

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pendrex Plus 4mg/1.25mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 4.00 mg of perindopril erbumine, equivalent to 3.338 mg perindopril, and 1.25 mg of indapamide.

Excipient with known effect

Each tablet contains 84.7 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, oblong, biconvex tablet debossed with PI on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of essential hypertension; Pendrex Plus 4mg/1.25mg Tablets are indicated in patients whose blood pressure is not adequately controlled on perindopril alone.

4.2 Posology and method of administration

Posology

One Pendrex Plus tablet per day as a single dose, preferably to be taken in the morning, and before a meal.

When possible individual dose titration with the components is recommended. Pendrex Plus should be used when blood pressure is not adequately controlled on Pendrex Plus 2 mg/0.625 mg tablets (where available). When clinically appropriate, direct change from monotherapy to perindopril/indapamide combination may be considered.

Special populations

Elderly (see section 4.4)

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

Renal impairment(see section 4.4)

In severe renal impairment (creatinine clearance below 30 ml/min), treatment is contraindicated.

In patients with moderate renal impairment (creatinine clearance 30–60 ml/min), it is recommended to start treatment with the adequate dose of the free combination.

In patients with creatinine clearance greater than or equal to 60 ml/min, no dose modification is required. Usual medical follow-up will include frequent monitoring of creatinine and potassium.

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.

Paediatric population

The safety and efficacy of perindopril erbumine/indapamide in the paediatric population have not yet been established. No data is available. Pendrex Plus should not be used in children and adolescents.

Method of administration

Oral use

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 (see section 4.4)
- Hereditary/idiopathic angioedema
- Second and third trimesters of pregnancy (see sections 4.4. and 4.6).
- The concomitant use of Pendrex Plus with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²) (see sections 4.5 and 5.1).
- Concomitant use with sacubitril/valsartan therapy. Pendrex Plus must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5),
- Significant bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney (see section 4.4).

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 medicinal product is inadvisable in combination with non-antiarrhythmic agents causing torsades de pointes (see section 4.5)
- Breast-feeding (see section 4.6).

Linked to Pendrex Plus:

Hypersensitivity to any of the excipients listed in section 6.1.

Due to the lack of sufficient therapeutic experience, Pendrex Plus should not be used in:

- Dialysis patients
- Patients with untreated decompensated heart failure.

4.4 Special warnings and precautions for use

Special warnings

Common to perindopril and indapamide:

Lithium

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

Linked to perindopril:

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Potassium-sparing medicinal products, potassium supplements or potassium-containing salt substitutes

The combination of perindopril and potassium-sparing medicinal products, potassium supplements or potassium-containing salt substitutes is usually not recommended (see section 4.5).

Neutropenia/agranulocytosis, thrombocytopenia/anaemia

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Perindopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy. If perindopril is used in such patients, 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) (see sections 4.5 and 4.8).

Renovascular hypertension

There is an increased risk of hypotension and renal insufficiency when patient with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors (see section 4.3). Treatment with diuretics may be a contributory factor. Loss of renal function may occur with only minor changes in serum creatinine even in patients with unilateral renal artery stenosis.

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 (see section 4.8). This may occur at any time during treatment. In such cases, perindopril should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient.

In those instances where swelling has been confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, which may include subcutaneous epinephrine solution 1:1000 (0.3 ml to 0.5 ml) and/or measures to ensure a patent airway, should be administered promptly.

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

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of Pendrex Plus. Treatment with Pendrex Plus must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking an ACE inhibitor.

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 patient's consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Primary aldosteronism

Patients with primary hyperaldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of this product is not recommended.

Pregnancy

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

Linked to indapamide:

Hepatic encephalopathy

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 patient's 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 medicinal product 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 sodium chloride solution.

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

Pendrex Plus contains lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Linked to perindopril:

Cough

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

Paediatric population

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

Risk of arterial hypotension and/or renal insufficiency (in cases of cardiac insufficiency, water and electrolyte depletion, etc...)

