Public Assessment Report

Decentralised Procedure

Perindopril/indapamide 2mg/0.625mg tablets
Perindopril/indapamide 4mg/1.25mg Tablets

UK/H/3495/01-02/DC
UK licence numbers: PL 25192/0002-3

Zentiva k.s
LAY SUMMARY

On 25th May 2011, the MHRA granted Zentiva k.s Marketing Authorisations (licences) for the medicinal products, Perindopril/indapamide 2mg/0.625mg and 4mg/1.25mg tablets (PL 25192/0002-3). These are prescription-only medicines (POM). They are anti-hypertensive medicines used in the treatment of high blood pressure (hypertension).

Perindopril/indapamide 2mg/0.625mg and 4mg/1.25mg tablets are medicines containing a combination of two active ingredients, perindopril and indapamide. Perindopril belongs to a class of medicines called ACE inhibitors. These types of medicines work by widening the blood vessels making it easier for your heart to pump blood through them. Indapamide is a diuretic. Diuretics increase the amount of urine produced by the kidneys. Both of these active ingredients reduce blood pressure and 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 Perindopril/indapamide 2mg/0.625mg and 4mg/1.25mg tablets outweigh the risks; hence Marketing Authorisations have been granted.
TABLE OF CONTENTS

Module 1: Information about initial procedure .................................................. Page 4
Module 2: Summary of Product Characteristics ................................................ Page 5
Module 3: Product Information Leaflet ............................................................. Page 20
Module 4: Labelling .......................................................................................... Page 27
Module 5: Scientific discussion during initial procedure .................................... Page 33
   I Introduction ............................................................................................... Page 33
   II About the product .................................................................................... Page 35
   III Scientific Overview and discussion ......................................................... Page 36
      III.1 Quality aspects ................................................................................ Page 36
      III.2 Non-clinical aspects .......................................................................... Page 40
      III.3 Clinical aspects ................................................................................. Page 40
   IV Overall conclusions and benefit-risk assessment ....................................... Page 43
Module 6: Steps taken after initial procedure .................................................... Page 44
## Module 1

### Information about Initial Procedure

| Product Name                      | Perindopril/indapamide 2mg/0.625mg tablets  
<table>
<thead>
<tr>
<th></th>
<th>Perindopril/indapamide 4mg/1.25mg tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Application</td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td>Active Substances</td>
<td>Perindopril tert-butylamine and indapamide</td>
</tr>
<tr>
<td>Form</td>
<td>Tablets</td>
</tr>
</tbody>
</table>
| Strength                          | Perindopril/indapamide 2mg/0.625mg tablets  
|                                  | Perindopril/indapamide 4mg/1.25mg tablets  |
| MA Holder                         | Zentiva k.s  
|                                  | U kabelovny 130,  
|                                  | Dolní Měcholupy,  
|                                  | 10237 Prague 10  
|                                  | Czech Republic                           |
| Reference Member State (RMS)      | UK                                       |
| Concerned Member States (CMS)     | UK/H/3495/01-02/DC: Czech Republic, France, Lithuania, Latvia, Portugal, Romania |
| Procedure Number                  | UK/H/3495/01-02/DC                       |
| Timetable                         | End of Procedure: Day 210 – 4th May 2011  |
Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Perindopril/indapamide 2mg/0.625mg and 4mg/1.25mg tablets (PL 25192/0002-3) is as follows. Differences between the individual SmPCs are highlighted:

1 NAME OF THE MEDICINAL PRODUCT

Perindopril/indapamide 2mg/0.625mg tablets
Perindopril/indapamide 4mg/1.25mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1.669 / 3.338 mg perindopril (as sodium salt), equivalent to 2 / 4 mg perindopril tert-butylamine and 0.625 / 1.25 mg indapamide.

Each Perindopril/indapamide 2mg/0.625mg / 4mg/1.25mg tablet contains 61.895 / 59.497 mg lactose anhydrous.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

2mg/0.625mg: white to creamy white, oblong tablets of 7.9-8.3mm length and 2.6-3.4mm height with a deep break mark on each side. An imprint “2” is located on one side of the breakline. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4mg/1.25mg: white to creamy white, oblong tablets of 7.9-8.3mm length and 2.6-3.4mm height with a deep break mark on each side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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 use.

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.

2mg/0.625mg

If blood pressure is not controlled after one month of treatment, the dose can be doubled.

4mg/1.25mg

When possible individual dose titration with the components is recommended, Perindopril/indapamide 4mg/1.25mg tablets 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 4mg/1.25mg tablets may be considered.

Elderly (see section 4.4)

Treatment should be started at the normal dose of one Perindopril/indapamide 2mg/0.625mg tablet per day. 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.
**2mg/0.625mg tablets**
In patients with moderate renal impairment (creatinine clearance 30-60 ml/min), the maximum dose should be one tablet of Perindopril/indapamide 2mg/0.625mg per day.

