Public Assessment Report

Decentralised Procedure

PERINDOPRIL INDAPAMIDE 2MG/0.625MG AND 4MG/1.25MG TABLETS

UK/H/1636 and 1638/001-2/DC
UK/H/1637/001/DC
UK Licence No: PL 04416/0900-1, 0903-5

SANDOZ LIMITED
LAY SUMMARY

On 19th May 2010, the UK granted Sandoz Limited Marketing Authorisations (licences) for Perindopril/Indapamide 2mg/0.625mg and 4mg/1.25mg Tablets.

These are medicines available on prescription from a doctor. The active ingredients in these medicines are perindopril and indapamide. The medicines are available in two different strength presentations. Perindopril & Indapamide 2mg/0.625mg Tablets contain 2mg of perindopril and 0.625mg indapamide. The higher strength product contains 4mg of perindopril and 1.25mg of indapamide.

Perindopril belongs to a group of medicines called ‘ACE inhibitors’. Perindopril works by widening the blood vessels, which makes it easier for your heart to pump blood through them.

Indapamide belongs to a group of medicines called ‘diuretics’. Diuretics increase the amount of urine produced by the kidneys and are sometimes called water tablets.

Each of the active ingredients reduces blood pressure and they work together to control your blood pressure.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Perindopril/Indapamide 2mg/0.625mg and 4mg/1.25mg Tablets outweigh the risks; hence these Marketing Authorisations have been granted.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Module 1: Information about initial procedure</th>
<th>Page 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Module 2: Summary of Product Characteristics</td>
<td>Page 5</td>
</tr>
<tr>
<td>Module 3: Product Information Leaflets</td>
<td>Page 33</td>
</tr>
<tr>
<td>Module 4: Labelling</td>
<td>Page 43</td>
</tr>
<tr>
<td>Module 5: Scientific Discussion</td>
<td>Page 47</td>
</tr>
<tr>
<td>1 Introduction</td>
<td></td>
</tr>
<tr>
<td>2 Quality aspects</td>
<td></td>
</tr>
<tr>
<td>3 Non-clinical aspects</td>
<td></td>
</tr>
<tr>
<td>4 Clinical aspects</td>
<td></td>
</tr>
<tr>
<td>5 Overall conclusions</td>
<td></td>
</tr>
<tr>
<td>Module 6: Steps taken after initial procedure</td>
<td>Page 58</td>
</tr>
</tbody>
</table>
# Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Perindopril/Indapamide 2mg/0.625mg and 4mg/1.25mg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Perindopril tert-butylamine</td>
</tr>
<tr>
<td></td>
<td>Indapamide</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Tablets</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>2mg/0.625mg and 4mg/1.25mg</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Sandoz Limited</td>
</tr>
<tr>
<td></td>
<td>Woolmer way</td>
</tr>
<tr>
<td></td>
<td>Bordon, Hants,</td>
</tr>
<tr>
<td></td>
<td>GU35 9QE</td>
</tr>
<tr>
<td></td>
<td>United Kingdom</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>CMS</strong></td>
<td>UK/H/1636/001-2: Belgium, the Czech Republic, Denmark,</td>
</tr>
<tr>
<td></td>
<td>Finland, France, Germany, Hungary, Malta, the Netherlands,</td>
</tr>
<tr>
<td></td>
<td>Poland, Portugal, Romania, Slovenia and the Slovak Republic</td>
</tr>
<tr>
<td></td>
<td>UK/H/1637/001: Germany and Ireland</td>
</tr>
<tr>
<td></td>
<td>UK/H/1638/001-2: Germany, Hungary and Portugal</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/1636 and 1638/001-2/DC</td>
</tr>
<tr>
<td></td>
<td>UK/H/1637/001/DC</td>
</tr>
<tr>
<td><strong>End of Procedure</strong></td>
<td>Day 210 – 22nd April 2010</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Perindopril/Indapamide 2 mg/0.625 mg Tablets

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

Excipient(s): lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet
White, oblong, biconvex tablet scored on one side and debossed with PI on the other side
The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Essential hypertension.

4.2 Posology and method of administration
Oral route
The usual dose is one Perindopril/Indapamide tablet per day as a single dose, preferably to be taken in the morning, and before a meal. If blood pressure is not controlled after one month of treatment, the dose can be doubled.

Elderly (see section 4.4)
Treatment should be started at the normal dose of one Perindopril/Indapamide tablet per day.

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 one tablet of Perindopril/Indapamide per day. In patients with creatinine clearance greater than or equal to 60 ml/min, no dose modification is required. Usual medical follow-up will include frequent monitoring of creatinine and 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
Perindopril/Indapamide 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 to any other sulphonamides
- Severe renal impairment (creatinine clearance below 30 ml/min)
- Hepatic encephalopathy
- Severe hepatic impairment
- Hypokalaemia
- As a general rule, this medicine is inadvisable in combination with non antiarrhythmic agents causing torsades de pointes (see section 4.5)
- Lactation (see section 4.6).

Linked to Perindopril/Indapamide:
Hypersensitivity to any of the excipients
Due to the lack of sufficient therapeutic experience, Perindopril/Indapamide 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:
For the low-dose combination Perindopril/Indapamide no significant reduction of adverse drug reactions as compared to the lowest approved dosages of the individual monocomponents has been shown except for hypokalaemia (see section 4.8). An increased frequency of idiosyncratic reactions cannot be excluded if the patient is simultaneously exposed to two antihypertensive agents new to him. To minimise this risk the patient should be carefully monitored.

