# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

**PRETERAX ARGININE 2.5 mg/0.625 mg, film-coated tablet**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Perindopril .....1.6975 mg

as perindopril arginine .....2.5 mg

Indapamide .....0.625 mg

For one film-coated tablet

Excipient with known effect: lactose monohydrate 74.455 mg

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.

White, rod-shaped film-coated tablet, with an embossed line on both faces.
The score line is not intended for breaking the tablet.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

PRETERAX ARGININE 2.5 mg/0.625 mg is indicated for the treatment of essential hypertension in adults.

### 4.2 Posology and method of administration

**Posology**

The usual posology is one PRETERAX ARGININE 2.5 mg/0.625 mg film-coated 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.

**Special populations**

*Elderly (see section 4.4)*

Treatment should be started at the usual dose of one PRETERAX ARGININE 2.5 mg/0.625 mg film-coated tablet per day.

*Patients with renal impairment (see section 4.4)*

In cases of severe renal impairment (creatinine clearance < 30 ml/min), the treatment is contraindicated. In patients with moderate renal impairment (creatinine clearance 30-60 ml/min), the maximum dose should be one tablet of PRETERAX ARGININE 2.5 mg/0.625 mg per day. In patients with creatinine clearance greater than or equal to 60 ml/min, no dose modification is required.

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

*Patients with hepatic impairment (see sections 4.3, 4.4 and 5.2)*

In severe hepatic impairment, the treatment is contraindicated.

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

*Paediatric population*

The safety and efficacy of ARGININE perindopril arginine/indapamide in the paediatric population have not yet been established. No data are available.

PRETERAX ARGININE 2.5 mg/0.625 mg should not be used in children and adolescents.

**Method of administration**

Oral use.

### 4.3 Contraindications

**Linked to perindopril**

- hypersensitivity to the active substance or any other angiotensin converting enzyme (ACE) inhibitor,
- history of angioedema (Quincke's oedema) associated with ACE inhibitor therapy (see section 4.4),
- hereditary/idiopathic angioedema,
- second and third trimesters of pregnancy (see sections 4.4 and 4.6),
- concomitant use of PRETERAX ARGININE 2.5 mg/0.625 mg with aliskiren-containing products 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. The perindopril-containing treatment must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see 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 the active substance or to any other sulphonamides,
- severe renal impairment (creatinine clearance < 30 ml/min),
- hepatic encephalopathy,
- severe hepatic impairment,
- hypokalaemia

**Linked to PRETERAX ARGININE 2.5 mg/0.625 mg**

- hypersensitivity to any of the excipients listed in section 6.1.

Due to the lack of sufficient therapeutic experience, PRETERAX ARGININE 2.5 mg/0.625 mg 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 PRETERAX ARGININE 2.5 mg/0.625 mg 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 can not be excluded if the patient is simultaneously exposed to two antihypertensive agents new to him. To minimise this risk the patient should be carefully monitored.

**Lithium**

The use 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, blood electrolytes and blood pressure. ACE inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

**Potassium-sparing drugs, potassium supplements or potassium-containing salt substitutes**

The combination of perindopril and potassium-sparing drugs, 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 risk factors, neutropenia occurs rarely. Perindopril should be used with caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these risk 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 patients 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 ACE 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).

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.

The combination of perindopril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see section 4.3). Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of perindopril therapy. If treatment with sacubitril/valsartan is stopped, perindopril therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5). Concomitant use of ACE inhibitors with NEP inhibitors (e.g. racecadotril), mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, 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 gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin) in a patient already taking an ACE inhibitor.

**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 (anti-venom serum). 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.

**Primary aldosteronism**

Patients with primary hyperaldosteronism generally will not respond to anti-hypertensive drugs 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, particularly in case of electrolyte imbalance, hepatic encephalopathy which can progress to hepatic coma. 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 a 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), the 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 the 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/sodium 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 imbalance, 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 rule out 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 with known effect**

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

**Level of sodium**

PRETERAX ARGININE 2.5 mg/0.625 mg, film-coated tablet contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

*Linked to perindopril*

**Cough**

A dry cough has been reported with the use of ACE 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 it is essential to prescribe an ACE inhibitor, 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/sodium depletion, etc...)**

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

The blocking of this system with an ACE 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 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/sodium 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, ACE inhibitors can be beneficial in patients presenting with renovascular hypertension who are awaiting corrective surgery or when such surgery is not possible.

Should Preterax ARGININE 2.5 mg/0.625 mg be 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 insufficiency/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), the treatment should be started under medical supervision with a reduced initial dose.