In patients with creatinine clearance greater than or equal to 60 ml/min, no dose modification is required.

**4mg/1.25mg tablets**
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.

It is not necessary to change the dose when creatinine clearance is greater than 60 mL / min.

Usual medical follow-up will include frequent monitoring of creatinine and plasma potassium.

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

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

**Children and adolescents**
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 section 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 of Perindopril/indapamide tablets 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 anti hypertensive 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 ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Perindopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procarbazine, 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, treatment with perindopril should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. When the oedema only affects the face and the lips, the effect generally recedes without treatment, even though anti-histamines may be used to relieve 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 patients:
Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g., AN 69®) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

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

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

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

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

Precautions for use
Common to perindopril and indapamide:

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

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

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

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

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

Children and adolescents:
The efficacy and tolerability of perindopril in children and adolescents, alone or in combination, have
not been established.
Risk of arterial hypotension and/or renal insufficiency (in cases of cardiac insufficiency, water and electrolyte depletion, etc.):  
Marked stimulation of the renin-angiotensin-aldosterone system has been observed particularly during marked water and electrolyte depletions (strict sodium restricted diet or prolonged diuretic treatment), in patients whose blood pressure was initially low, in cases of renal artery stenosis, congestive heart failure with oedema and ascites.  
The blocking of this system with an angiotensin converting enzyme inhibitor may therefore cause, particularly at the time of the first administration and during the first two weeks of treatment, a sudden drop in blood pressure and/or an increase in plasma levels of creatinine, showing a functional renal insufficiency. Occasionally this can be acute in onset, although rare, and with a variable time to onset.  
In such cases, the treatment should then be initiated at a lower dose and increased progressively.  

Elderly:  
Renal function and potassium levels should be tested before the start of treatment. The initial dose is subsequently adjusted according to blood pressure response, especially in cases of water and electrolyte depletion, in order to avoid sudden onset of hypotension.  

Patients with known atherosclerosis:  
The risk of hypotension exists in all patients but particular care should be taken in patients with ischaemic heart disease or cerebral circulatory insufficiency, with treatment being started at a low dose.  

Renovascular hypertension:  
The treatment for renovascular hypertension is revascularisation. Nonetheless, angiotensin converting enzyme inhibitors can be beneficial in patients presenting with renovascular hypertension who are awaiting corrective surgery or when such a surgery is not possible.  
If 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 converting enzyme inhibitors, perindopril is apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.  

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

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

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

**Hyperkalaemia:**
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril.

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

Linked to indapamide:

**Water and electrolyte balance:**

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

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

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

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

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

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

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

**Uric acid:**
Tendency to gout attacks may be increased in hyperuricaemic patients.

**Renal function and diuretics:**
Thiazide diuretics and thiazide-related diuretics are only fully effective when renal function is normal or only slightly impaired (creatinine levels lower than approximately 25 mg/l, i.e. 220 μmol/l for an adult).
In the elderly the value of plasma creatinine levels should be adjusted to take account of the age, weight and sex of the patient, according to the Cockroft formula:

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

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.

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

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

**Common to perindopril and indapamide:**

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

**Concomitant use which requires special care:**
- Baclofen: Potentiation of antihypertensive effect. Monitoring of blood pressure and renal function, and dose adaptation of the antihypertensive if necessary.
- Non-steroidal anti-inflammatory medicinal products (including acetylsalicylic acid at high doses): 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 angiotensin converting enzyme inhibitors may increase the hypoglycaemic effect in diabetics receiving treatment with insulin or with hypoglycaemic sulphonamides. The onset of hypoglycaemic episodes is very rare (improvement in glucose tolerance with a resulting reduction in insulin requirements).

Concomitant use which requires some care:
- Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids or 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 requires special care:
- Torsades de pointes inducing drugs: Due to the risk of hypokalaemia, indapamide should be administered with caution when associated with medicinal products that induced torsades de pointes such as class IA antiarrhythmic agents (quinidine, hydroquinidine, disopyramide); class III antiarrhythmic agents (amiodarone, dofetilide, ibutilide, bretylium, sotalol); some neuroleptics (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine), benzamides (amisulpride, sulpiride, sulpride, tiapride, tiapride), butyrophenones (droperidol, haloperidol), other neuroleptics (pimozide), other substances such as bepridil, cisapride, diphenamid, IV erythromycin, halofantrine, mizolastine, sparfloxacin, pentamidine, sultopride, sparfloxacin, IV vincamine, methadone, astemizole, terfenadine. Prevention of low potassium levels and correction if necessary: monitoring of the QT interval.
- Potassium-lowering drugs: amphotericin B (IV route), glucocorticoids and mineralocorticoids (systemic route), tetracosactide, stimulant laxatives: Increased risk of low potassium levels (additive effect). Monitoring of potassium levels, and correction if necessary; particular consideration required in cases of treatment with cardiac glycosides.
Non stimulant laxatives should be used.
- Cardiac glycosides: Low potassium levels favour the toxic effects of cardiac glycosides. Potassium levels and ECG should be monitored and treatment reconsidered if necessary.