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 angiotensin converting enzyme 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 procarinamide, 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:
Angioedema 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 the lips, the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, 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:**
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:**
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive 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.

**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 containing a diuretic, regular monitoring of plasma potassium levels should be carried out.

**Excipients:**
Perindopril/Indapamide contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

**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 ACE 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-free 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 (see sections 4.2)

**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 Perindopril/Indapamide is 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 convertin 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, 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. 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 micromol/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:

\[
c_{cr} = \frac{(140 - \text{age}) \times \text{body weight}}{0.814 \times \text{plasma creatinine level}}
\]

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.

**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. However, if the combination of an ACE inhibitor and a diuretic 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 (included acetylsalicylic acid at high doses):**

When ACE inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e.
acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

**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 hypokalemia 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 ACE 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 procainamide:**
  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 require 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, sulthiopine, tiapride), butyrophenones (droperidol, haloperidol), other neuroleptics (pimozide); other substances such as bepridil, cisapride,
diphenamid, IV erythromycin, halofantrine, mizolastine, moxifloxacin, pentamidine, sparflouxacin, IV
vinccamine, 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:**
  Lacte 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

Given the effects of the individual components in this combination product on pregnancy and lactation,
Perindopril/Indapamide is not recommended during the first trimester of pregnancy.
Perindopril/Indapamide is contraindicated during the second and third trimesters of pregnancy.

Perindopril/Indapamide is contraindicated during lactation. A decision should therefore be made
whether to discontinue nursing or to discontinue Perindopril/Indapamide taking account the importance
of this therapy for the mother.

**Pregnancy**

*Linked to perindopril:*

| 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 anti-hypertensive 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
fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal
toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

Should exposure to ACE inhibitors 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).

Linked to indapamide:
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 ischaemia and growth retardation. Moreover, rare cases of hypoglycemia and thrombocytopenia in neonates have been reported following exposure near term.

Lactation
Perindopril/Indapamide is contra-indicated during lactation.

Linked to perindopril:
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 breastfeeding are preferable, especially while nursing a newborn or preterm infant.

Linked to indapamide:
Indapamide is excreted in human milk. Indapamide is closely related to thiazide diuretics which have been associated, during breastfeeding, with decrease or even suppressed lactation. Hypersensitivity to sulfonamide-derived drugs, hypokalaemia and nuclear icterus might occur.

4.7 Effects on ability to drive and use machines
Linked to perindopril, indapamide and Perindopril/Indapamide
Neither the two active substances nor Perindopril/Indapamide 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 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 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.
**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).

**Vascular disorders:**
*Common:* Hypotension whether orthostatic or not (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, epigastric pain, anorexia, vomiting, abdominal pain, taste disturbance, dyspepsia, diarrhoea.
*Very rare:* Pancreatitis.

**Hepatobiliary 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 epidermic necrolysis, Stevens-Johnson syndrome.
Cases of photosensitivity reactions have been reported (see section 4.4).

**Musculoskeletal and connective tissue disorders:**
*Common:* 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:**

**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
Perindopril/Indapamide 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
Perindopril/Indapamide produces an additive synergy of the antihypertensive effects of the two components.

Linked to perindopril:
Perindopril is an inhibitor of the angiotensin converting enzyme (ACE) 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 vasoconstricting 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:*

In hypertensive patients regardless of age, Perindopril/Indapamide 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.

PICXEL, a multicenter, randomised, double blind active controlled study has assessed on echocardiography the effect of perindopril/indapamide combination on LVH versus enalapril monotherapy.

In PICXEL, hypertensive patients with LVH (defined as left ventricular mass index (LVMI) > 120 g/m² in male and > 100 g/m² in female) were randomised either to perindopril 2 mg/indapamide 0.625 mg or to enalapril 10 mg once a day for a one-year treatment. The dose was adapted according to blood pressure control, up to perindopril 8 mg and indapamide 2.5 mg or enalapril 40 mg once a day. Only 34% of the subjects remained treated with perindopril 2mg/indapamide 0.625mg (versus 20% with enalapril 10mg).

At the end of treatment, LVMI had decreased significantly more in the perindopril/indapamide group (-10.1 g/m²) than in the enalapril group (-1.1 g/m²) in the all randomised patients population. The between group difference in LVMI change was -8.3 (95% CI (-11.5,-5.0), p < 0.0001).

A better effect on LVMI was reached with higher perindopril/indapamide doses than those licensed for Perindopril/Indapamide 2mg / 0.625mg tablets and Perindopril/Indapamide 4mg / 1.25mg tablets.

Regarding blood pressure, the estimated mean between-group differences in the randomised population were -5.8 mmHg (95% CI (-7.9, -3.7), p < 0.0001) for systolic blood pressure and -2.3 mmHg (95% CI (-3.6,-0.9), p = 0.0004) for diastolic blood pressure respectively, in favour of the perindopril/indapamide group.