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

**Ethnic specificities**

As with other ACE 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 population.

**Surgery/anaesthesia**

ACE 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 ACE inhibitors such as perindopril should be discontinued where possible the 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 potassium levels 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. Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g., spironolactone, eplerenone, triamterene, amiloride…), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in potassium levels (e.g. heparins, co-trimoxazole also known as trimethoprim/sulfamethoxazole, other ACE inhibitors, angiotensin-II receptor antagonists, acetylsalicylic acid ≥ 3 g/day, COX-2 inhibitors and non-selective NSAIDs, immunosuppressant agents such as ciclosporin or tacrolimus, trimethoprim) and especially aldosterone antagonists or angiotensin-receptor blockers. 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 potassium levels. Hyperkalaemia can cause serious, sometimes fatal arrhythmias.

Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored. If concomitant use of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of potassium levels (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 even more frequent in elderly and cirrhotic patients (see sections 4.8 and 4.9). All diuretic treatments can cause a reduction in sodium levels, which may have serious consequences. Hyponatraemia associated with hypovolemia may result in dehydration and orthostatic hypotension. The concomitant loss of chloride ions could lead to a compensatory secondary metabolic alkalosis; the incidence and amplitude of this effect are low.

Potassium levels

Potassium depletion with hypokalaemia is a major risk with thiazide diuretics and thiazide-related diuretics. Hypokalaemia may cause muscle disorders. Cases of rhabdomyolysis have been reported, mainly in the context of severe hypokalaemia. 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 potassium levels should be carried out during the first week following the start of treatment.

If low potassium levels are detected, correction is required. Hypokalaemia found in association with low serum magnesium concentration can be refractory to treatment unless serum magnesium is corrected.

Calcium levels

Thiazide diuretics and thiazide-related diuretics may reduce urinary excretion of calcium and cause a mild and transient increase in 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.

Plasma magnesium

Thiazides and related diuretics including indapamide have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia (see section 4.5 and 4.8).

**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:

$Cl_{cr}$ = (140 - age) x body weight / 0.814 x plasma creatinine level
with: age expressed in years
body weight in kg
plasma creatinine level in µmol/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 pre-existing renal impairment.

**Athletes**

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

**Choroidal effusion, acute myopia and secondary angle-closure glaucoma**

Sulfonamide or sulfonamide derivative drugs 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 drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. A history of sulfonamide or penicillin allergy is a risk factor for developing acute angle-closure glaucoma.

## 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. 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 dosage 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 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 potassium levels, 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**

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 (ARBs) 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).

- **Drugs 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). Sacubitril/valsartan must not be started until 36 hours after taking the last dose of perindopril therapy. Perindopril therapy must not be started until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.4).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin) may lead to an increased risk for angioedema (see section 4.4).

- **Drugs inducing hyperkalaemia**

Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with PRETERAX ARGININE 2.5 mg/0.625 mg. Some drugs or certain therapeutic classes may increase the risk of onset of hyperkalaemia such as: aliskiren, potassium salts, potassium sparing diuretics (e.g. spironolactone, triamterene or amiloride), ACE inhibitors, ARBs, NSAIDs, heparins, immunosuppressants such as ciclosporin or tacrolimus and trimethoprim. and cotrimoxazole (trimethoprim/sulfamethoxazole), as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. The combination of these drugs increases the risk of hyperkalaemia. Therefore, the combination of PRETERAX ARGININE 2.5 mg/0.625 mg with the above-mentioned drugs is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

**Concomitant use contraindicated (see section 4.3)**

- **Aliskiren**

The risk of hyperkalaemia, impairment of renal function and cardiovascular morbidity-mortality increases in patients with diabetes or renal impairment.

- **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 are contraindicated 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.

**Concomitant use not recommended**

- **Aliskiren**

The risk of hyperkalaemia, impairment of renal function and cardiovascular morbidity-mortality increases in patients other than those with diabetes or renal impairment (see section 4.4).

- **Concomitant use of ACE inhibitor with ARB treatment**

There are literature reports in patients suffering from diagnosed atherosclerosis, heart failure or diabetic patients with organ lesions, that indicate that concomitant use of ACE inhibitors and ARBs is associated with a higher frequency of hypotension, syncope, hyperkalaemia and renal function impairment (including acute renal failure) compared to the monotherapy treatment with a molecule that acts on the renin-angiotensin-aldosterone system. Dual blockade (e.g.: concomitant use of an ACE inhibitor and an ARB) must be limited to individual and defined cases, with reinforced monitoring of the renal function, potassium levels and blood pressure (see section 4.4).

