hypotension in cases of anaesthesia, especially when the anaesthetic administered is an agent with hypotensive potential. It is therefore recommended that treatment with long-acting angiotensin converting enzyme inhibitors such as perindopril should be discontinued where possible one day before surgery.

**Aortic or mitral valve stenosis / hypertrophic cardiomyopathy:**
ACE inhibitors should be used with caution in patient with an obstruction in the outflow tract of the left ventricle.

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

**Hyperkalaemia:**
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Risk factors for the development of hyperkalemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g., spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalemia can cause serious, sometimes fatal arrhythmias.
If concomitant use of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

**Linked to indapamide:**

**Water and electrolyte balance:**

**Sodium levels:**

These should be tested before treatment is started, then at regular intervals. All diuretic treatment can cause a reduction in sodium levels, which may have serious consequences. Reduction in sodium levels can be initially asymptomatic and regular testing is therefore essential. Testing should be more frequent in elderly and cirrhotic patients (see sections 4.8 and 4.9).

**Potassium levels:**

Potassium depletion with hypokalaemia is a major risk with thiazide diuretics and thiazide-related diuretics. The risk of onset of lowered potassium levels (<3.4 mmol/l) should be prevented in some high risk populations such as elderly and/or malnourished subjects, whether or not they are taking multiple medications, cirrhotic patients with oedema and ascites, coronary patients and patients with heart failure.

In such cases hypokalaemia increases the cardiac toxicity of cardiac glycosides and the risk of rhythm disorders.

Subjects presenting with a long QT interval are also at risk, whether the origin is congenital or iatrogenic. Hypokalaemia, as with bradycardia, acts as a factor which favours the onset of severe rhythm disorders, in particular torsades de pointes, which may be fatal.

In all cases more frequent testing of potassium levels is necessary. The first measurement of plasma potassium levels should be carried out during the first week following the start of treatment.

If low potassium levels are detected, correction is required.

**Calcium levels:**

Thiazide diuretics and thiazide-related diuretics may reduce urinary excretion of calcium and cause a mild and transient increase in plasma calcium levels. Markedly raised levels of calcium may be related to undiagnosed hyperparathyroidism. In such cases the treatment should be stopped before investigating the parathyroid function.

**Blood glucose:**

Monitoring of blood glucose is important in diabetic patients, particularly when potassium levels are low.

**Uric acid:**

Tendency to gout attacks may be increased in hyperuricaemic patients.

**Renal function and diuretics:**

Thiazide diuretics and thiazide-related diuretics are only fully effective when renal function is normal or only slightly impaired (creatinine levels lower than approximately 25 mg/l, i.e. 220 µmol/l for an adult).

In the elderly the value of plasma creatinine levels should be adjusted to take account of the age, weight and sex of the patient, according to the Cockroft formula:

\[ \text{CrCl} = (140 - \text{age}) \times \text{body weight} / 0.814 \times \text{plasma creatinine level} \]

with: age expressed in years

body weight in kg

plasma creatinine level in micromol/l

This formula is suitable for an elderly male and should be adapted for women by multiplying the result by 0.85.

Hypovolaemia, resulting from the loss of water and sodium caused by the diuretic at the start of treatment, causes a reduction in glomerular filtration. It may result in an increase in blood urea and creatinine levels. This transitory functional renal insufficiency is of no adverse consequence in patients with normal renal function but may however worsen a pre-existing renal impairment.

**Athletes:**

Athletes should note that this product contains an active substance which may cause a positive reaction in doping tests.

4.5 **Interaction with other medicinal products and other forms of interaction**

**Common to perindopril and indapamide:**

Concomitant use not recommended:
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 further increase lithium levels and enhance the risk of lithium toxicity with ACE inhibitors. Use of perindopril combined with indapamide with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Concomitant use which requires special care:
- Baclofen: Potentiation of antihypertensive effect. Monitoring of blood pressure and renal function, and dose adaptation of the antihypertensive if necessary.
- Non-steroidal anti-inflammatory medicinal products (including acetylsalicylic acid at high doses > 3 g): the administration of a non-steroidal anti-inflammatory medicinal product may reduce the diuretic, natriuretic and antihypertensive effects in some patients. In elderly patients and patients who may be dehydrated there is a risk of acute renal failure, therefore monitoring of renal function at the initiation of treatment is recommended. Patients should be well hydrated.