*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:
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 salt 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 has slightly increased toxicity than that of its components. Renal manifestations do not seem to be potentiated in the rat. However, the combination produces gastrointestinal 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
Hydroxypropylbetadex
Lactose monohydrate
Povidone K25
Silicified Microcrystalline Cellulose
Silica, colloidal hydrated
Colloidal anhydrous silica
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years
PVC / PVDC // Al blister in Al bag with added desiccant
After opening the bag: 6 months

6.4 Special precautions for storage
Alu/Alu blisters
Do not store above 30°C
PVC / PVDC // Al blister in Al bag with added desiccant
Do not store above 30°C

After opening the bag do not store above 25°C.

6.5 Nature and contents of container
Alu/Alu blisters
PVC / PVDC // Al blister in Al bag with added desiccant.
Pack sizes
PL 04416/0900: Blister containing 7, 10, 14, 20, 28, 30, 50, 60, 90, 100 tablets
PL 04416/0904: Blister containing 14, 20, 28, 30, 50, 60, 90, 100 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Sandoz Limited
Woolmer way
Bordon, Hants,
GU35 9QE
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 04416/0900 and 4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/05/2010

10 DATE OF REVISION OF THE TEXT
19/05/2010
1 NAME OF THE MEDICINAL PRODUCT
Perindopril/Indapamide 4 mg/1.25 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 4.00 mg of perindopril tert-butylamine, equivalent to 3.338 mg perindopril, and 1.25 mg of indapamide.
Excipient(s): lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.
white, oblong, biconvex tablet debossed with PI on one side

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

4.2 Posology and method of administration
Oral route.
One Perindopril/Indapamide 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 is recommended. Perindopril/Indapamide should be used when blood pressure is not adequately controlled on Perindopril/Indapamide 2mg/0.625mg tablets (where available). When clinically appropriate, direct change from monotherapy to perindopril/indapamide combination may be considered.

Elderly (see section 4.4)
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), it is recommended to start treatment with the adequate dosage of the free combination.
In patients with creatinine clearance greater than or equal to 60 ml/min, no dose modification is required. Usual medical follow-up will include frequent monitoring of creatinine and 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
Perindopril/Indapamide 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 to any other sulphonamides
- Severe renal impairment (creatinine clearance below 30 ml/min)
- Hepatic encephalopathy
- Severe hepatic impairment
- Hypokalaemia
- As a general rule, this medicine is inadvisable in combination with non antiarrhythmic agents causing torsades de pointes (see section 4.5)
- Lactation (see section 4.6).

Linked to Perindopril/Indapamide:
Hypersensitivity to any of the excipients

Due to the lack of sufficient therapeutic experience, Perindopril/Indapamide 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 angiotensin converting enzyme inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Perindopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy. If perindopril is used in such patients, 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/angioedema:**
Angioedema 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. Angioedema 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:** 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:**
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive 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.

**Precautions for use**

*Common to perindopril and indapamid:*

**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 containing a diuretic, regular monitoring of plasma potassium levels should be carried out.

Excipients:
Perindopril/Indapamide contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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 ACE 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-free 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 (see sections 4.2).

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 Perindopril/Indapamide is 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 convertin 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, 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. 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 micromol/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:

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

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.

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. However, if the combination of an ACE inhibitor and a diuretic 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 (included acetylsalicylic acid at high-doses):**
When ACE inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function.
The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

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 ACE 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 procainamide:*
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 require 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, sulpoxide, tiapride), butyrophenones (droperidol, haloperidol), other neuroleptics (pimozide); other substances such as bepridil, cisapride, diphenamid, IV erythromycin, halofantrine, mizolastine, moxifloxacin, pentamidine, sparflaxacin, 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:
Lactacidosis 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
Given the effects of the individual components in this combination product on pregnancy and lactation, Perindopril/Indapamide is not recommended during the first trimester of pregnancy. Perindopril/Indapamide is contraindicated during the second and third trimesters of pregnancy. Perindopril/Indapamide is contraindicated during lactation. A decision should therefore be made whether to discontinue nursing or to discontinue Perindopril/Indapamide taking account the importance of this therapy for the mother.

Pregnancy
Linked to perindopril:

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 anti-hypertensive 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 exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3). Should exposure to ACE inhibitors 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).

Linked to indapamide:
Prolonged exposure to thiazide during the third trimester of pregnancy can reduce maternal plasma volume as well as uteroplacental blood flow, which may cause feto-placental ischaemia and growth retardation. Moreover, rare cases of hypoglycemia and thrombocytopenia in neonates have been reported following exposure near term.

**Lactation**
Perindopril/Indapamide is contra-indicated during lactation.

**Linked to perindopril:**
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 breastfeeding are preferable, especially while nursing a newborn or preterm infant.

**Linked to indapamide:**
Indapamide is excreted in human milk. Indapamide is closely related to thiazide diuretics which have been associated, during breastfeeding, with decrease or even suppressed lactation. Hypersensitivity to sulfonamide-derived drugs, hypokalaemia and nuclear icterus might occur.

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

**Linked to perindopril, indapamide and Perindopril/Indapamide**
Neither the two active substances nor Perindopril/Indapamide 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 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 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.

**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).

**Vascular disorders:**
*Common:* Hypotension whether orthostatic or not (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, epigastric pain, anorexia, vomiting, abdominal pain, taste disturbance dyspepsia, diarrhoea.
*Very rare:* Pancreatitis.

**Hepatobiliary 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).
*Uncommon:* Hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions.
*Uncommon:* Purpura.

**Musculoskeletal and connective tissue disorders:**
*Common:* 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 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

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

Linked to perindopril:

Perindopril is an inhibitor of the angiotensin converting enzyme (ACE) 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:**
In hypertensive patients regardless of age, Perindopril/Indapamide exerts 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.