Marked stimulation of the renin-angiotensin-aldosterone system has been observed particularly during marked water and electrolyte depletions (strict sodium-free diet or prolonged diuretic treatment), in patients whose blood pressure was initially low, in cases of renal artery stenosis, congestive heart failure or cirrhosis with oedema and ascites.

The blocking of this system with an angiotensin converting enzyme inhibitor may therefore cause, particularly at the time of the first administration and during the first two weeks of treatment, a sudden drop in blood pressure and/or an increase in plasma levels of creatinine, showing a functional renal insufficiency. Occasionally this can be acute in onset, although rare, and with a variable time to onset.

In such cases, the treatment should then be initiated at a lower dose and increased progressively.

Elderly

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

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 Pendrex Plus 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.

Cardiac failure/severe cardiac insufficiency

In patients with severe cardiac insufficiency (grade IV), 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

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. The glycaemia levels should be closely monitored in diabetic patients previously treated with oral antidiabetic medicinal products or insulin, namely during the first month of treatment with an ACE inhibitor (see section 4.5).

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 patients 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. ACE inhibitors can cause hyperkalaemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function, worsening of renal function, aged more than 70 years, diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and in patients taking potassium supplements (including salt substitutes), potassium-sparing diuretics (e.g., spironolactone, eplerenone, triamterene, or amiloride), or those patients taking other medicinal products associated with increases in serum potassium (e.g. heparin, trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole, other ACE inhibitors, acetylsalicylic acid ≥ 3 g/day, COX2 inhibitors and non-selective NSAIDs, immunosuppressant agents such as ciclosporin or tacrolimus, and especially aldosterone antagonists or angiotensin-receptor blockers), hyperkalaemia can occur. The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal arrhythmias. If concomitant use of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium and renal function (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. 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). Any diuretic treatment may cause hyponatraemia, sometimes with very serious consequences. Hyponatraemia with hypovolaemia may be responsible of dehydration and orthostatic hypotension. Concomitant loss of chloride ions may lead to secondary compensatory metabolic alkalosis: the incidence and degree of this effect are slight.

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 medicinal products, 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 micromole/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 Cockcroft formula:

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

with: age expressed in years

body weight in kg

plasma creatinine level in micromole/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.

Choroidal effusion acute myopia and secondary angle-closure glaucoma

Sulphonamide, or sulphonamide derivative, medicinal products can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of medicinal product initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue medicinal product intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

4.5 Interaction with other medicinal products and other forms of interactions

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. 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**

Increased antihypertensive effect. Monitor blood pressure and adapt antihypertensive dose if necessary.

Non-steroidal anti-inflammatory medicinal products (NSAIDs) (including acetylsalicylic acid ≥ 3 g/day)

When ACE inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dose 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).

Linked to perindopril:

- Dual blockade of the renin-angiotensin-aldosterone system (RAAS) with ACE-inhibitors, angiotensin II receptor blockers or aliskiren

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

- Medicinal products inducing hyperkalaemia

Some medicinal products or therapeutic classes may increase the occurrence of hyperkalaemia: aliskiren, potassium salts, potassium-sparing diuretics, ACE inhibitors, angiotensin-II receptor antagonists, NSAIDs, heparins, immunosuppressant agents such as ciclosporin or tacrolimus, trimethoprim. The combination of these medicinal products increases the risk of hyperkalaemia.

Concomitant use contra-indicated (see section 4.3):

- Aliskiren

In diabetic or impaired renal patients, risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increase.

- Extracorporeal treatments

Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitril membranes) and low density lipoprotein apheresis with dextran sulphate due to increased risk of severe anaphylactoid reactions (see section 4.3). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

- Medicinal products increasing the risk of angioedema

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4).

Concomitant use not recommended:

- Aliskiren

In patients other than diabetic or impaired renal patients, risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increase (see section 4.4).