Concomitant use which requires some care:
- Imipramine-like antidepressants (tricyclics), neuroleptics: Increased antihypertensive effect and increased risk of orthostatic hypotension (additive effect).
- Corticosteroids, tetracosactide: Reduction in antihypertensive effect (salt and water retention due to corticosteroids).
- Other antihypertensive agents: use of other antihypertensive medicinal products with perindopril/indapamide could result in additional blood pressure lowering effect.

Linked to perindopril:
Concomitant use not recommended:
- Potassium-sparing diuretics (spironolactone, triamterene, alone or in combination), potassium (salts): ACE inhibitors attenuate diuretic induced potassium loss. Potassium-sparing diuretics e.g. spironolactone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium (potentially lethal). If concomitant use is indicated because of documented hypokalaemia they should be used with caution and with frequent monitoring of serum potassium and by ECG.

Concomitant use which requires special care:
- Antidiabetic agents (insulin, hypoglycaemic sulphonamides): Reported with captopril and enalapril.

The use of angiotensin converting enzyme inhibitors may increase the hypoglycaemic effect in diabetics receiving treatment with insulin or with hypoglycaemic sulphonamides. The onset of hypoglycaemic episodes is very rare (improvement in glucose tolerance with a resulting reduction in insulin requirements).

Concomitant use which requires some care:
- Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids or procarcinamide: Concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia.
- Anaesthetic drugs: ACE inhibitors may enhance the hypotensive effects of certain anaesthetic drugs.
- Diuretics (thiazide or loop diuretics): Prior treatment with high dose diuretics may result in volume depletion and in a risk of hypotension when initiating therapy with perindopril.

Gold: Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including perindopril.

Linked to indapamide:
Concomitant use which requires special care:
- Torsades de pointes inducing drugs: Due to the risk of hypokalaemia, indapamide should be administered with caution when associated with medicinal products that induced torsades de pointes such as class IA antiarrhythmic agents (quinidine, hydroquinidine, disopyramide); class III antiarrhythmic agents (amiodarone, dofetilide, ibutilide, bretylium, sotalol); some neuroleptics (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine), benzamides (amisulpride, sulpiride, sulpropride, tiapride), butyrophenones (droperidol,
haloperidol), other neuroleptics (pimozide); other substances such as bepridil, cisapride, diphenamid, IV erythromycin, halofantrine, mizolastine, moxifloxacin, pentamidine, sparflloxacin, IV vincamine, methadone, astemizole, terfenadine. Prevention of low potassium levels and correction if necessary: monitoring of the QT interval.

- Potassium-lowering drugs: amphotericin B (IV route), glucocorticoids and mineralocorticoids (systemic route), tetracosactide, stimulant laxatives: Increased risk of low potassium levels (additive effect). Monitoring of potassium levels, and correction if necessary; particular consideration required in cases of treatment with cardiac glycosides. Non stimulant laxatives should be used.

- Cardiac glycosides: Low potassium levels favour the toxic effects of cardiac glycosides. Potassium levels and ECG should be monitored and treatment reconsidered if necessary. Concomitant use which requires some care:

- Metformin: Lactic acidosis due to metformin caused by possible functional renal insufficiency linked to diuretics and in particular to loop diuretics. Do not use metformin when plasma creatinine levels exceed 15 mg/l (135 micromol/l) in men and 12 mg/l (110 micromol/l) in women.

- Iodinated contrast media: In cases of dehydration caused by diuretics, there is an increased risk of acute renal insufficiency, particularly when high doses of iodinated contrast media are used. Rehydration should be carried out before the iodinated compound is administered.

- Calcium (salts): Risk of increased levels of calcium due to reduced elimination of calcium in the urine.

- Ciclosporin: Risk of increased creatinine levels with no change in circulating levels of ciclosporin, even when there is no salt and water depletion.