PICXEL, a multicenter, randomised, double blind active controlled study has assessed on echocardiography the effect of perindopril/indapamide combination on LVH versus enalapril monotherapy.

In PICXEL, hypertensive patients with LVH (defined as left ventricular mass index (LVMI) > 120 g/m² in male and > 100 g/m² in female) were randomised either to perindopril 2 mg/indapamide 0.625 mg or to enalapril 10 mg once a day for a one-year treatment. The dose was adapted according to blood pressure control, up to perindopril 8 mg and indapamide 2.5 mg or enalapril 40 mg once a day. Only 34% of the subjects remained treated with perindopril 2mg/indapamide 0.625mg (versus 20% with enalapril 10mg).

At the end of treatment, LVMI had decreased significantly more in the perindopril/indapamide group (-10.1 g/m²) than in the enalapril group (-1.1 g/m²) in the all randomised patients population. The between group difference in LVMI change was -8.3 (95% CI (-11.5,-5.0), p < 0.0001).

A better effect on LVMI was reached with higher perindopril/indapamide doses than those licensed for Perindopril/Indapamide 2mg / 0.625mg tablets and Perindopril/Indapamide 4mg / 1.25mg tablets.

Regarding blood pressure, the estimated mean between-group differences in the randomised population were -5.8 mmHg (95% CI (-7.9, -3.7), p < 0.0001) for systolic blood pressure and -2.3 mmHg (95% CI (-3.6,-0.9), p = 0.0004) for diastolic blood pressure respectively, in favour of the perindopril/indapamide group.

**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:
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 salt 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 has slightly increased toxicity than that of its components. Renal manifestations do not seem to be potentiated in the rat. However, the combination produces gastrointestinal 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
Hydroxypropylbetadex
Lactose monohydrate
Povidone K25
Silicified Microcrystalline Cellulose
Silica, colloidal hydrated
Colloidal anhydrous silica
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years
PVC / PVDC // Al blister in Al bag with added desiccant
After first opening the bag: 6 months

6.4 Special precautions for storage
Alu/Alu blisters
Do not store above 30°C
PVC / PVDC // Al blister in Al bag with added desiccant
Do not store above 30°C
After opening the bag do not store above 25°C.

6.5 Nature and contents of container
Alu/Alu blisters
PVC / PVDC // Al blister in Al bag with added desiccant.
Pack sizes
PL 04416/0901: Blister containing 7, 10, 14, 20, 28, 30, 50, 60, 90, 100 tablets
PL 04416/0903: Blister containing 7, 14, 20, 28, 30, 56, 60, 90, 98, 100 tablets
PL 04416/0905: Blister containing 14, 20, 28, 30, 50, 60, 90, 100 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Sandoz Limited
Woolmer way
Bordon, Hants,
GU35 9QE
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 04416/0901, 3 and 5

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/05/2010

10 DATE OF REVISION OF THE TEXT
19/05/2010
Module 3
Product Information Leaflet

The Patient Information Leaflet (PIL) below is the leaflet agreed at the end of the decentralised procedure. No mock-ups have been submitted. The marketing authorisation holder has committed to submit the PIL and labelling Mock-ups for review to the regulatory authority before marketing either product.

PACKAGE LEAFLET: INFORMATION FOR THE USER

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

Perindopril tert-butyamine/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 effect not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Perindopril/Indapamide is and what it used for
2. Before you take Perindopril/Indapamide
3. How to take Perindopril/Indapamide
4. Possible side effects
5. How to store Perindopril/Indapamide
6. Further information

1. WHAT PERINDOPRIL/INDAPAMIDE IS AND WHAT IT IS USED FOR

Perindopril/Indapamide tablets are a combination of two active ingredients, perindopril and indapamide. This medicine 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

Do NOT take Perindopril/Indapamide if you:

- are allergic (hypersensitive) to perindopril or any other ACE inhibitor, or indapamide or other sulphonamides or any other ingredient in these tablets (see Section 6)
- 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 a severe liver disease or a condition called hepatic encephalopathy (degenerative disease of the brain)
- have a severe kidney disease or 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 in early pregnancy – see pregnancy section.)
- are breast-feeding (see breast-feeding).

Do NOT give these tablets to children.

Take special care with Perindopril/Indapamide

Consult your doctor BEFORE taking these tablets if you:

- have narrowing of the main blood vessel leading from the heart (aortic stenosis)
- have narrowing of heart’s left valve (mitral valve stenosis)
- have cardiac muscle disease (hypertrophic cardiomyopathy)
- have narrowing of the artery supplying the kidney with blood (renal artery stenosis)
- have any other heart problems or problems with your kidneys
- have liver problems
- suffer from a collagen disease (skin disease) such as systemic lupus erythematosus or scleroderma
- have atherosclerosis (hardening of the arteries)
- suffer from hyperparathyroidism (disfunctioning of the parathyroid gland)
- have gout
- have diabetes
- are on a salt restricted diet or use salt substitutes which contain potassium
- take lithium or water tablets called potassium-sparing diuretics (spironolactone, triamterene) as their use with Perindopril/Indapamide should be avoided (see “Taking other medicines”)
- are more than 70 years old
- think you are (or might become) pregnant. Perindopril/Indapamide 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 these tablets if you:
- are to **undergo anaesthesia** and/or **surgery**
- have recently suffered from **diarrhoea** or **vomiting**, or are **dehydrated**
- have noticed increased sensitivity of the skin to **sunlight**
- have a persistent **dry cough**
- have **abdominal pain with or without nausea or vomiting**; these may be symptoms of serious allergic reaction called intestinal angioedema
- are to undergo **dialysis** or **LDL aphaeresis** (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).

