SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PRETERAX, scored tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 1.669 mg of perindopril corresponding to 2 mg of perindopril tert-butylamine and 0.625 mg indapamide.

Excipient: lactose monohydrate 64.175 mg.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet. Box of 30

White, rod-shaped, scored on each face.

The tablet can be divided into two equal half-doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Essential arterial hypertension.

4.2 Posology and method of administration

Oral route.

The usual dose is one PRETERAX tablet daily in a single administration, preferably in the morning and before a meal. The dose may be doubled in the event of non-control of blood pressure after one month of treatment.

Elderly subjects (see section 4.4)
Treatment must be initiated at the usual dose of one PRETERAX tablet per day.

Renal insufficiency (see section 4.4)
Treatment is contraindicated in the event of severe renal insufficiency (creatinine clearance < 30 ml/min).
In patients with moderate renal insufficiency (creatinine clearance 30-60 ml/min), the maximum dose must be one PRETERAX tablet per day. In patients with a creatinine clearance greater than or equal to 60 ml/min no dose adjustment is necessary.
The usual follow-up includes periodic control of creatinine and potassium.

Liver failure (see sections 4.3, 4.4 and 5.2)
Treatment is contraindicated in the event of severe liver failure.
In patients with moderate liver failure, no dose adjustment is necessary.

Children and adolescents
PRETERAX should not be used in children and adolescents as the efficacy and safety of perindopril in children and adolescents, alone or in combination, have not been established.

4.3 Contraindications

Linked to perindopril:
- hypersensitivity to perindopril or to any other angiotensin-converting enzyme inhibitor,
- previous history of angioedema (Quincke's oedema) linked to taking an angiotensin-converting enzyme inhibitor,
- hereditary or idiopathic angioedema,
- second and third trimesters of pregnancy (see section 4.6).

Linked to indapamide:
- hypersensitivity to indapamide or to any other sulphonamide,
- severe renal insufficiency (creatinine clearance < 30 ml/min),
- hepatic encephalopathy,
- severe liver failure,
- hypokalaemia,
- as a general rule, use of this medicinal product is not recommended in combination with non-antiarrhythmic medicines that can cause torsade de pointes (see section 4.5),
- breast-feeding (see section 4.6).

Linked to PRETERAX:
- hypersensitivity to one of the excipients.

Due to the lack of data, PRETERAX must 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 to indapamide

Apart from hypokalaemia, no significant reduction of adverse effects has been demonstrated for the low-dose Preterax combination, in comparison with the lowest doses approved for each of the components (see section 4.8).

An increase in the frequency of idiosyncratic reactions in patients exposed simultaneously to two new antihypertensive agents cannot be ruled out. To minimise this risk, the patient must be followed-up attentively.

Lithium

Use of lithium with the perindopril/indapamide combination is generally not recommended (see section 4.5).

Linked to perindopril

Neutropaenia/agranulocytosis

Cases of neutropaenia/agranulocytosis, thrombocytopaenia and anaemia have been reported in patients receiving angiotensin-converting enzyme inhibitors. It is rare for neutropaenia to occur in patients with normal renal function and no other risk factor. Perindopril must be used with care in patients presenting with a collagen vascular disease, receiving immunosuppressant therapy, allopurinol or procainamide, or a combination of these risk factors, in particular if there is pre-existing renal function impairment. Some of these patients have presented serious infections which, in some cases, did not respond to intensive antibiotic therapy. If perindopril is to be used in such patients, regular blood count monitoring (white blood cell count) is advised and the patients should be warned to report any sign of infection (e.g. sore throat, fever).

Hypersensitivity/Angioneurotic oedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients receiving treatment with an angiotensin-converting enzyme inhibitor, including perindopril. This may occur at any time during treatment.

In such cases, perindopril should be stopped immediately and the patient monitored until the symptoms have cleared up completely.

When the oedema only affects the face and the lips, the effect generally recedes without treatment, even though antihistamines have been proven useful in the relief of symptoms.