4.6 Pregnancy and lactation

Linked to perindopril:

**Pregnancy**

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section 5.3.). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

**Lactation**

Because no information is available regarding the use of perindopril during breastfeeding, perindopril is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Linked to indapamide:

**Pregnancy:**

Prolonged exposure to thiazide during the third trimester of pregnancy can reduce maternal plasma volume as well as uteroplacental blood flow, which may cause a feto-placental ischemia and growth retardation. Moreover, rare cases of hypoglycemia and thrombocytopenia in neonates have been reported following exposure near term.
Lactation:
Indapamide is excreted in human milk. Indapamide is closely related to thiazide diuretics which have been associated, during breast-feeding, with decrease or even suppression of milk lactation. Hypersensitivity to sulfonamide-derived drugs, hypokalaemia and nuclear icterus might occur.

Linked to perindopril and indapamide:
Lactation:
Perindopril/Indapamide Tablets is contraindicated during lactation.
As, with both drugs, serious adverse reactions might occur in nursing infants, a decision should be made whether to discontinue nursing or to discontinue therapy taking account the importance of this therapy for the mother.

4.7 Effects on ability to drive and use machines
Neither of the two active substances nor Perindopril/Indapamide Tablets affect alertness but individual reactions related to low blood pressure may occur in some patients, particularly at the start of treatment or in combination with another antihypertensive medication.

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

4.8 Undesirable effects
The administration of perindopril inhibits the renin-angiotensin-aldosterone axis and tends to reduce the potassium loss caused by indapamide. Four percent of the patients on treatment with Perindopril/Indapamide 4mg/1.25mg Tablets experience hypokalaemia (potassium level < 3.4 mmol/l).

The following undesirable effects could be observed during treatment 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), not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders:
Very rare:
Thrombocytopenia, leucopenia/neutropenia, agranulocytosis, aplastic anaemia, haemolytic anaemia.
Anaemia (see section 4.4) has been reported with angiotensin converting enzyme inhibitors in specific circumstances (patients who have had kidney transplants, patients undergoing haemodialysis).

Psychiatric disorders:
Uncommon: mood or sleep disturbances.

Nervous system disorders:
Common: Paresthesia, headache, dizziness, vertigo.
Very rare: Confusion.

Eye disorders:
Common: Vision disturbance.

Ear and labyrinth disorders:
Common: Tinnitus.

Vascular disorders:
Common: Hypotension whether orthostatic or not (see section 4.4).

Cardiac disorders:
Very rare: Arrhythmia including bradycardia, ventricular tachycardia, atrial fibrillation, angina pectoris and myocardial infarction possibly secondary to excessive hypotension in high-risk patients (see section 4.4).
Respiratory, thoracic and mediastinal disorders:
Common: A dry cough has been reported with the use of angiotensin converting enzyme inhibitors. It is characterised by its persistence and by its disappearance when treatment is withdrawn. An iatrogenic aetiology should be considered in the presence of this symptom.
Dyspnoea.
Uncommon: Bronchospasm.
Very rare: Eosinophilic pneumonia, rhinitis.

Gastrointestinal disorders:
Common: Constipation, dry mouth, nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea.
Very rare: Pancreatitis, intestinal angioedema.

Hepato-biliary disorders:
Very rare: Hepatitis either cytolytic or cholestatic (see section 4.4).
Not known: In case of hepatic insufficiency, there is a possibility of onset of hepatic encephalopathy (see sections 4.3 and 4.4).

Skin and subcutaneous tissue disorders:
Common: Rash, pruritus, maculopapular eruptions.
Uncommon: Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see section 4.4).
Hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions.
Blisters.
Possible aggravation of pre-existing acute disseminated lupus erythematosus.
Very rare: erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome.
Cases of photosensitivity reactions have been reported (see section 4.4).

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 and administration site conditions:
Common: Asthenia.
Uncommon: Sweating.

Investigations:
Potassium depletion with particularly serious reduction in levels of potassium in some at risk populations (see section 4.4).
Reduced sodium levels with hypovolaemia causing dehydration and orthostatic hypotension.
Increased in uric acid levels and in blood glucose levels during treatment.
Slight increase in urea and in plasma creatinine levels, reversible when treatment is stopped.
This increase is more frequent in cases of renal artery stenosis, arterial hypertension treated with diuretics, renal insufficiency.
Increased levels of potassium, usually transitory.
Rare: Raised plasma calcium levels.