Concomitant use which requires some care:
- Metformin: Lactic acidosis due to metformin caused by possible functional renal insufficiency linked to diuretics and in particular to loop diuretics. Do not use metformin when plasma creatinine levels exceed 15 mg/l (135 micromol/l) in men and 12 mg/l (110 micromol/l) in women.
- Iodinated contrast media: In cases of dehydration caused by diuretics, there is an increased risk of acute renal insufficiency, particularly when high doses of iodinated contrast media are used. Rehydration should be carried out before the iodinated compound is administered.
- Calcium (salts): Risk of increased levels of calcium due to reduced elimination of calcium in the urine.
- Ciclosporin: Risk of increased creatinine levels with no change in circulating levels of ciclosporin, even when there is no salt and water depletion.

4.6 Pregnancy and lactation
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 2nd and 3rd trimester of pregnancy (see section 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 also section 5.3). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see also section 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 ischemia and growth retardation. Moreover, rare cases of hypoglycemia and thrombocytopenia in neonates have been reported following exposure near term.

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

A decision should be made whether to discontinue nursing or to discontinue therapy taking account the importance of this therapy for the mother.

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

*Linked to perindopril, indapamide and perindopril/indapamide:*

The two active substances, individually or combined in perindopril/indapamide, have no influence on the ability to drive and use machines but individual reactions related to low blood pressure may occur in some patients, particularly at the start of treatment or in combination with another antihypertensive medication.

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

**4.8 Undesirable effects**

The administration of perindopril inhibits the renin-angiotensin-aldosterone axis and tends to reduce the potassium loss caused by indapamide.

*Two percent of the patients on treatment with Perindopril/indapamide 2mg/0.625mg tablets experience hypokalaemia (potassium level < 3.4 mmol/l).*
Four percent of the patients on treatment with Perindopril/indapamide 4mg/1.25mg tablets experience hypokalaemia (potassium level < 3.4 mmol/l).

The following undesirable effects could be observed during treatment and ranked under the following frequency:
- Very common (>1/10);
- common (>1/100, <1/10);
- uncommon (>1/1000, <1/100);
- rare (>1/10000, <1/1000), very rare (<1/10000), not known (cannot be estimated from the available data).

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

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

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

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

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

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

**Cardiac disorders:**
- Very rare: Arrhythmia including bradycardia, ventricular tachycardia, atrial fibrillation, angina pectoris and myocardial infarction possibly secondary to excessive hypotension in high-risk patients (see section 4.4).

**Respiratory, thoracic and mediastinal disorders:**
- Common: A dry cough has been reported with the use of angiotensin converting enzyme inhibitors. It is characterised by its persistence and by its disappearance when treatment is withdrawn. An iatrogenic aetiology should be considered in the presence of this symptom. Dyspnoea.
- Uncommon: Bronchospasm.
- Very rare: Eosinophilic pneumonia, rhinitis.

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

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

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

Renal and urinary disorders:
Uncommon: Renal insufficiency.
Very rare: Acute renal failure.

Reproductive system and breast disorders:
Uncommon: Impotence.

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

Investigations:
Potassium depletion with particularly serious reduction in levels of potassium in some at risk populations (see section 4.4).
Reduced sodium levels with hypovolaemia causing dehydration and orthostatic hypotension. Increase in uric acid levels and in blood glucose levels during treatment.
Slight increase in urea and in plasma creatinine levels, reversible when treatment is stopped. This increase is more frequent in cases of renal artery stenosis, arterial hypertension treated with diuretics, renal insufficiency.
Increased levels if 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: ACE INHIBITORS, COMBINATIONS- ACE Inhibitors 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 inhibitor) which converts angiotensin I to angiotensin II, a vasoconstricting substance; in addition the enzyme stimulates the
secretion of aldosterone by the adrenal cortex and stimulates the degradation of bradykinin, a vasodilatory substance, into inactive heptapeptides.

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

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

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

*Perindopril reduces the work of the heart*:
- by a vasodilatory effect on veins, probably caused by changes in the metabolism of prostaglandins: reduction in preload,
- 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.

*2mg/0.625mg*

The effect of the low-dose combination Perindopril/indapamide tablets on cardiovascular morbidity and mortality has not been studied.

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 2 mg/indapamid 0.625 mg (versus 20% with Enalapril 10 mg).

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**
Lactose anhydrous  
Magnesium stearate  
Microcrystalline cellulose  
Sodium hydrogen carbonate  
Maize starch  
Talc

6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
18 months

6.4 **Special precautions for storage**
Do not store above 25°C.