- Concomitant therapy with ACE inhibitor and angiotensin-receptor blocker

It has been reported in the literature that in patients with established atherosclerotic disease, heart failure, or with diabetes with end organ damage, concomitant therapy with an ACE inhibitor and an angiotensin-receptor blocker is associated with a higher frequency of hypotension, syncope, hyperkalaemia, and worsening renal function (including acute renal failure) as compared to use of a single renin-angiotensin-aldosterone system agent. Dual blockade (e.g., by combining an ACE- inhibitor with an angiotensin II receptor antagonist) should be limited to individually defined cases with close monitoring of renal function, potassium levels, and blood pressure (see section 4.4).

- Estramustine

Risk of increased adverse events such as angioneurotic oedema (angioedema).

- Potassium-sparing diuretics (spironolactone, triamterene, alone or in combination), potassium supplements or potassium-containing salt substitutes

Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with perindopril. 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). Care should also be taken when perindopril is co-administered with other agents that increase serum potassium, such as trimethoprim and co-trimoxazole (trimethoprim/sulfamethoxazole) as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Therefore, the combination of perindopril with the above-mentioned medicinal products is not recommended. If concomitant use is indicated because of documented hypokalaemia they should be used with caution and with frequent monitoring of serum potassium and by ECG (see section 4.4).

Concomitant use which requires special care:**- Antidiabetic agents (insulin, oral hypoglycaemic agents)**

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

- Medicinal products increasing the risk of angioedema

ACE inhibitors (e.g. perindopril) are known to cause angioedema. Concomitant use of ACE inhibitors with racecadotril (a medicinal product used against acute diarrhea), mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (linagliptin, saxagliptin, sitagliptin, vildagliptin due to dipeptidyl peptidase IV (DPP-IV) decreased activity by the gliptin) may lead to an increased risk for angioedema (see section 4.4).

- Non-potassium-sparing diuretics

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

In arterial hypertension, when prior diuretic therapy can have caused salt/volume depletion, either the diuretic must be discontinued before initiating the ACE inhibitor, in which case a non-potassium-sparing diuretic can be thereafter reintroduced or the ACE inhibitor must be initiated with a low dose and progressively increased.

In diuretic-treated congestive heart failure, the ACE inhibitor should be initiated at a very low dose, possibly after reducing the dose of the associated non-potassium-sparing diuretic.

In all cases, renal function (creatinine levels) must be monitored during the first few weeks of ACE inhibitor therapy.

- Potassium-sparing diuretics (eplerenone, spironolactone)

With eplerenone or spironolactone at doses between 12.5 mg to 50 mg per day and with low doses of ACE inhibitors:

In the treatment of class II-IV heart failure (NYHA) with an ejection fraction <40%, and previously treated with ACE inhibitors and loop diuretics, risk of hyperkalaemia, potentially lethal, especially in case of non-observance of the prescription recommendations about this combination.

Before initiating the combination, check the absence of hyperkalaemia and renal impairment.

Close monitoring of the kalaemia and creatininaemia is recommended in the first month of the treatment once a week at the beginning and, monthly thereafter.

- Ciclosporin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin. Monitoring of serum potassium is recommended.

- Heparin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

Concomitant use which requires some care:**- Antihypertensive agents and vasodilators**

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

- Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids or procainamide

Concomitant administration with ACE inhibitors may lead to an increased risk for leukopenia (see section 4.4).

- Anaesthetic medicinal products

ACE inhibitors may enhance the hypotensive effects of certain anaesthetic medicinal products (see section 4.4).

- Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

- 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 medicinal products**

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, sultopride, tiapride), butyrophenones (droperidol, haloperidol), other neuroleptics (pimozide); other substances such as bepridil, cisapride, diphemanil, IV erythromycin, halofantrine, mizolastine, moxifloxacin, pentamidine, sparfloxacin, IV vincamine, methadone, astemizole, terfenadine. Prevention of low potassium levels and correction if necessary: monitoring of the QT interval.

- Potassium-lowering medicinal products: 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 digitalis. Non-stimulant laxatives should be used.

- Digitalis preparations

Low potassium levels favour the toxic effects of digitalis. Potassium levels and ECG should be monitored and treatment reconsidered if necessary.

- Allopurinol

Concomitant treatment with indapamide may increase the incidence of hypersensitivity reactions to allopurinol.