4.9 Overdose
The most likely adverse reaction in cases of overdose is hypotension, sometimes associated with nausea, vomiting, cramps, dizziness, sleepiness, mental confusion, oliguria which may progress to anuria (due to hypovolaemia). Salt and water disturbances (low sodium levels, low potassium levels) may occur.
The first measures to be taken consist of rapidly eliminating the product(s) ingested by gastric lavage and/or administration of activated charcoal, then restoring fluid and electrolyte balance in a specialised centre until they return to normal. If marked hypotension occurs, this can be treated by placing the patient in a supine position with the head lowered. If necessary an intravenous infusion of isotonic saline may be given, or any other method of volaemic expansion may be used. Perindoprilat, the active form of perindopril, can be dialysed (see section 5.2).

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: perindopril and diuretics, ATC code: C09BA04
Perindopril/Indapamide Tablets is a combination of perindopril tert-butylamine salt, an angiotensin converting enzyme inhibitor, and indapamide, a chlorosulphamoyl diuretic. Its pharmacological properties are derived from those of each of the components taken separately, in addition to those due to the additive synergic action of the two products when combined.

Pharmacological mechanism of action
Linked to Perindopril/Indapamide Tablets:
Perindopril/Indapamide Tablets produce an additive synergy of the antihypertensive effects of the two components.
Linked to perindopril:
Perindopril is an inhibitor of the angiotensin converting enzyme (ACE inhibitor) which converts angiotensin I to angiotensin II, a vasoconstricting substance; in addition the enzyme stimulates the secretion of aldosterone by the adrenal cortex and stimulates the degradation of bradykinin, a vasodilatory substance, into inactive heptapeptides.
This results in:
- a reduction in aldosterone secretion
- an increase in plasma renin activity, since aldosterone no longer exercises negative feedback
- a reduction in total peripheral resistance with a preferential action on the vascular bed in muscle and the kidney, with no accompanying salt and water retention or reflex tachycardia, with chronic treatment.
The antihypertensive action of perindopril also occurs in patients with low or normal renin concentrations.
Perindopril acts through its active metabolite, perindoprilat. The other metabolites are inactive.
Perindopril reduces the work of the heart:
- by a vasodilatory effect on veins, probably caused by changes in the metabolism of prostaglandins : reduction in pre-load
- by reduction of the total peripheral resistance: reduction in afterload

Studies carried out on patients with cardiac insufficiency have shown:
- a reduction in left and right ventricular filling pressures
- a reduction in total peripheral vascular resistance
- an increase in cardiac output and an improvement in the cardiac index
- an increase in regional blood flow in muscle
Exercise test results also showed improvement

Linked to indapamide:
Indapamide is a sulphonamide derivative with an indole ring, pharmacologically related to the thiazide group of diuretics. Indapamide inhibits the reabsorption of sodium in the cortical dilution segment. It increases the urinary excretion of sodium and chlorides and, to a lesser extent, the excretion of potassium and magnesium, thereby increasing urine output and having an antihypertensive action.

Characteristics of antihypertensive action
Linked to Perindopril/Indapamide Tablets:
In hypertensive patients regardless of age, these tablets exert a dose-dependent antihypertensive effect on diastolic and systolic arterial pressure whilst supine or standing.
This antihypertensive effect lasts for 24 hours. The reduction in blood pressure is obtained in less than one month without tachyphylaxis; stopping treatment has no rebound effect. During clinical trials, the concomitant administration of perindopril and indapamide produced antihypertensive effects of a synergic nature in relation to each of the products administered alone.

**Linked to perindopril:**
Perindopril is active in all grades of hypertension: mild to moderate or severe. A reduction in systolic and diastolic arterial pressure is observed in the lying and standing position. The antihypertensive activity after a single dose is maximal at between 4 and 6 hours and is maintained over 24 hours.

There is a high degree of residual blocking of angiotensin converting enzyme at 24 hours, approximately 80%.