Perindopril/Indapamide may be less effective in **Black people**.

**Taking other medicines**

Please tell your doctor or pharmacist, if you are taking or have recently taken any other medicines, including medicines obtained without a prescription, herbal medicines or natural products.

**Avoid** taking these tablets with:
- **lithium** (used to treat depression)
- **water tablets** (potassium-sparing diuretics such as spironolactone, triamterene)
- **potassium salts**.

In particular, **before taking** these tablets check with your doctor if you are taking any of the following:

- other medicines for treating **high blood pressure**
- medicines used for **heart rhythm problems** (e.g. procainamide, digoxin, hydroquinidine, disopyramide, quinidine, amiodarone, sotalol, diphenamid)
- **antihistamines** for hay fever or allergies e.g. terfenadine, astemizole, mizolastine
- **bepridil** (for angina pectoris)
- **benzamides** (for psychotic disorders e.g. sultopride)
- **butoxyphenones** (for psychotic disorders e.g. haloperidol)
- **cisapride** (intestinal medicine)
- **erythromycin** by injection (an antibiotic)
- **moxifloxacin** or **sparfloxacin** (antibiotics)
- methadone (anti-addiction medicine)
- allopurinol (for gout)
- 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 (e.g. ciclosporin)
- medicines for treating cancer
- halofantrine (for malaria)
- pentamidine (for pneumonia)
- vincamine (for symptomatic cognitive disorders in elderly)
- baclofen (for muscle stiffness occurring in diseases such as multiple sclerosis)
- diabetes medicines such as insulin, metformin or glimepiride
- calcium
- stimulant laxatives (e.g. senna)
- non-steroidal anti-inflammatory drugs (NSAIDs) for pain relief or high dose salicylates (e.g. aspirin)
- amphotericin B by injection (for severe fungal disease)
- medicines to treat mental disorders such as depression, anxiety, schizophrenia (e.g. tricyclic antidepressants, neuroleptics)
- tetracycline (to treat Crohn’s disease)
- gold (sodium aurothiomalate) by injection (medicine for rheumatic disorders).

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

Taking Perindopril/Indapamide with food and drink

Take your tablet with a glass of water preferably in the morning and before a meal. Take special care if you are on a salt-restricted diet. See your doctor before you take these tablets.

Pregnancy and breast-feeding

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 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. Perindopril/Indapamide 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.

Breast-feeding
You must not take Perindopril/Indapamide if you are breast-feeding.
Tell your doctor immediately if you are breast-feeding or about to start breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicine.
Driving and using machines
This medicine does not affect your alertness but you may feel dizzy or weak due to a decrease in your blood pressure, especially at the beginning of treatment or when increasing the dose. If this happens, your ability to drive or to operate machinery may be affected.

Important information about some of the ingredients of Perindopril/Indapamide
- **Lactose** is an ingredient in this medicine. 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

Always take this medicine exactly as your doctor told you. Please ask your doctor or pharmacist if you are not sure.

Take your tablet with a glass of water preferably in the morning and before a meal.

**Adults**
The usual dose is one tablet once a day.

Patients taking Perindopril/Indapamide 2mg/0.625mg tablets: Your doctor may decide to increase the dosage to 2 tablets per day.

**Elderly**
Your doctor will decide on the best dose for you.

Patients taking Perindopril/Indapamide 2mg/0.625mg tablets: Usually the doctor would start the treatment with one tablet of Perindopril/Indapamide once a day.

**Patients with kidney insufficiency**
Your doctor may decide to modify the dosage regimen if you suffer from kidney impairment.

**Children**
These tablets are not suitable for use in children.

If you take more Perindopril/Indapamide than you should
If you take too many tablets, contact your nearest hospital casualty department or tell your doctor immediately. 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 your legs raised can help.
If you forget to take Perindopril/Indapamide
It is important to take your medicine every day as regular treatment is more effective. However, if you forget to take one or more doses, take another as soon as you remember and then go on as prescribed. Do NOT take a double dose to make up for the forgotten one.

If you stop taking Perindopril/Indapamide
Always consult your doctor, if you wish to stop taking this medicine. Even if you feel well, it may be necessary to continue taking this medicine.

*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 can cause side effects, although not everybody gets them.

If you notice any of the following side effects, STOP taking the tablets and contact your doctor immediately. These are symptoms of a **serious allergic reaction** and must be treated immediately, usually in a hospital.

- swelling of the face, lips, mouth, tongue, eyes or throat
- difficulty in breathing
- severe dizziness or fainting
- blistering of the skin, mouth, eyes and genitals.

Also contact your doctor immediately if you notice any of the following side effects:

- unusual fast or irregular heart beat
- chest pain.