- **Estramustine**

Risk of increase in adverse drug reactions such as angioneurotic oedema (angioedema).

- **Potassium-sparing diuretics (e.g. triamterene, amiloride, etc.), potassium (salts)**

Hyperkalaemia (potentially fatal), in particular in a renal impairment context (additive hyperkalaemia effects). Concomitant use of perindopril and these medicinal products is not recommended (see section 4.4). If concomitant use is nonetheless indicated, it should be used with caution and with frequent monitoring of potassium levels. For the use of spironolactone in heart failure, see the section "Concomitant use which requires special care".

**<u>Concomitant use which requires special care</u>**

- **Antidiabetic agents (insulin, oral hypoglycaemic agents)**

Epidemiological studies have suggested that concomitant use of ACE inhibitors and antidiabetic agents (insulin, oral hypoglycaemic agents) may cause an increase in the hypoglycaemic effect with a risk of hypoglycaemia. This phenomenon seems to appear especially during the first weeks of concomitant use of these treatments and in patients with renal impairment.

- **Non-potassium sparing diuretics**

Patients treated with diuretics, and especially those with volume depletion and/or water/sodium depletion, may experience a major reduction in the blood pressure after starting an ACE inhibitor treatment.

The hypotensive effect may be reduced by suspending the diuretic, increasing the blood volume or the salt intake prior to starting the treatment with low and progressive doses of perindopril.

In hypertension, when a previous diuretic treatment may have caused volume depletion and/or water/sodium depletion, the diuretic must be suspended before starting an ACE inhibitor. In that case, a non-potassium sparing diuretic may be reintroduced or the ACE inhibitor started at a low dose which is progressively increased.

In the diuretic treatment of congestive heart failure, the ACE inhibitor must be started at a very low dose and after having reduced the dose of the non-potassium sparing diuretic coadministered.

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

- **Potassium-sparing diuretics (eplerenone, spironolactone)**

With eplerenone and spironolactone at doses comprised between 12.5 mg and 50 mg daily and low doses of ACE inhibitor:

In the treatment of class II-IV heart failure (NYHA) with an ejection fraction of < 40% and previously treated with an ACE inhibitor and a loop diuretic, there is a risk of hyperkalaemia, potentially fatal, especially if the prescription recommendations for this combination are not respected. Verify the absence of hyperkalaemia and renal impairment prior to starting concomitant use.

A strict control of blood potassium and creatinine is recommended once a week during the first month of treatment and once a month afterwards.

**Concomitant use which requires some care**

- **Antihypertensive agents and vasodilators**

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

- **Allopurinol, cytostatic or immunosuppressive agents, corticosteroids (systemic route) or procainamide**

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

- **Anaesthetic drugs**

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

- **Sympathomimetics**

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

- **Gold salts**

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold salts (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 induce torsades de pointes, such as but not limited to:

- class Ia antiarrhythmic agents (e.g quinidine, hydroquinidine, disopyramide),
- class III antiarrhythmic agents (e.g amiodarone, dofetilide, ibutilide, bretylium, sotalol),
- some antipsychotics
- phenothiazines (e.g chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine),
- benzamides (e.g amisulpride, sulpiride, sultopride, tiapride),
- butyrophenones (e.g droperidol, haloperidol),
- other antipsychotics (e.g pimozide),
- other substances (e.g bepridil, cisapride, diphemanil, erythromycin IV, halofantrine, mizolastine, moxifloxacin, pentamidine, sparfloxacin, vincamine IV, methadone, astemizole, terfenadine).

Prevention of hypokalaemia 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 hypokalaemia (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**

Hypokalaemia and/or hypomagnesaemia predispose to the toxic effects of digitalis. Monitoring of plasma potassium, magnesium and ECG is recommended and, if necessary, adjusting the treatment.

- **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. Potassium levels 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 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, tacrolimus**

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

- **Corticosteroids, tetracosactide (systemic route)**

Decreased antihypertensive effect (water/sodium retention due to corticosteroids).

### 4.6 Fertility, pregnancy and lactation

Given the effects of the individual components in this combination product on pregnancy and lactation, PRETERAX ARGININE 2.5 mg/0.625 mg is not recommended during the first trimester of pregnancy. PRETERAX ARGININE 2.5 mg/0.625 mg is contraindicated during the second and third trimesters of pregnancy.

PRETERAX ARGININE 2.5 mg/0.625 mg is not recommended during lactation. A decision should therefore be made whether to discontinue nursing or to discontinue the treatment 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 contra-indicated during the second and third trimesters 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 is no or limited amount of data (less than 300 pregnancy outcomes) from the use of indapamide in pregnant women.