In patients who respond, normalised blood pressure is reached after one month and is maintained without tachyphylaxis. **Withdrawal of treatment has no rebound effect on hypertension.**

Perindopril has vasodilatory properties and restores elasticity of the main arterial trunks, corrects histomorphometric changes in resistance arteries and produces a reduction in left ventricular hypertrophy.

If necessary, the addition of a thiazide diuretic leads to an additive synergy. The combination of an angiotensin converting enzyme inhibitor with a thiazide diuretic decreases the hypokalaemia risk associated with the diuretic alone.

**Linked to indapamide:**
Indapamide, as monotherapy, has an antihypertensive effect which lasts for 24 hours. This effect occurs at doses at which the diuretic properties are minimal. Its antihypertensive action is proportional to an improvement in arterial compliance and a reduction in total and arteriolar peripheral vascular resistance. Indapamide reduces left ventricular hypertrophy.

When a dose of thiazide diuretic and thiazide-related diuretics is exceeded, the antihypertensive effect reaches a plateau, whereas the adverse effects continue to increase. If the treatment is ineffective, the dose should not be increased.

Furthermore, it has been shown that in the short-term, mid-term and long-term in hypertensive patients, indapamide:
- has no effect on lipid metabolism: triglycerides, LDL-cholesterol and HDL-cholesterol
- has no effect on carbohydrate metabolism, even in diabetic hypertensive patients

### 5.2 Pharmacokinetic properties

**Linked to Perindopril/Indapamide Tablets:**

The co-administration of perindopril and indapamide does not change their pharmacokinetic properties by comparison to separate administration.

**Linked to perindopril:**

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

Perindopril is a prodrug. Twenty seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.

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

It has been demonstrated a linear relationship between the dose of perindopril and its plasma exposure.

The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Protein binding of perindoprilat to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration-dependent. Perindoprilat is eliminated in the urine and the terminal half-life of the unbound fraction is approximately 17 hours, resulting in steady-state within 4 days. 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 sections 4.2 and 4.4).

Linked to indapamide:
Indapamide is rapidly and completely absorbed from the digestive tract. The peak plasma level is reached in humans approximately one hour after oral administration of the product. Plasma protein binding is 79%.

The elimination half-life is between 14 and 24 hours (average 18 hours). Repeated administration does not produce accumulation. Elimination is mainly in the urine (70% of the dose) and faeces (22%) in the form of inactive metabolites. The pharmacokinetics are unchanged in patients with renal insufficiency.

5.3 Preclinical safety data
Perindopril/Indapamide Tablets has slightly increased toxicity than that of its components. Renal manifestations do not seem to be potentiated in the rat. However, the combination produces gastro-intestinal toxicity in the dog and the toxic effects on the mother seem to be increased in the rat (compared to perindopril).

Nonetheless, these adverse effects are shown at dose levels corresponding to a very marked safety margin by comparison to the therapeutic doses used.

Preclinical studies performed separately with perindopril and indapamide did not show genotoxic, carcinogenic or teratogenic potential.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Colloidal hydrophobic silica
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 30°C. Store in the original package

6.5 Nature and contents of container
Tablets in blisters packed in an aluminium pouch containing desiccant silica gel. The tablets are available in pack sizes of 1, 7, 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98, 100 and 500 tablets.

Not all pack sizes may be marketed.

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

7 MARKETING AUTHORISATION HOLDER
Lupin (Europe) Limited
Victoria Court
Bexton Road
Knutsford
Cheshire WA16 0PF
United Kingdom
8 MARKETING AUTHORISATION NUMBER(S)
   PL 20092/0059

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   30/03/2010

10 DATE OF REVISION OF THE TEXT
    30/03/2010
PATIENT INFORMATION LEAFLET

PERINDOPRIL / INDA Pamela 2mg/0.625mg AND
4mg/1.25mg TABLETS

Perindopril tert-butylamine and Indapamide

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects 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 / Indapamide Tablets are and what they are used for
2. Before you take Perindopril / Indapamide Tablets
3. How to take Perindopril / Indapamide Tablets
4. Possible side effects
5. How to store Perindopril / Indapamide Tablets
6. Further information

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

Perindopril / Indapamide Tablets are a combination of two active ingredients, Perindopril and Indapamide. This medicine is an anti-hypertensive and is used in the treatment of high blood pressure (hypertension).