*Other side effects*

**Common (affects 1 to 10 users in 100)**

- constipation
- dry mouth
- nausea
- vomiting
- stomach discomfort after meal (dyspepsia)
- abdominal pains
- epigastric pains
- anorexia
- diarrhoea
- taste disturbance
- dry cough
- difficulty breathing
- vision disturbances
• ringing or buzzing in the ears
• muscle cramps
• feeling of weakness (asthenia)
• low blood pressure and dizziness, fainting on standing up
• headache
• feelings of dizziness
• sensations of tickling, itching or tingling without an apparent cause (paresthesia)
• spinning sensation (vertigo)
• skin reactions (rash, raised rash eruptions, itching)
• low potassium blood levels.

Uncommon *(affects 1 to 10 users in 1,000)*
• purple skin patches (purpura)
• skin itchy rash (urticaria)
• mood disturbances and/or sleep disturbances
• difficulty breathing with wheezing or coughing (bronchospasm)
• swelling of the face, lips, mouth, tongue, eyes or throat
• kidney disorder (renal insufficiency)
• impotence
• sweating.

If you already suffer from *systemic lupus erythematosus* (a type of collagen disease) this might get worse.

Rare *(affects 1 to 10 users in 10,000)*
• elevated plasma calcium levels
• intestinal angioedema (presented with abdominal pain with or without nausea or vomiting).

Very rare *(affects less than 1 user in 10,000)*
• pancreas inflammation (pancreatitis)
• reduction in the number of platelets
• reduction in the number of white blood cells, which makes infections more likely
• reduction in the number of red blood cells which can make the skin pale and cause weakness or breathlessness (anaemia in patients who have had kidney transplants, or in patients undergoing haemodialysis, aplastic anaemia, haemolytic anaemia)
• liver inflammation (hepatitis)
• kidney disorder with severely decreased urine output (acute renal failure)
• pneumonia
• nasal stuffiness or runny nose
• heart disorders (slow or unusual fast or irregular heart beat, chest pain or heart attack)
• severe skin reactions (manifested as rash, skin reddening, blistering of lips, eyes or mouth, skin peeling with or without fever)
• increased sensitivity of the skin to sunlight
• confusion.

Not known (frequency cannot be estimated from the available data)
• in case of liver failure (liver problems), there is a possibility of a brain disorders (personality change, confusion, stupor, tremor, convulsions, confusion, impaired consciousness)
• changes in laboratory parameters seen on blood tests.

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

Keep out of the reach and sight of children.

Do not use Perindopril/Indapamide after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Alu/Alu blisters
Do not store above 30°C.

PVC / PVDC / Al blister in Al bag with added desiccant
Do not swallow the desiccant.
Do not store above 30°C
After first opening the bag: 6 months
After opening the bag do not store above 25°C.

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 contains

The active substances are perindopril tert-butyamine and indapamide.

Perindopril/Indapamide 2 mg/0.625 mg Tablets:
Each tablet contains 2.00 mg of perindopril tert-butylamine, equivalent to 1.669 mg perindopril, and 0.625 mg of indapamide.

Perindopril/Indapamide 4 mg/1.25 mg Tablets:
Each tablet contains 4.00 mg of perindopril tert-butylamine, equivalent to 3.338 mg perindopril, and 1.25 mg of indapamide.

The other ingredients are:
Hydroxypropylbetadex, lactose monohydrate, povidone K25, silicified microcrystalline cellulose, Silica, colloidal hydrated, colloidal anhydrous silica, magnesium stearate.

What Perindopril/Indapamide looks like and contents of the pack

Perindopril/Indapamide 2 mg/0.625 mg Tablets are white, oblong, biconvex tablet scored on one side and debossed with PI on the other side.

Perindopril/Indapamide 4 mg/1.25 mg Tablets are white, oblong, biconvex tablet debossed with PI on one side

Alu/Alu blister
Pack sizes: 7, 10, 14, 20, 28, 30, 50, 60, 90, 100 tablets

Not all pack sizes may be marketed

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Sandoz Limited
Woolmer way
Bordon, Hants,
GU35 9 QE
United Kingdom

Manufacturer:
Lek Pharmaceuticals d.d.
Verovškova 57
1526 Ljubljana
Slovenia

Or

Lek S.A.
ul. Podlipie 16
95-010 Stryków
Poland
Or

Lek S.A.
ul. Domaniewska 50 C
02-672 Warszawa
Poland

Or

Salutas Pharma GmbH
Otto-von-Guericke-Allee 1
39179 Barleben
Germany

Or

Salutas Pharma GmbH
Dieselstrasse 5
70839 Gerlingen
Germany
Module 4
Labelling

The labelling below is the label agreed at the end of the decentralised procedure. No mock-ups have been submitted. The marketing authorisation holder has committed to submit the mock-up PIL and labelling for review to the regulatory authority before marketing either product. Please note that the labelling text shown below is for PL 04416/0901 only.

| PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING |
| CARTON (for blisters) |

1. NAME OF THE MEDICINAL PRODUCT

Perindopril/Indapamide 4 mg/1.25 mg Tablets
Perindopril tert-butylamine/indapamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 4.00 mg of perindopril tert-butylamine, equivalent to 3.338 mg perindopril, and 1.25 mg of indapamide.

3. LIST OF EXCIPIENTS

Contains amongst others: Lactose monohydrate
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

7 tablets
10 tablets
14 tablets
20 tablets
28 tablets
30 tablets
50 tablets
60 tablets
90 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE
STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
The bag inside the carton contains desiccant. Dispense intact.