Prolonged exposure to thiazide diuretics during the third trimester of pregnancy can reduce maternal plasma volume as well as uteroplacental blood flow, which may cause feto-placental ischemia and growth retardation.

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

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

**Breast-feeding**

PRETERAX ARGININE 2.5 mg/0.625 mg is not recommended during lactation.

*Linked to perindopril*

Because no information is available regarding the use of perindopril during breast-feeding, PRETERAX ARGININE 2.5 mg/0.625 mg 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 products and hypokalaemia might occur. A risk to the newborns/infants cannot be excluded.

Indapamide is structurally closely related to thiazide diuretics which have been associated, during breast-feeding, with decrease or even suppression of lactation.

Indapamide is not recommended during lactation.

**Fertility**

*Linked 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 PRETERAX ARGININE 2.5 mg/0.625 mg**

Neither the two active substances taken separately or in combination as PRETERAX ARGININE 2.5 mg/0.625 mg affect the ability to drive vehicules or to use machines but individual reactions related to decreased 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

**Summary of safety profile**

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 PRETERAX **ARGININE**2.5 mg/0.625 mg experience hypokalaemia (potassium level < 3.4 mmol/l).

**The most commonly observed undesirable effects are:**

- with perindopril: dizziness, headache, paraesthesia, dysgeusia, visual disturbances, vertigo, tinnitus, hypotension, cough, dyspnoea, abdominal pain, constipation, dyspepsia, diarrhoea, nausea, vomiting, pruritus, rash, muscle cramps and asthenia,

- with indapamide: hypokalaemia, hypersensitivity reactions, mainly dermatological, in patients with a predisposition to allergic and asthmatic reactions and maculopapular rashes.

**Tabulated list of undesirable effects**

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

Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <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 | - |
| **Endocrine disorders** | Syndrome of inappropriate antidiuretic hormone secretion (SIADH) | 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 |
| | Thrombocytopenia (see section 4.4) | Very rare | Very rare |
| **Immune system disorders** | Hypersensitivity (hypersensitivity reactions, mainly dermatological in patients 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* | Uncommon |
| | Hypochloraemia | - | Rare |
| | Hypomagnesaemia | - | Rare |
| | Hypercalcaemia | - | Very rare |
| | Hypokalaemia | - | Common |
| **Psychiatric disorders** | Mood altered | Uncommon | - |
| | Depression | 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 disturbances | Common | Not known |
| | Myopia (see section 4.4) | - | Not known |

| MedDRA System Organ Class | Undesirable Effects | Frequency | |
|---|---|---|---|
| | | Perindopril | Indapamide |
| | Acute angle-closure glaucoma | - | Not known |
| | Choroidal effusion | - | Not known |
| | Vision blurred | - | 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* | - |
| | Flushing | Rare* | - |
| | 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 spasms | Common | Not known |
| | Possible worsening of pre-existing acute disseminated lupus erythematosus | - | Not known |

| MedDRA System Organ Class | Undesirable Effects | Frequency | |
|---|---|---|---|
| | | **Perindopril** | **Indapamide** |
| | Arthralgia | Uncommon* | - |
| | Myalgia | Uncommon* | Not known |
| | Muscular weakness | - | Not known |
| | Rhabdomyolysis | - | Not known |
| **Renal and urinary disorders** | Renal insufficiency | Uncommon | Very rare |
| | Anuria/oliguria | Rare* | - |
| | Acute renal failure | Rare* | - |
| **Reproductive system and breast disorders** | Erectile dysfunction | Uncommon | Uncommon |
| **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 estimated from clinical trial data for the undesirable effects reported after marketing (spontaneous notifications).

**Description of selected adverse reactions**

During phase II and III studies comparing indapamide 1.5 mg and 2.5 mg, plasma potassium analysis showed a dose-dependent effect of indapamide:

- Indapamide 1.5 mg: Plasma potassium < 3.4 mmol/l was seen in 10 % of patients and < 3.2 mmol/l in 4 % of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.23 mmol/l.
- Indapamide 2.5 mg: Plasma potassium < 3.4 mmol/l was seen in 25 % of patients and < 3.2 mmol/l in 10 % of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.41 mmol/l.

**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 the national reporting system.

### 4.9 Overdose

**Symptoms**

The most likely adverse reaction in cases of overdose is hypotension, sometimes associated with nausea, vomiting, cramps, dizziness, somnolence, mental confusion, oliguria which may progress to anuria (due to hypovolaemia). Water and electrolyte disturbances (hyponatraemia, hypokalaemia) 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 saline may be given, or any other method of volemic expansion may be used.