Perindopril belongs to a class of medicines called ACE inhibitors. These work by widening the blood vessels, which makes it easier for your heart to pump blood through them. Indapamide is a diuretic. Diuretics increase the amount of urine produced by the kidneys and are sometimes called water tablets. However, Indapamide is different from other diuretics, as it only causes a slight increase in the amount of urine produced. Each of the active ingredients reduces blood pressure and they work together to control your blood pressure.

2. BEFORE YOU TAKE PERINDOPRIL / INDAPAMIDE TABLETS

Do not take Perindopril / Indapamide Tablets if you
- are allergic to Perindopril or any other ACE inhibitor, or to indapamide or any other sulphonamides or any other ingredients of these tablets
- have experienced symptoms such as wheezing, swelling of the face or tongue, intense itching or severe skin rashes with previous ACE inhibitor treatment or if you or a member of your family have had these symptoms in any other circumstances (a condition called angioedema)
- have severe liver disease or suffer from a condition called hepatic encephalopathy (degenerative disease of the brain)
- have a severe kidney disease or if you are receiving dialysis
- have low or high blood potassium
- are suspected of having untreated decompensated heart failure (severe water retention, difficulty in breathing)
- are more than 3 months pregnant. (It is also better to avoid Perindopril / Indapamide Tablets in early pregnancy – see pregnancy section.)
- are breastfeeding.

Take special care with Perindopril / Indapamide Tablets
Before taking these tablets, tell your doctor if you
- have aortic stenosis (narrowing of the main blood vessel leading from the heart) or hypertrophic cardiomyopathy (heart muscle disease) or renal artery stenosis (narrowing of the artery supplying the kidney with blood)
- have any other heart problems or problems with your kidneys
• have liver problems
• suffer from a collagen disease such as systemic lupus erythematosus (allergic condition which causes joint pain, skin rashes and fever) or scleroderma
• have atherosclerosis (hardening of the arteries)
• suffer from hyperparathyroidism (overactive parathyroid gland)
• suffer from gout
• have diabetes
• are on a salt restricted diet or use salt substitutes which contain potassium
• take lithium or potassium-sparing diuretics (spironolactone, triamterene) as their use with these tablets should be avoided (see “Taking other medicines”)
• think you are (or might become) pregnant. Perindopril / Indapamide Tablets is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section)

You should also inform your doctor or the medical staff that you are taking Perindopril / Indapamide Tablets if you:
• are to undergo anaesthesia and/or surgery
• have recently suffered from diarrhoea or vomiting
• are to undergo LDL apheresis (which is removal of cholesterol from your blood by a machine)
• are going to have desensitisation treatment to reduce the effects of an allergy to bee or wasp stings
• are to undergo a medical test that requires injection of an iodinated contrast agent (a substance that makes organs like kidney or stomach visible on an X-ray)

Athletes should be aware that Perindopril / Indapamide Tablets contain an active ingredient (indapamide) which may give a positive reaction in drug tests.

Perindopril / Indapamide Tablets should not be given to children.

Taking Perindopril / Indapamide Tablets with other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

You should avoid Perindopril / Indapamide Tablets with:
• lithium (used to treat depression)
• potassium-sparing diuretics (spironolactone, triamterene), potassium salts