8. EXPIRY DATE
EXP
After opening the bag use within 6 months

9. SPECIAL STORAGE CONDITIONS

Alu/Alu blisters
Do not store above 30°C

PVC / PVDC // Al blister in Al bag with added desiccant
Do not store above 30°C
After opening the bag do not store above 25°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER
Sandoz Limited
Woolmer way
Bordon, Hants,
GU35 9QE
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)
PL 04416/0901

13. MANUFACTURER’S BATCH NUMBER
Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
POM
15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Perindopril/Indapamide 4 mg/1.25 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Perindopril/Indapamide 4 mg/1.25 mg Tablets

Perindopril tert-butylamine/indapamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sandoz Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PL 04416/0901
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Aluminium bag

1. NAME OF THE MEDICINAL PRODUCT

Perindopril/Indapamide 4 mg/1.25 mg Tablets

Perindopril tert-butylamine/indapamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sandoz Limited

3. Expiry date

Exp

4. BATCH NUMBER

Lot

5. OTHER

Use within 6 months of opening. Pack contains a desiccant, DO NOT SWALLOW

PL 04416/0901
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, Germany, Hungary, Portugal and the UK considered that the applications for Perindopril/Indapamide 2mg/0.625mg and 4mg/1.25mg Tablets could be approved. These products are prescription only medicines (POM) and are indicated in adults for the treatment of essential hypertension.

These applications for Perindopril/Indapamide 2mg/0.625mg and 4mg/1.25mg Tablets are submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products to Conversyl 2mg/0.625mg and 4mg/1.25mg Tablets, first authorised in the EEA to Les Laboratoires Servier in October 1998.

No new preclinical studies were conducted, which is acceptable given that the products contain a widely-used, well-known active substance. No clinical studies with the exception of the bioequivalence study have been performed and none are required for these applications as the pharmacology of perindopril tert-butylamine and indapamide is well-established.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation Holder has provided adequate justification for not submitting a risk management plan (RMP).
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Perindopril/Indapamide 2mg/0.625mg and 4mg/1.25mg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Perindopril tert-butylamine</td>
</tr>
<tr>
<td></td>
<td>Indapamide</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Perindopril and diuretics (C09BA04)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>2mg/0.625mg and 4mg/1.25mg Tablets</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/1636 and 1638/001-2/DC</td>
</tr>
<tr>
<td></td>
<td>UK/H/1637/001/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Germany, Hungary, Portugal</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 04416/0900-1, 0903-5</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Sandoz Limited</td>
</tr>
<tr>
<td></td>
<td>Woolmer way</td>
</tr>
<tr>
<td></td>
<td>Bordon, Hants,</td>
</tr>
<tr>
<td></td>
<td>GU35 9QE</td>
</tr>
<tr>
<td></td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

Perindopril tert-butylamine

INN/Ph.Eur name: Perindopril Erbumine (in the form of complex with hydroxypropylbetadex)

EP: Perindopril tert-butylamine


Structural formula:

Molecular formula: C_{23}H_{43}N_3O_5
Molecular weight: 441.6

Hydroxypropylbetadex (a derivative of betadex)

INN/Ph.Eur name: Hydroxypropylbetadex (HPBCD)

Chemical name: β-cyclodextrin, 2-hydroxypropyl ether

Structural formula:
Molecular formula: \( \text{C}_{42}\text{H}_{43}\text{N}_{3}\text{O}_{5} \)
Molecular weight: 441.6

Appearance: The lyophilisate is a white or almost white powder
Solubility: Freely soluble in water.

Perindopril tert-butylamine – hydroxypropylbetadex lyophilizate contains approximately 20% of the active substance perindopril tert-butylamine and about 80% of hydroxypropylbetadex.

Both Perindopril tert-butylamine and Hydroxypropylbetadex are described by a European pharmacopoeia monograph.

Complete information has been provided covering the manufacture and control of the active substance perindopril tert-butylamine in complex with hydroxypropylbetadex.

Synthesis of the drug substance from the designated starting materials 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.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and certificates of analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Suitable certificates of analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

**Indapamide**

INN/Ph.Eur name: Indapamide
Chemical name: 4-Chloro-N-(2-methylindolin-1-yl)-3-sulphamoylbenzamide

Structural formula:
Molecular formula: $C_{16}H_{16}ClN_{3}O_{3}S$
Molecular weight: 365.8

Appearance: A white or almost white powder
Solubility: Practically insoluble in water, soluble in ethanol.

Indapamide is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture of the active substance indapamide from its starting materials are controlled by a Certificate of Suitability.

An appropriate retest period has been proposed based on stability data submitted for the active substance indapamide.

An appropriate specification is provided for the active substance, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specification.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable Certificates of Analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

P. Medicinal Product
Other Ingredients
Other ingredients consist of pharmaceutical excipients hydroxypropylbetadex, lactose monohydrate, povidone K25, silicified microcrystalline cellulose, colloidal hydrated silica, colloidal anhydrous silica, magnesium stearate.

The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption. The supplier of magnesium stearate has confirmed that it is of vegetable origin.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development
The objective of the development programme was to produce products that could be considered generic medicinal products of Conversyl 2mg/0.625mg and 4mg/1.25mg Tablets.

The applicant has provided suitable product development sections. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative impurity profiles have been provided for the finished products versus the reference products.
Comparative in vitro dissolution profiles and impurity profiles have been provided for the proposed and originator products.