6.5 **Nature and contents of container**
Aluminium/Aluminium blister

20, 28, 30, 84, 90 tablets per carton

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements.
MARKETING AUTHORITY

Zentiva k.s
U kabelovny 130,
Dolní Měcholupy,
10237 Prague 10
Czech Republic

MARKETING AUTHORITY NUMBER(S)

PL 25192/0002
PL 25192/0003

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25/05/2011

DATE OF REVISION OF THE TEXT
25/05/2011
Module 3

Patient Information Leaflet text

PACKAGE LEAFLET: INFORMATION FOR THE USER

Perindopril/indapamide 2mg/0.625mg and 4mg/1.25mg Tablets
Perindopril tert-butyramine + Indapamide

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

In this leaflet:
-What perindopril/indapamide is and what it is used for
-Before you take perindopril/indapamide
-How to take perindopril/indapamide
-Possible side effects
-How to store perindopril/indapamide
-Further information

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

The name of your medicine is Perindopril/indapamide 2mg/0.625mg and 4mg/1.25mg tablets (called perindopril/indapamide throughout this leaflet).

Perindopril/indapamide is a combination of two active ingredients, perindopril and indapamide. It is an anti-hypertensive and is used in the treatment of high blood pressure (hypertension).

Perindopril belongs to a class of medicines called ACE inhibitors. These types of medicines work by widening the blood vessels making it easier for your heart to pump blood through them.

Indapamide is a diuretic. Diuretics increase the amount of urine produced by the kidneys. However, indapamide only increases the amount of urine produced very slightly.

Both of these active ingredients reduced blood pressure and work together to control your blood pressure.

2. BEFORE YOU TAKE PERINDOPRIL/INDAPAMIDE

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

**Take special care with perindopril/indapamide**

If any of the following applies to you, please talk to your doctor before taking perindopril/indapamide:
- if you have aortic stenosis (narrowing of the main blood vessel leading from the heart) or hypertrophic cardiomyopathy (cardiac muscle disease) or renal artery stenosis (narrowing of the artery supplying the kidney with blood);
- if you have any other heart problems or problems with your kidneys;
- if you have liver problems
- if you suffer from a collagen disease such as systemic lupus erythematosus or scleroderma;
- if you have atherosclerosis (hardening of the arteries);
- if you suffer from hyperparathyroidism (a dysfunction of the parathyroid gland);
- if you suffer from gout;
- if you have diabetes;
- if you are on a salt restricted diet or use salt substitutes which contain potassium;
- if you take lithium or potassium-sparing diuretics (spironolactone, triamterene) – as their use with perindopril/indapamide should be avoided.

You must tell your doctor if you think that 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).**

**Perindopril/indapamide is not recommended for use in children and adolescents.**

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

**Athletes should be aware that perindopril/indapamide contains an active ingredient (indapamide) which may give a positive reaction in drug tests.**

**Perindopril/indapamide should not be given to children.**

**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.

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

Taking perindopril/indapamid with food and drink
It is preferable to take perindopril/indapamid before a meal.

Pregnancy and breastfeeding
Ask your doctor or pharmacist for advice before taking any medicine.

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

Breastfeeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Perindopril/indapamid is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

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

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

3. **HOW TO TAKE PERINDOPRIL/INDAPAMIDE**

Always take perindopril/indapamide exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The starting dose is normally one tablet once a day. Your doctor may decide to modify the dose if your kidneys are not working properly.

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

**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 fainting), lying down with the 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 a dose of perindopril/indapamide, take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

**If you stop taking perindopril/indapamide**
As the treatment for high blood pressure is usually life-long, you should discuss with your doctor before stopping 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 experience any of the following, stop taking the medicinal product at once and tell your doctor immediately:
- Swelling of the face, lips, mouth, tongue or throat, difficulty in breathing,
- Severe dizziness or fainting,
- Unusual fast or irregular heart beat.

In decreasing order of frequency, side effects can include:

*Common side effects (occurring in more than 1 in 100 but less than 1 in 10 people):*
- Headache
- Dizziness
- Vertigo
• Pins and needles
• Vision disturbances
• Tinnitus (sensation of noises in the ears)
• Light-headedness due to low blood pressure
• Cough
• Shortness of breath
• Nausea, vomiting, abdominal pain, taste disturbances, dry mouth, indigestions or difficulty of digestion, diarrhoea, constipation
• Red, raised skin rash, skin rashes, itching
• Muscle cramps
• Feeling of weakness

Uncommon side effects (occurring in more than 1 in 1000 but less than 1 in 100 people):
• Mood swings,
• Sleep disturbances,
• Bronchospasm (tightening of the chest, wheezing and shortness of breath)
• Angioedema (symptoms such as wheezing, swelling of the face or tongue
• Urticaria (a raised itchy and painful rash)
• Purpura (red pinpoints on skin)
• Kidney problems
• Impotence
• Sweating
• If you suffer from systemic lupus erythematosus (a type of collagen disease) this might get worse.