Concomitant use which requires some care:**- Potassium-sparing diuretics (amiloride, spironolactone, triamterene)**

Whilst rational combinations are useful in some patients, hypokalaemia or hyperkalaemia (particularly in patients with renal failure or diabetes) may still occur. Plasma potassium and ECG should be monitored and, if necessary, treatment reviewed.

- 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 micromole/l) in men and 12 mg/l (110 micromole/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, tacrolimus

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

- Corticosteroids, tetracosactide (systemic route)

Reduction in antihypertensive effect (salt and water retention due to corticosteroids).

4.6 Fertility, pregnancy and lactation

Given the effects of the individual components in this combination product on pregnancy and breast-feeding, Pendrex Plus is not recommended during the first trimester of pregnancy. Pendrex Plus is contraindicated during the second and third trimesters of pregnancy.

Pendrex Plus is contraindicated during breast-feeding. A decision should therefore be made whether to discontinue nursing or to discontinue Pendrex Plus taking account the importance of this therapy for the mother.

Pregnancy

Linked to perindopril:

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

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

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

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

Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

Linked to indapamide:

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of indapamide in pregnant women. Prolonged exposure to thiazide during the third trimester of pregnancy can reduce maternal plasma volume as well as uteroplacental blood flow, which may cause foeto-placental ischaemia and growth retardation.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of indapamide during pregnancy.

Breast-feeding

Pendrex Plus is contra-indicated during breast-feeding.

Linked to perindopril:

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

Linked to indapamide:

There is insufficient information on the excretion of indapamide/metabolites in human milk. Hypersensitivity to sulphonamide-derived medicinal products and hypokalaemia might occur. A risk to the newborns/infants cannot be excluded. Indapamide is closely related to thiazide diuretics which have been associated, during breast-feeding, with decrease or even suppression of lactation.

Indapamide is contra-indicated during breast-feeding.

Fertility

Common to perindopril and indapamide:

Reproductive toxicity studies showed no effect on fertility in female and male rats (see section 5.3). No effects on human fertility are anticipated.

4.7 Effects on ability to drive and use machines

Linked to perindopril, indapamide and Pendrex Plus

The two active substances, individually or combined in Pendrex Plus 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 treatment. As a result, the ability to drive or operate machinery may be impaired.

4.8 Undesirable effectsSummary of safety profile

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

The most commonly reported adverse reactions observed are:

- with perindopril: dizziness, headache, paraesthesia, dysgeusia, visual impairment, vertigo, tinnitus, hypotension, cough, dyspnoea, abdominal pain, constipation, dyspepsia, diarrhoea, nausea, vomiting, pruritus, rash, muscle cramps and asthenia.
- with indapamide: hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions and maculopapular rashes.

Tabulated list of adverse reactions

The following undesirable effects have been observed during clinical trials and/or post-marketing use and ranked under the following frequency:

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data).

| MedDRA system organ class | Undesirable effects | Frequency | |
|---|--|-------------|------------|
| | | Perindopril | Indapamide |
| Infections and infestations | Rhinitis | Very rare | - |
| Blood and lymphatic system disorders | Eosinophilia | Uncommon* | - |
| | Agranulocytosis (see section 4.4) | Very rare | Very rare |
| | Aplastic anaemia | - | Very rare |
| | Pancytopenia | Very rare | - |
| | Leukopenia | Very rare | Very rare |
| | Neutropenia (see section 4.4) | Very rare | - |
| | Haemolytic anaemia | Very rare | Very rare |
| Immune system disorders | Thrombocytopenia (see section 4.4) | Very rare | Very rare |
| | Hypersensitivity (reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions) | - | Common |
| Metabolism and nutrition disorders | Hypoglycaemia (see sections 4.4 and 4.5) | Uncommon* | - |
| | Hyperkalaemia, reversible on discontinuation (see section 4.4) | Uncommon* | - |
| | Hyponatraemia (see section 4.4) | Uncommon* | Not known |
| | Hypercalcaemia | - | Very rare |
| | Potassium depletion with hypokalaemia, particularly serious in certain high risk populations (see section 4.4) | - | Not known |
| Psychiatric disorders | Mood altered | Uncommon | - |
| | Sleep disorder | Uncommon | - |
| | Confusion | Very rare | - |
| Nervous system disorders | Dizziness | Common | - |
| | Headache | Common | Rare |
| | Paraesthesia | Common | Rare |
| | Dysgeusia | Common | - |
| | Somnolence | Uncommon* | - |
| | Syncope | Uncommon* | Not known |