Conversyl Plus 4mg/1.25mg Tablets licensed in the UK was used as the reference product in the bioequivalence study.

**Manufacturing Process**
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on three consecutive production-scale batches of each strength have been provided.

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

**Container-Closure System**
These products are packaged in aluminium blisters or blisters composed of polyvinyl chloride (PVC), polyvinylidene chloride (PVDC) and aluminium packaged in an aluminium bag with added desiccant.
The product comes in the following pack sizes;  
PL 04416/0900 and 1: 7, 10, 14, 20, 28, 30, 50, 60, 90, 100 tablets  
PL 04416/0903: 7, 14, 20, 28, 30, 50, 56, 60, 90, 98,100 tablets  
PL 04416/0904 and 5: 14, 20, 28, 30, 50, 60, 90, 100 tablets

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with EU legislation regarding contact with food.

**Stability of the product**
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of two years. For the product packaged in an aluminium bag, once the bag has been opened the shelf life is six months.

The special storage instructions are ‘Do not store above 30°C’. For the product packaged in an aluminium bag, ‘After opening the bag do not store above 25°C’.

**Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels**
The SPCs, PILs and labelling are pharmaceutically acceptable.

User testing results have been submitted for typical PILs for these products. The results indicate that the PILs are 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 they contain.

**MAA forms**
The MAA forms are pharmaceutically satisfactory.
Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.
III.2 PRE-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of perindopril tert-butylamine and indapamide are well-known. As perindopril tert-butylamine and indapamide are widely used, well-known active substances, the applicant has not provided any additional studies and none are required.

The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment.
III.3 CLINICAL ASPECTS

1. Introduction
This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier. For more details, the reader should refer to the company’s clinical overview and summary and to the clinical file.

The clinical overview has been written by an appropriately qualified physician. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

2. Clinical study reports
To support these applications, the marketing authorisation holder has submitted a single dose bioequivalence study:

**Study 1**
An open-label, single-dose, randomised, two-treatment, two-sequence, two-period, two-way cross-over bioequivalence study of Perindopril/Indapamide 4mg/1.25mg Tablets versus Coversyl® Plus 4mg/1.25mg Tablets in healthy subjects under fasting conditions.

All subjects were in a fasted state before dosing. Blood sampling was performed pre-dose, at baseline and up to 120 hours post dose in each treatment period. The washout period between phases was 21 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC₀₋ₜ (ng/ml/h)</th>
<th>AUC₀₋∞ (ng/ml/h)</th>
<th>Cmax (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perindopril:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>80.393</td>
<td>81.394</td>
<td>54.510</td>
</tr>
<tr>
<td>Reference</td>
<td>79.733</td>
<td>80.830</td>
<td>53.579</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>100.83</td>
<td>100.73</td>
<td>101.74</td>
</tr>
<tr>
<td>(96.51 – 105.34)</td>
<td>(96.36 – 105.23)</td>
<td>(94.77 – 109.22)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC₀₋ₜ (ng/ml/h)</th>
<th>AUC₀₋∞ (ng/ml/h)</th>
<th>Cmax (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perindoprilat:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>156.758</td>
<td>244.617</td>
<td>9.387</td>
</tr>
<tr>
<td>Reference</td>
<td>149.001</td>
<td>243.189</td>
<td>8.690</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>105.21</td>
<td>100.59</td>
<td>108.01</td>
</tr>
<tr>
<td>(101.57 – 108.97)</td>
<td>(95.08 – 106.41)</td>
<td>(102.25 – 114.10)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC₀₋ₜ (ng/ml/h)</th>
<th>AUC₀₋∞ (ng/ml/h)</th>
<th>Cmax (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indapamid:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>1172.232</td>
<td>1182.031</td>
<td>60.043</td>
</tr>
<tr>
<td>Reference</td>
<td>1149.618</td>
<td>1160.295</td>
<td>58.132</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>101.97</td>
<td>101.87</td>
<td>103.29</td>
</tr>
</tbody>
</table>
The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC\textsubscript{0-t} and C\textsubscript{max} for perindopril and the metabolite perindoprilat lie within 80-125% boundaries. Thus, bioequivalence has been shown between the test and reference products in this study.

As the 4mg/1.25mg strength product meet all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 4mg/1.25mg strength can be extrapolated to Perindopril/Indapamide 2mg/0.625mg Tablets.

3. **Post marketing experience**

Perindopril tert-butylamine and indapamide have well-recognised efficacy and an acceptable level of safety in the indications approved for Conversyl Tablets and corresponding products have been widely used in many countries. Therefore, the submission of PSUR at the renewal of the marketing authorisation is supported.

4. **Benefit-Risk assessment**

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with perindopril tert-butylamine and indapamide is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

5. **Conclusions**

The grant of Marketing Authorisations for Perindopril/Indapamide 2mg/0.625mg and 4mg/1.25mg Tablets is recommended from a clinical viewpoint.
IV OVERALL CONCLUSION AND BENEFIT-RISK 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
No new preclinical data were submitted and none are required for an application of this type.

EFFICACY
The application has been supported with evidence of bioequivalence between the product proposed for marketing and a suitable reference product.

No new or unexpected safety concerns arise from these applications.

The SPCs, PILs and labelling are satisfactory and consistent with that for the innovator products.

RISK-BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with perindopril tert-butylamine and indapamide is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>