Rare side effects (occurring in more than 1 in 10,000 but less than 1 in 1000).
• Raised levels of calcium in the blood

Very rare side effects (occurring in less than 1 in 10,000 people):
• Bone marrow depression which makes infections more likely
• Reduction in red blood cells
• Reduction in blood platelets which increases risk of bleeding or bruising
• Severe reduction in number of white blood cells which makes infection more likely
• Illness resulting from the destruction of red blood cells
• Confusion
• Inflammation of the pancreas with severe upper stomach pain
• Swellings in the intestine
• Hepatitis with yellowing of the skin
• Irregular heart beat, angina, heart attack
• Eosinophilic pneumonia (a rare type of pneumonia)
• Rhinitis (blocked up or runny nose)
• Rash involving reddening, swelling and peeling of the skin that resembles severe burns
• A severe and widespread reddening of the skin with blistering
• A painful reddening of the skin with lumps and blisters
• Sensitivity to the sun or artificial UVA
• Acute kidney failure
• Changes in laboratory parameters (blood tests) for different salts in the body and sugar levels. Your doctor may need to give you blood tests to monitor your condition.
• In cases of liver problems, there is a possibility of onset of hepatic encephalopathy (degenerative disease in the brain).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
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 carton and container. The expiry date refers to the last day of that month.

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.

Do not store above 25°C.

6. **FURTHER INFORMATION**

**What perindopril/indapamide contains**

The active substances are perindopril tert-butylamine and indapamide.

Perindopril/indapamide 2mg/0.625mg: Each tablet contains 1.669 mg perindopril (as sodium salt), equivalent to 2 mg perindopril tert-butylamine and 0.625 mg indapamide.

Perindopril/indapamide 4mg/1.25mg: Each tablet contains 3.338 mg perindopril (as sodium salt), equivalent to 4 mg perindopril tert-butylamine and 1.25 mg indapamide.

The other ingredients are:
- Lactose anhydrous, Maize starch, Microcrystalline cellulose, Sodium hydrogen carbonate, Talc, Magnesium stearate.

**What perindopril/indapamide looks like and contents of the pack**

Perindopril/indapamide 2mg/0.625mg: white to creamy white, oblong tablets of with a deep break mark on each side. An imprint ‘2’ is located on one side of the breakline. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Perindopril/indapamide 4mg/1.25mg: white to creamy white, oblong tablets of with a deep break mark on each side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The tablets are available in containers of

- 20, 28, 30, 84, 90 tablets per carton

Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

Zentiva k.s
U Kabelovny 130.
Dolni Mecholepy.
10237 Prague 10
Czech Republic

Manufacturer
Weiner Pharma GmbH, Im Steingerust 30, 76437 Rastatt, Germany
Or
Galex, d.d., Tlmska ulica 29g, 9000 Marska Sobota, Slovenia

This leaflet was last revised in May 2011
Module 4

Labelling texts

Perindopril/indapamide 2mg/0.625mg tablets – PL 25192/0002

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Perindopril/indapamide 2 mg / 0.625 mg tablets
Perindopril tert-butylamine / Indapamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1.669 mg perindopril (as sodium salt), equivalent to 2 mg perindopril tert-butylamine and 0.625 mg indapamide.

3. LIST OF EXCIPIENTS

Contains lactose anhydrous.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet
20 tablets
28 tablets
30 tablets
84 tablets
90 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
8. **EXPIRY DATE**

EXP:

9. **SPECIAL STORAGE CONDITIONS**

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**

Zentiva k.s
U kabelovny 130,
Dolni Měcholupy,
10237 Prague 10
Czech Republic

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 25192/0002

13. **BATCH NUMBER**

Lot:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Perindopril/indapamide 2 mg / 0.625 mg tablets
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blister</td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

   Perindopril/indapamide 2 mg / 0.625 mg tablets
   Perindopril tert-butylamine / Indapamine

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

   Zentiva, k.s

3. **EXPIRY DATE**

   EXP:

4. **BATCH NUMBER**

   Lot:

5. **OTHER**
Perindopril/indapamide 4mg/1.25mg tablets – PL 25192/0003

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Perindopril/indapamide 4 mg / 1.25 mg tablets
Perindopril tert-butyamine / Indapamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 3.338 mg perindopril (as sodium salt), equivalent to 4 mg perindopril tert-butyamine and 1.25 mg indapamide

3. LIST OF EXCIPIENTS

Contains lactose anhydrous.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

20 tablets
28 tablets
30 tablets
50 tablets
84 tablets
90 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
8. **EXPIRY DATE**

EXP:

9. **SPECIAL STORAGE CONDITIONS**

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**

Zenitva k.s  
U kabelovny 130,  
Dolni Mécholupy,  
10237 Prague 10  
Czech Republic

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 25192/0003

13. **BATCH NUMBER**

Lot:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Perindopril/indapamide 4 mg / 1.25 mg tablets
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 / Indapamine

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

Zenitha, k.s

3. **EXPIRY DATE**

EXP:

4. **BATCH NUMBER**

Lot:

5. **OTHER**
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Zentiva k.s. Marketing Authorisations for the medicinal products, Perindopril/indapamide 2mg/0.625mg and 4mg/1.25mg tablets (PL 25192/0002-3; UK/H/3495/01-02/DC) on 25th May 2011. The products are prescription-only medicines.