Angioedema combined with laryngeal oedema may be fatal. When the tongue, glottis or larynx are affected and may lead to an obstruction of the airways, a subcutaneous injection of adrenaline solution at 1/1000 (0.3 ml to 0.5 ml) should be administered quickly and/or other measures taken to free the airways.
The frequency of reported angioedemas is higher in Black patients than in other patients.
Patients with a history of angioedema that is not linked to the administration of an angiotensin-converting enzyme inhibitor can have an accrued risk of angioedema under angiotensin-converting enzyme inhibitor treatment (see section 4.3).
Intestinal angioedemas have been reported rarely by patients being treated with an angiotensin-converting enzyme inhibitor. These patients presented with abdominal pains (with or without nausea or vomiting); in certain cases this was not preceded by facial angioedema and C-1 esterase levels were normal. The diagnosis was carried out by abdominal scanner, ultrasound, or during surgery and the symptoms disappeared upon withdrawal of the ACE inhibitor. The intestinal angioedema has to be part of the differential diagnosis in the event of abdominal pain in a patient on ACE inhibitors.

Anaphylactoid reactions during desensitisation
Isolated cases of prolonged life-threatening anaphylactoid reactions have been reported in patients treated with an angiotensin-converting enzyme inhibitor while undergoing hymenoptera (bees, wasps) venom desensitisation.
Angiotensin-converting enzyme inhibitor treatment should be initiated with caution in allergic patients undergoing desensitisation and must be avoided in patients who will receive venom immunotherapy (anti-venom serum).
These reactions can be avoided by temporarily discontinuing for at least 24 hours the angiotensin-converting enzyme inhibitor treatment in patients requiring both angiotensin-converting enzyme inhibitor treatment and desensitisation.

Anaphylactoid reactions during low-density lipoprotein (LDL) apheresis
In rare cases, patients taking ACE inhibitors have presented with, possibly fatal, anaphylactoid reactions during LDL apheresis with dextran sulfate adsorption. It was possible to avoid these reactions in patients by temporarily suspending ACE inhibitor treatment before each apheresis.

Haemodialysis patients
Anaphylactoid reactions have been reported in patients dialysed using high-permeability membranes (e.g. AN 69®) and under ACE inhibitor treatment. It is advisable to use another type of dialysis membrane or another class of antihypertensive in these patients.

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

Pregnancy and breastfeeding
Perindopril must not be used during the first trimester of pregnancy. PRETERAX is contraindicated during the second and third trimesters of pregnancy (see paragraph 4.3.). If pregnancy is envisaged or confirmed, perindopril treatment should be stopped as soon as possible (see paragraph 4.6.). The use of perindopril is not recommended during breastfeeding.

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

Photosensitivity
Cases of photosensitivity have been reported with thiazide diuretics or related substances (see section 4.8). If a photosensitive reaction occurs during treatment it is recommended to interrupt it. If diuretic administration is deemed necessary, it is recommended to protect the exposed areas from the sun and from artificial UVAs.

Precautions for use
Common to perindopril and indapamide
Renal insufficiency
Treatment is contraindicated in the event of severe renal insufficiency (creatinine clearance < 30 ml/min).
In certain hypertensive patients without preexisting apparent renal lesion and for whom blood tests show functional renal insufficiency, the treatment should be stopped and possibly restarted either at a low dose or with only one of the constituents.

In these patients, normal medical practice includes periodic control of potassium and creatinine after 2 weeks of treatment and then every 2 months during the therapeutic stability period.
Renal insufficiency has been reported mainly in patients with severe heart failure or with underlying renal insufficiency, particularly through renal artery stenosis.
This medicinal product is generally not advised in the event of bilateral renal artery stenosis or in the event of a single functional kidney.

Hypotension and sodium and water depletion
There is a risk of sudden hypotension in subjects with pre-existing sodium depletion (particularly in patients presenting with renal artery stenosis). Therefore, systematic testing should be carried out for the clinical signs of hydroelectrolytic 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 for 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.

Kalaemia
The combination of perindopril and indapamide does not prevent the onset of hypokalaemia, in particular in diabetic patients or in those with renal insufficiency. As with any antihypertensive agent associated with a diuretic, regular monitoring of plasma potassium levels should be carried out.

Excipients
Due to the presence of lactose, patients presenting with congenital galactosaemia, glucose and galactose malabsorption or lactase deficiency 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 angiotensin-converting enzyme inhibitor is judged indispensable, continuation of treatment may be considered.