| | | | |
|--|--|-----------|-----------|
| | Stroke possibly secondary to excessive hypotension in high-risk patients (see section 4.4) | Very rare | - |
| | Possibility of onset of hepatic encephalopathy in case of hepatic insufficiency (see sections 4.3 and 4.4) | - | Not known |
| Eye disorders | Visual impairment | Common | Not known |
| | Myopia (see section 4.4) | - | Not known |
| | Vision blurred | - | Not known |
| | Choroidal effusion (see section 4.4) | - | Not known |
| | Angle-closure glaucoma (see section 4.4) | - | Not known |
| Ear and labyrinth disorders | Vertigo | Common | Rare |
| | Tinnitus | Common | - |
| Cardiac disorders | Palpitations | Uncommon* | - |
| | Tachycardia | Uncommon* | - |
| | Angina pectoris (see section 4.4) | Very rare | - |
| | Arrhythmia (including bradycardia, ventricular tachycardia, atrial fibrillation) | Very rare | Very rare |
| | Myocardial infarction possibly secondary to excessive hypotension in high risk patients (see section 4.4) | Very rare | - |
| | Torsade de pointes (potentially fatal) (see sections 4.4 and 4.5) | - | Not known |
| Vascular disorders | Hypotension (and effects related to hypotension) (see section 4.4) | Common | Very rare |
| | Vasculitis | Uncommon* | - |
| | Raynaud's phenomenon | Not known | |
| Respiratory, thoracic and mediastinal disorders | Cough (see section 4.4) | Common | - |
| | Dyspnoea | Common | - |
| | Bronchospasm | Uncommon | - |
| | Eosinophilic pneumonia | Very rare | - |
| Gastrointestinal disorders | Abdominal pain | Common | - |
| | Constipation | Common | Rare |
| | Diarrhoea | Common | - |
| | Dyspepsia | Common | - |
| | Nausea | Common | Rare |
| | Vomiting | Common | Uncommon |
| | Dry mouth | Uncommon | Rare |
| Pancreatitis | Very rare | Very rare | |
| Hepatobiliary disorders | Hepatitis (see section 4.4) | Very rare | Not known |
| | Hepatic function abnormal | - | Very rare |
| Skin and subcutaneous tissue disorders | Pruritus | Common | - |
| | Rash | Common | - |
| | Rash maculo-papular | - | Common |
| | Urticaria (see section 4.4) | Uncommon | Very rare |
| | Angioedema (see section 4.4) | Uncommon | Very rare |
| | Purpura | - | Uncommon |
| | Hyperhidrosis | Uncommon | - |
| | Photosensitivity reaction | Uncommon* | Not known |
| | Pemphigoid | Uncommon* | - |
| | Psoriasis aggravation | Rare* | - |
| | Erythema multiforme | Very rare | - |
| | Toxic epidermal necrolysis | - | Very rare |
| Stevens Johnson syndrome | - | Very rare | |
| Musculoskeletal and connective tissue disorders | Muscle cramps | Common | - |
| | Possible worsening of pre-existing acute disseminated lupus erythematosus | - | Not known |
| | Arthralgia | Uncommon* | - |
| | Myalgia | Uncommon* | - |
| Renal and urinary disorders | Renal insufficiency | Uncommon | - |
| | Renal failure acute | Very rare | Very rare |
| Reproductive | Erectile dysfunction | Uncommon | - |