These are generic applications for Perindopril/indapamide 2mg/0.625mg and 4mg/1.25mg tablets, submitted under Article 10.1 of Directive 2001/83 EC, as amended. The applications refer to their respective UK products, Perindopril-Indapamide 2mg/0.625mg Tablets (PL 05815/0026) and Preterax double strength 4/1.25 Tablets (PL 05815/0014), authorised to Les Laboratoires Servier in the UK on 23rd October 2001 and 23rd September 1998 respectively, through incoming Mutual Recognition procedures [FR/H/0131/01/E01 & FR/H/0130/01] where France was the Reference Member State (RMS). The European originator product is BiPreterax 4mg/1.25mg Tabletten, authorised to Servier Deutschland GmbH in Germany on 9th October 1998. The originator product has been authorised in the EU for more than 10 years, thus the period of data exclusivity has expired.

With the UK as the RMS in these Decentralised Procedures, Zentiva k.s. applied for Marketing Authorisations for Perindopril/indapamide 2mg/0.625mg and 4mg/1.25mg tablets in the Czech Republic, France, Lithuania, Latvia, Portugal and Romania.

Perindopril/indapamide is a combination (ATC code: C09BA04; ACE inhibitors and diuretics) 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 actives when combined.

Perindopril, a lipophilic carboxyl-containing ACE inhibitor, is indicated for the treatment of hypertension, symptomatic heart failure, in stable coronary artery disease and for the reduction of cardiac events in patients with myocardial infarction and/or revascularisation. Indapamide is a thiazide-related diuretic, primarily used for the treatment of high blood pressure. The action and uses of indapamide are similar to those of a thiazide diuretic. Indapamide tablets are approved for the treatment of hypertension either alone or in combination with other antihypertensives.

Perindopril/indapamide 2mg/0.625mg and 4mg/1.25mg tablets are indicated for treatment of essential hypertension in patients whose blood pressure is not adequately controlled on perindopril alone.

The applications are supported by a bioequivalence study comparing the pharmacokinetic profile of the test product, Perindopril/indapamide 4mg/1.25mg tablets, to that of the reference product, Perindopril/indapamide 4mg/1.25mg (Coversyl Plus) tablets (Les Laboratoires Servier). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).
The Reference Member State (RMS) has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products. 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.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) 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 MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). As the applications are for generic versions of already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profiles of the actives are well-established.

The MAH has provided adequate justification for not submitting a detailed Environmental Risk Assessment (ERA). These were applications for generic products and there is no reason to conclude that marketing of these products will change the overall use pattern of the existing market. There are no environmental concerns associated with the method of manufacture or formulation of the products.
## II. ABOUT THE PRODUCT

| **Name of the product in the Reference Member State** | Perindopril/indapamide 2mg/0.625mg tablets  
| Perindopril/indapamide 4mg/1.25mg tablets |
| **Name(s) of the active substance(s) (INN)** | Perindopril tert-butylamine and indapamide |
| **Pharmacotherapeutic classification (ATC code)** | ACE inhibitors and diuretics (C09 BA04) |
| **Pharmaceutical form and strength(s)** | Perindopril/indapamide 2mg/0.625mg tablets  
| Perindopril/indapamide 4mg/1.25mg tablets |
| **Reference numbers for the Decentralised Procedure** | UK/H/3495/01-02/DC |
| **Reference Member State** | United Kingdom |
| **Member States concerned** | UK/H/3495/01-02/DC: CZ, FR, LT, LV, PT, RO |
| **Marketing Authorisation Number(s)** | PL 25192/0002-3 |
| **Name and address of the authorisation holder** | Zentiva k.s  
U kabelovny 130,  
Dolní Měcholupy,  
10237 Prague 10  
Czech Republic |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

Perindopril tert-butylamine

Nomenclature:

INN: Perindopril tert-butylamine

Structure:

Molecular formula: C₁₉H₃₂N₂O₅, C₄H₁₁N
Molecular weight: 441.6 g/mol
CAS No: 107133-36-8
Physical form: white or almost white, slightly hygroscopic, crystalline powder
Solubility: freely soluble in water and in ethanol (96 per cent), soluble or sparingly soluble in methylene chloride

The active substance, perindopril tert-butylamine, is the subject of a British Pharmacopeia (B.P.) monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

Appropriate specifications have been provided for the active substance. 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 specifications. Satisfactory Certificates of Analysis have been provided for reference standards used.