Treatment with Perindopril / Indapamide Tablets can be affected by other medicines. Make sure to tell your doctor if you are taking any of the following medicines as special care may be needed:
• other medicines for treating high blood pressure
• procainamide (for the treatment of an irregular heart beat)
• allopurinol (for the treatment of gout)
• terfenadine or astemizole (antihistamines for hay fever or allergies)
• corticosteroids used to treat various conditions including severe asthma and rheumatoid arthritis
• immunosuppressants used for the treatment of auto-immune disorders or following transplant surgery to prevent rejection (e.g. ciclosporin)
• medicines for the treatment of cancer
• erythromycin by injection (an antibiotic)
• halofantrine (used to treat certain types of malaria)
• pentamidine (used to treat pneumonia)
• vincamine (used to treat symptomatic cognitive disorders in the elderly including memory loss)
• bepridil (used to treat angina pectoris)
• medicines used for heart rhythm problems (e.g. quinidine, hydroquinidine, disopyramide, amiodarone, sotalol)
• digoxin (for the treatment of heart problems)
• ibuprofen (to treat muscle stiffness occurring in diseases such as multiple sclerosis)
• medicines to treat diabetes such as insulin or metformin
• calcium
• stimulant laxatives (e.g. senna)
• non-steroidal anti-inflammatory drugs (e.g. ibuprofen) or high dose salicylates (e.g. aspirin)
• amphotericin B by injection (to treat severe fungal disease)
• medicines to treat mental disorders such as depression, anxiety, schizophrenia (e.g. tricyclic antidepressants, neuroleptics)
• tetracosactide (to treat Cushing’s disease)
• gold (used to treat rheumatoid arthritis)

**Taking Perindopril / Indapamide Tablets with food and drink**
It is preferable to take Perindopril / Indapamide Tablets before a meal.

**Pregnancy and breastfeeding**

**Pregnancy**
You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Perindopril / Indapamide Tablets before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Perindopril / Indapamide Tablets. Perindopril / Indapamide Tablets is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

**Breastfeeding**
Tell your doctor if you are breastfeeding or about to start breastfeeding. Perindopril / Indapamide Tablets is not recommended for mothers who are breastfeeding, and your doctor may choose another treatment for you if you wish to breastfeed, especially if your baby is newborn, or was born prematurely. Ask your doctor or pharmacist for advice before taking this medicine.

**Driving and using machines**
Perindopril / Indapamide Tablets do not affect alertness but different reactions such as dizziness or weakness in relation to the decrease in blood pressure may occur in certain patients. If affected, your ability to drive or to operate machinery may be impaired.

**Important information about some of the ingredients of Perindopril / Indapamide Tablets**
This product contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. **HOW TO TAKE PERINDOPRIL / INDAPAMIDE TABLETS**
Always take Perindopril / Indapamide Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
The usual dose is one tablet once a day. Your doctor may decide to modify your dose if your kidneys are not working properly. Take your tablet with a glass of water preferably in the morning and before a meal. Swallow the tablet with a glass of water. Treatment for high blood pressure is usually life-long.

**If you take more Perindopril / Indapamide Tablets than you should**
If you take too many tablets, contact your doctor or nearest hospital casualty department. The most likely effect in case of overdose is low blood pressure. If marked low blood pressure occurs (symptoms such as dizziness or faintness), lying down with the legs raised can help.

**If you forget to take Perindopril / Indapamide Tablets**
It is important to take your medicine every day as regular treatment is more effective. However, if you forget to take a dose, take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.
If you stop taking Perindopril / Indapamide Tablets
As the treatment for high blood pressure is usually life-long, you should discuss with your doctor before stopping this medicinal product.
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 / Indapamide Tablets can cause side effects, although not everybody gets them.
You should stop taking your tablets at once and tell your doctor immediately if you experience any of the following effects of angioedema:
- swelling of the face, lips, mouth, tongue or throat, difficulty in breathing
- dizziness or fainting
- unusually fast or irregular heartbeat
This is an uncommon but serious reaction which can occur with all drugs of this type (ACE inhibitors). It must be treated immediately, usually in hospital.
Common side effects (affects more than 1 in 100 patients treated but less than 1 in 10):
- headache
- dizziness
- vertigo
- pins and needles
- vision disturbances
- tinnitus (sensation of noises in the ears)
- light-headedness due to low blood pressure
- cough
- shortness of breath
- nausea, vomiting, abdominal pain, taste disturbances, dry mouth, indigestion or difficulty of digestion, diarrhoea, constipation
- red, raised skin rash, skin rashes, itching
- muscle cramps
- feeling of weakness
Uncommon side effects (affects more than 1 in 1000 patients treated but less than 1 in 100):
- mood swings
- sleep disturbances
- bronchospasm (tightening of the chest, wheezing and shortness of breath)
- angioedema (symptoms such as wheezing, swelling of the face or tongue)
- urticaria (a raised itchy and painful rash)
- purpura (red pinpoints on skin)
- kidney problems
- impotence
- sweating
- If you suffer from systemic lupus erythematosus (a type of collagen disease), this might get worse
Rare side effects (affects more than 1 in 10000 patients treated but less than 1 in 1000):
- raised levels of calcium in the blood
Very rare side effects (affects less than 1 in 10,000 patients treated):
- bone marrow depression which makes infections more likely
- reduction in red blood cells
- reduction in blood platelets which increases risk of bleeding or bruising
- severe reduction in number of white blood cells which makes infection more likely
- illness resulting from the destruction of red blood cells
- confusion
- inflammation of the pancreas with severe upper stomach pain
• swellings in the intestine
• hepatitis with yellowing of the skin
• irregular heart beat, angina, heart attack
• eosinophilic pneumonia (a rare type of pneumonia)
• rhinitis (blocked up or runny nose)
• rash involving reddening, swelling and peeling of the skin that resembles severe burns
• a severe and widespread reddening of the skin with blistering
• a painful reddening of the skin with lumps and blisters
• sensitivity to the sun or artificial UVA
• acute kidney failure
• changes in laboratory parameters (blood tests) for different salts in the body and sugar levels. Your doctor may need to give you blood tests to monitor your condition
• in cases of liver problems, there is a possibility of onset of hepatic encephalopathy (degenerative disease in the brain)