| | | | |
|---|---|-----------|-----------|
| system and breast disorders | | | |
| General disorders and administration site conditions | Asthenia | Common | - |
| | Chest pain | Uncommon* | - |
| | Malaise | Uncommon* | - |
| | Oedema peripheral | Uncommon* | - |
| | Pyrexia | Uncommon* | - |
| | Fatigue | - | Rare |
| Investigations | Blood urea increased | Uncommon* | - |
| | Blood creatinine increased | Uncommon* | - |
| | Blood bilirubin increased | Rare | - |
| | Hepatic enzyme increased | Rare | Not known |
| | Haemoglobin decreased and haematocrit decreased (see section 4.4) | Very rare | - |
| | Blood glucose increased | - | Not known |
| | Blood uric acid increased | - | Not known |
| | Electrocardiogram QT prolonged (see sections 4.4 and 4.5) | - | Not known |
| Injury, poisoning and procedural complications | Fall | Uncommon* | - |

* Frequency calculated from clinical trials for adverse events detected from spontaneous report.

Cases of SIADH have been reported with other ACE inhibitors. SIADH can be considered as a very rare but possible complication associated with ACE inhibitor therapy including perindopril.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance; website: www.hpra.ie

4.9 Overdose

Symptoms

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.

Management

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 sodium chloride solution 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: Agents acting on the renin-angiotensin system, perindopril and diuretics, ATC code: C09BA04

Pendrex Plus is a combination of perindopril erbumine, 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.

Mechanism of action

Linked to Pendrex Plus:

Pendrex Plus produces an additive synergy of the antihypertensive effects of the two components.

Linked to perindopril:

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

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

The antihypertensive action of perindopril also occurs in patients with low or normal renin concentrations. Perindopril acts through its active metabolite, perindoprilat. The other metabolites are inactive.

Perindopril reduces the work of the heart:

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

Studies carried out on patients with cardiac insufficiency have shown:

- a reduction in left and right ventricular filling pressures,
- a reduction in total peripheral vascular resistance,
- an increase in cardiac output and an improvement in the cardiac index,
- an increase in regional blood flow in muscle.

Exercise test results also showed improvement.

Linked to indapamide:

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

Pharmacodynamic effects

Linked to perindopril/indapamide:

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

PICXEL, a multicentre, 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/indapamide 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 patient's 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 Pendrex Plus 2 mg/0.625 mg tablets and Pendrex Plus 4 mg/1.25 mg 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.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) clinical trial data

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

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 events 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.

Paediatric population

No data are available with perindopril/indapamide in children.

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:*Absorption and bioavailability

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.

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

Distribution

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.

Biotransformation

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.

Elimination

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.

Linearity/non-linearity

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

Special populations*Elderly*

Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure.

Renal impairment

Dose adjustment in renal insufficiency is desirable depending on the degree of impairment (creatinine clearance).

In case of dialysis

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

Cirrhosis

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 dose adjustment is required (see sections 4.2 and 4.4).

*Linked to indapamide:*Absorption

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.

Distribution

Plasma protein binding is 79 %.

Biotransformation and elimination

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.

Special populations

Renal impairment

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 events 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 or carcinogenic potential. Reproduction toxicology studies showed no embryotoxicity or teratogenicity and fertility was not impaired.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylbetadex
Lactose monohydrate
Povidone K25
Silicified Microcrystalline Cellulose
Silica, colloidal hydrated
Colloidal anhydrous silica
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

PVC/PVDC/Alu blister in Alu bag with added desiccant:

Shelf life after first opening of the bag:

6 months

6.4 Special precautions for storage

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

PVC/PVDC/Alu blister in Alu bag with added desiccant:

Storage conditions after first opening of the bag:

Do not store above 25°C.

6.5 Nature and contents of container

The tablets are packed in Alu/Alu blisters or in PVC/PVDC/ Al blister in Al bag with added desiccant and inserted in a carton.

Pack sizes: 7, 14, 20, 28, 30, 50, 56, 60, 90, 98, 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd,
Bantry,
Co. Cork,
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/171/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th July 2010

Date of last renewal: 22nd April 2015

10 DATE OF REVISION OF THE TEXT

June 2021