The active substance is stored in appropriate packaging. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary packaging in direct contact with the active substance complies with relevant Ph. Eur. requirements and satisfies Directive 2002/72/EC (as amended); it is suitable for contact with foodstuffs.
Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and support the 24-month retest period that has been applied.

ACTIVE SUBSTANCE

Indapamide

Nomenclature:
INN: Indapamide
Chemical names: 4-Chloro-N-(2-methylindolin-1-yl)-3-sulphamoylbenzamide
Structure:

![Chemical structure of indapamide]

Molecular formula: C₁₆H₁₆ClN₃O₃S
Molecular weight: 365.8 g/mol
CAS No: 26807-65-8
Physical form: white or almost white powder, practically insoluble in water, soluble in ethanol
Solubility: practically insoluble in water, soluble in ethanol (96 per cent)

The active substance, indapamide, is the subject of a European Pharmacopeia (Ph. Eur.) monograph.

All aspects of the manufacture and control of indapamide are supported by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability (CEP). The certificate is accepted as confirmation of the suitability of indapamide for inclusion in these medicinal products.
MEDICINAL PRODUCT

Description and Composition

Perindopril/indapamide 2mg/0.625mg and 4mg/1.25mg tablets are presented as white to creamy white, oblong-shaped tablets with scorelines on both sides. The 2mg /0.625mg tablets are imprinted with ‘2’ on one side. Each tablet contains 1.669 / 3.338 mg perindopril (as sodium salt), equivalent to 2 / 4 mg perindopril tert-butylamine and 0.625 / 1.25 mg indapamide.

Other ingredients consist of pharmaceutical excipients, namely lactose anhydrous, magnesium stearate, microcrystalline cellulose, sodium hydrogen carbonate, maize starch and talc. Appropriate justification for the inclusion of each excipient has been provided.

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

The magnesium stearate has been confirmed as being of vegetable origin. The only excipient used that contains material of animal or human origin is lactose anhydrous. The applicant has provided a declaration that milk used in the production of lactose anhydrous is sourced from healthy animals under the same conditions as that for human consumption. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used and no overages.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The objective was to develop stable, generic formulations, bioequivalent to the reference products, Perindopril-Indapamide 2mg/0.625mg Tablets and Preterax double strength 4/1.25 Tablets (PL 05815/0026 and 0014, Les Laboratoires Servier).

Comparative dissolution and impurity data were provided for batches of the test products and appropriate reference products. The dissolution and impurity profiles were satisfactory.

Manufacture

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

In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted and the results were satisfactory.

Finished product specification

The finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.
Container Closure System
Perindopril/indapamide 2mg/0.625mg and 4mg/1.25mg tablets are packed in bulk packs for repackaging into marketable packs. The bulk pack consists of Low Density Polyethylene (LDPE) bags as a primary packaging material, contained in High Density Polyethylene (HDPE) containers (with lids and seals).

The medicinal products are licensed for marketing in aluminium foil blister strips, which are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 20, 28, 30, 84 and 90 tablets. The MAH has stated that not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. These data support a shelf-life of 18 months with the storage instructions ‘Do not store above 25°C’. Stability data of the tablets in bulk packaging support a holding time of 3 months.

Quality Overall Summary
A satisfactory quality overall summary is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Product Information
The approved Summaries of Product Characteristics (SmPCs), and Patient Information Leaflet (PIL) and labelling texts are satisfactory. The labelling texts fulfil the statutory requirements for Braille. The user testing of the PIL text has been evaluated and is accepted. The MAH has submitted text versions and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

Conclusion
All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of Perindopril/indapamid 2mg/0.625mg and 4mg/1.25mg tablets from a pharmaceutical point of view.
III.2  NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable considering that these are applications for generic versions of products that have been licensed for many years and the European originator product, BiPreterax 4mg/1.25mg Tabletten, has been licensed for more than 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of perindopril/indapamide in combination, a widely used and well-known combination. The overview, dated October 2008, cites 72 references from the published literature dated up to year 2008. The CV of the non-clinical expert has been supplied. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the EU originator medicinal product, BiPreterax 4mg/1.25mg Tabletten (Servier Deutschland GmbH).

There are no objections to approval of Perindopril/indapamide 2mg/0.625mg and 4mg/1.25mg tablets from a non-clinical point of view.

III.3  CLINICAL ASPECTS

INDICATIONS

Perindopril/indapamide 2mg/0.625mg and 4mg/1.25mg tablets are indicated for treatment of essential hypertension in patients whose blood pressure is not adequately controlled on perindopril alone.

The indications are in line with those for the UK reference products and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

The usual dose is one Perindopril/indapamide 2mg/0.625mg 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 to the Perindopril/indapamide 4mg/1.25mg tablet.