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.

• dry mouth
• dry cough
• gastro-intestinal disorders (stomach or abdominal pain, loss of appetite, nausea, constipation and taste disturbance)

Uncommon side effects (affects more than 1 in 1000 patients treated but less than 1 in 100):

• feeling of tiredness
• dizziness
• headache
• mood swings
• sleep disturbances
• cramps
• pins and needles
• allergic reactions such as skin rashes
• purpura (red pinpoints on skin)
• hypotension (low blood pressure) whether orthostatic (lightheadedness occurring when standing up) or not
• If you suffer from systemic lupus erythematosus (allergic condition which causes joint pain, skin rashes and fever) this might get worse

Very rare side effects (affects less than 1 in 10,000 patients treated):

• increased risk of dehydration in the elderly and patients suffering from heart failure
• in cases of hepatic insufficiency (liver problems), there is a possibility of onset of hepatic encephalopathy (degenerative disease of the brain)
• increase in levels of calcium in your blood
• changes in blood cell count associated with increased susceptibility to infections or with bruises and a tendency to bleeding or feeling generally unwell
• disorders of the kidney, liver or pancreas and changes in laboratory parameters (blood tests) can occur. Your doctor may need to give you blood tests to monitor your condition.

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.

5. HOW TO STORE PERINDOPRIL / INDAPAMIDE TABLETS

Keep out of the reach and sight of children.

Do not take this medicine after the expiry date which is stated on the carton. The expiry date refers to the last day of the month.

Do not store your tablets above 30°C. Store in the original package to protect from moisture.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Perindopril / Indapamide Tablets contain

Active ingredients
Perindopril/Indapamide 2mg/0.625mg Tablets, contain perindopril tert-butylamine equivalent to 1.669mg perindopril and 0.625mg indapamide.
Perindopril/Indapamide 4mg/1.25mg Tablets, contain perindopril tert-butylamine equivalent to 3.338mg perindopril and 1.25mg indapamide.

Other ingredients
Lactose monohydrate, microcrystalline cellulose, magnesium stearate and colloidal hydrophobic silica.

What Perindopril / Indapamide Tablets looks like and the contents of the pack
Perindopril/Indapamide 2mg/0.625mg Tablets are white to off-white; capsule shaped uncoated tablets, with a scoreline on both sides. The tablets can be divided into equal halves.
Perindopril / Indapamide 4mg/1.25mg Tablets are white to off-white; capsule shaped uncoated tablets, plain on both sides.
Perindopril / Indapamide 2mg/0.625mg and 4mg/1.25mg Tablets are supplied in blisters packed in an aluminium pouch containing desiccant silica gel. The tablets are available in pack sizes of 1, 7, 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98, 100 and 500 tablets.
Not all pack sizes may be marketed.

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