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

**Pharmacotherapeutic group: PERINDOPRIL AND DIURETICS, ATC code: C09BA04.**

PRETERAX ARGININE 2.5 mg/0.625 mg is a combination of perindopril arginine salt, an ACE 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 PRETERAX* ARGININE *2.5 mg/0.625 mg:*

PRETERAX ARGININE 2.5 mg/0.625 mg produces an additive synergy of the antihypertensive effects of the two components.

*Linked to perindopril*

Perindopril is an inhibitor of the ACE inhibitor which converts angiotensin I to angiotensin II, a vasoconstricting substance, which also stimulates the secretion of aldosterone by the adrenal cortex; it also 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 water/sodium 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 PRETERAX* ARGININE *2.5 mg/0.625 mg*

In hypertensive patients regardless of age, PRETERAX *ARGININE* 2.5 mg/0.625 mg exerts a dose-dependent antihypertensive effect on diastolic and systolic arterial pressure whilst supine or standing. This antihypertensive effect lasts for 24 hours. Blood pressure reduction is achieved in less than one month, without tachyphylaxis; discontinuation of treatment is not accompanied by a rebound effect. In clinical studies, concomitant administration of perindopril and indapamide resulted in synergistic antihypertensive effects compared to each product alone.

The effect of the low-dose combination PRETERAX ARGININE 2.5 mg/0.625 mg on cardiovascular morbidity and mortality has not been studied.

PICXEL, a multicentre, randomised, double blind controlled study assessed on echocardiography the effect of perindopril/indapamide combination on left ventricular hypertrophy (LVH) versus enalapril monotherapy.

In PICXEL, hypertensive patients with LVH (defined as left ventricular mass index (LVMI) > 120 g/m$^2$ in men and > 100 g/m$^2$ in women) were randomised either to perindopril tert-butylamine 2 mg (equivalent to 2.5 mg perindopril arginine)/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 tert-butylamine 8 mg (equivalent to 10 mg perindopril arginine)/indapamide 2.5 mg or enalapril 40 mg once a day. Only 34% of the subjects remained treated with perindopril tert-butylamine 2 mg (equivalent to 2.5 mg perindopril arginine)g/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 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 a dose of perindopril/indapamide higher than that in PRETERAX 2.5 mg/0.625 mg and BIPRETERAX 5 mg/1.25 mg.

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 the arterial system 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 ACE 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 in relation with 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.

**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)) examined the use of 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 renal impairment 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. CV death and stroke were both 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.

**Paediatric population**

There is no data available on the use of PRETERAX ARGININE in children.

## 5.2 Pharmacokinetic properties

**Linked to PRETERAX ARGININE 2.5 mg/0.625 mg**

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 ARGININE 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**

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

**Special populations**

*Elderly*

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

*Patients with renal impairment*

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

*In case of dialysis*

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

*For patients suffering from 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 dosage 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

PRETERAX ARGININE 2.5 mg/0.625 mg has a slightly higher toxicity than that of its components. Renal manifestations do not seem to be potentiated in rats. However, the combination produces gastro-intestinal toxicity in dogs and the toxic effects on the mother seem to be increased in rats.

Nonetheless, these adverse effects are shown at dose levels corresponding much higher than 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

Core:
Lactose monohydrate, magnesium stearate (E470B), maltodextrin, silica colloidal anhydrous (E551), sodium starch glycolate (type A).

Film-coating:
Glycerol (E422), hypromellose (E464), macrogol 6000, magnesium stearate (E470B), titanium dioxide (E171).

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Store below 30°C. Store in the original package.
Keep the container tightly closed in order to protect from moisture.

### 6.5 Nature and contents of container

14, 20, 28, 30 or 50 tablets in white polypropylene tablet container equipped with a low density polyethylene flow reducer and a white opaque low density polyethylene stopper containing a white desiccant gel.
Pack sizes: 1 x 14, 1 x 20, 1 x 28, 1 x 30 or 1 x 50 tablets
2 x 28, 2 x 30 or 2 x 50 tablets
3 x 30 tablets
10 x 50 tablets
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER

**LES LABORATOIRES SERVIER**
50, RUE CARNOT
92284 SURESNES CEDEX
FRANCE

## 8. MANUFACTURER

**SERVIER (IRELAND) INDUSTRIES LTD**
GOREY ROAD
ARKLOW, CO. WICKLOW
IRELAND

## 9. DATE OF REVISION OF THE TEXT

05.2022