Full details concerning the posology are provided in the SmPCs. The posology is consistent with that for the UK reference products and is satisfactory.

TOXICOLOGY

The toxicology of perindopril/indapamide in combination is well-known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY

The clinical pharmacology of perindopril/indapamide in combination is well-known. With the exception of the bioequivalence study, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for these applications.

Pharmacokinetics – bioequivalence study

The applications are supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profile of the test product, Perindopril/indapamide 4mg/1.25mg tablets, to that of the reference product, Perindopril/indapamide 4mg/1.25mg (Coversyl Plus) tablets (Les Laboratoires Servier). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP). Certificates of Analysis were provided for both the test and reference products.
This was an open-label, randomised, two-way, two-period, single dose crossover bioequivalence study conducted in 34 healthy adult human subjects under fasting conditions. A single dose of the investigational products was administered orally to each subject in each period. A satisfactory washout period of 35 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 216.0 hours after administration of test or reference product. Plasma levels of perindopril, its metabolite perindoprilat, and indapamide were detected by a validated LC-MS / MS method.

The primary pharmacokinetic parameters for this study were $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$. Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 0.80-1.25 (80.00%-125.00%), for log-transformed $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$.

Results:

34 subjects were enrolled in the study; 30 of these completed the study and were included in the pharmacokinetic evaluation and statistical analysis. The discontinuation, and non-inclusion in the pharmacokinetic analysis, of 4 subjects was satisfactorily justified.

Safety - A total of 36 treatment emergent adverse events were reported by 16 of the 34 subjects. All reported adverse events were graded as mild or moderate in severity. The most commonly reported treatment emergent adverse event was “headache”. No deaths or serious adverse events were reported during the study.

The summary of the results of the bioequivalence study are tabulated below:

Pharmacokinetic results for perindopril, perindoprilat and indapamide for a randomised, two-way, two-period, single-dose crossover study between the test and reference products. $n=30$ healthy subjects, dosed fasted; $t=216$ hours. Wash-out period: 35 days.

### Conclusion on Bioequivalence

The results of the bioequivalence study show that the test and reference products are bioequivalent under fasting conditions, as the confidence intervals for $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$ for perindopril, perindoprilat and indapamide fall within the acceptance criteria ranges of 80.00-125.00%, in line with current CHMP guidelines.
Satisfactory justification is provided for a bio-waiver for Perindopril/indapamide 2mg/0.625mg. As Perindopril/indapamide 2mg/0.625mg and 4mg/1.25mg tablets meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev. 1/Corr), the results and conclusions of the bioequivalence study on the 4mg/1.25mg strength can be extrapolated to the 2mg/0.625mg strength tablets.

Clinical efficacy
No new data have been submitted and none are required. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of perindopril/indapamide in combination is well-established from its extensive use in clinical practice.

Clinical safety
No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of perindopril/indapamide in combination is well-known.

PRODUCT INFORMATION:
Summary of Product Characteristics (SmPC)
The approved SmPCs are consistent with those for the UK reference products and are acceptable.

Patient Information Leaflet
The final PIL text is in line with the approved SmPCs and is satisfactory.

Labelling
The labelling texts are satisfactory.

Clinical overview
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The overview, dated October 2008, cites 120 references from the published literature dated up to year 2008. The CV of the clinical expert has been supplied.

CONCLUSIONS
For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the EU originator medicinal product, BiPreterax 4mg/1.25mg Tabletten (Servier Deutschland GmbH).

All issues have been adequately addressed by the applicant. Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was therefore recommended on medical grounds.
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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Perindopril/indapamide 4mg/1.25mg tablets and the reference product, Perindopril/indapamide 4mg/1.25mg (Coversyl Plus) tablets (Les Laboratoires Servier).

As the proposed products, Perindopril/indapamide 2mg/0.625mg and 4mg/1.25mg tablets, meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev. 1/Corr), the results and conclusions of the bioequivalence study on the 4mg/1.25mg strength were extrapolated to the 2mg/0.625mg strength tablets, and omission of further bioequivalence studies on the lower strength can be accepted.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPCs are consistent with those of the UK reference products and are satisfactory.

The final PIL text is in line with the SmPCs and is satisfactory. The leaflet text has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the leaflet text meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling texts are satisfactory and fulfil the statutory requirements for Braille.

The MAH has submitted text versions for the PIL and labelling, and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant’s Perindopril/indapamide 2mg/0.625mg and 4mg/1.25mg tablets are generic versions of the reference products, Perindopril-Indapamide 2mg/0.625mg Tablets and Preterax double strength 4/1.25 Tablets (Les Laboratoires Servier). Extensive clinical experience with perindopril/indapamide in combination is considered to have demonstrated the therapeutic value of these medicinal products. The benefit: risk ratio is considered to be positive.
Module 6

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

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<th>Application type</th>
<th>Scope</th>
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