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

Risk of hypotension and/or renal insufficiency (in cases of heart failure, sodium and water depletion, etc...)
Marked stimulation of the renin-angiotensin-aldosterone system has been observed particularly during marked sodium and water depletion (strict low-sodium 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 a sudden drop in blood pressure, particularly at the time of the first administration and during the first two weeks of treatment, and/or an increase in plasma creatinine, showing functional renal insufficiency. Occasionally this can occur, albeit rarely, in an acute manner and at any time during treatment.
In these patients, the treatment should be initiated at a low dose and increased progressively.

Elderly
Renal function and kalaemia must be assessed before the start of treatment. The initial dose is subsequently adjusted according to blood pressure response, especially in cases of sodium and water depletion, in order to avoid any sudden onset of hypotension.

Subjects with known atherosclerosis
The risk of hypotension exists in all patients, but particular care should be taken in patients with coronary 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 and who are awaiting corrective surgery or when such surgery is not possible.
If PRETERAX is prescribed for patients with known or suspected renal artery stenosis, treatment should be initiated in a hospital at a low dose and renal function and kalaemia should be monitored, since some patients developed functional renal insufficiency which was reversed when treatment was stopped.

Other populations at risk
In patients with severe heart failure (grade IV) or in patients with insulin dependent diabetes mellitus (spontaneous tendency to hyperkalaemia), treatment should be started under medical supervision with a reduced initial dose. Treatment with beta-blockers in hypertensive patients with ischaemic heart disease should not be stopped: the ACE inhibitor should be added to the beta-blocker.

Diabetic patients
In diabetic patients under oral antidiabetic or insulin treatment, blood glucose should be tightly monitored, in particular during the first month of ACE inhibitor treatment.

Ethnic differences
As with other ACE inhibitors, perindopril is apparently less effective on lowering blood pressure in Black patients than in other patients, most likely due to the higher frequency of low renin states in the Black population.

Surgery/anaesthesia
ACE inhibitors can cause hypotension in the event of anaesthesia, and particularly when the anaesthetic agent used possesses hypotensive potential.
It is therefore recommended that treatment with long-acting ACE inhibitors such as perindopril be discontinued where possible the day before surgery.

Aortic or mitral valve stenosis/hypertrophic cardiomyopathy
Angiotension-converting enzyme inhibitors must be used with caution in patients presenting with an obstruction at the level of the left ventricle ejection system.

Liver failure
ACE inhibitors have rarely been linked to a syndrome beginning with cholestatic jaundice and which can then lead to fulminant necrotic hepatitis and (sometimes) to death. The mechanism of this syndrome has not been elucidated. Patients under ACE inhibitors who develop jaundice or who present a marked rise in liver enzymes must stop ACE inhibitor treatment and receive appropriate medical monitoring (see section 4.8).

Hyperkalaemia
Increases in kalaemia have been observed in certain patients treated with ACE inhibitors, including perindopril. Hyperkalaemia risk factors are renal insufficiency, renal function degradation, age (> 70 years), diabetes, intercurrent events such as dehydration, acute cardiac decompensation, metabolic acidosis, concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, amiloride), of potassium supplements or salt substitutes containing potassium or other treatments that increase kalaemia (e.g. heparin). The use of potassium supplements, of potassium-sparing diuretics or salt substitutes containing potassium, in particular in patients with impaired renal function, may provoke a significant rise in kalaemia. Hyperkalaemia may result in serious, sometimes fatal, arrhythmia. If the concomitant use of the agents mentioned above is deemed necessary, they must be used with caution and regular kalaemia monitoring must be performed (see section 4.5).

Linked to indapamide
Hydroelectrolytic balance
Natraemia:
This should be tested before treatment is started, and then at regular intervals. All diuretic treatment can cause a reduction in sodium levels, likely to have serious consequences. Reduction in natraemia can be initially

asymptomatic, and regular testing is therefore essential. Testing should be more frequent in elderly and cirrhotic subjects (see sections 4.8 and 4.9).

Kalaemia:
Potassium depletion with hypokalaemia is a major risk with thiazide diuretics and related substances. The risk of onset of hypokalaemia (<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 those with heart failure.
In such cases hypokalaemia increases the cardiac toxicity of digitalis 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, like bradycardia, thus acts as a factor favouring the onset of severe rhythm disorders, in particular torsade de pointes, which may be fatal.

In all cases more frequent testing of kalaemia is necessary. The first control of plasma potassium should be carried out during the first week of treatment.

If hypokalaemia is detected, this requires correction.

Calcaemia:
Thiazide diuretics and related substances are liable to reduce urinary excretion of calcium and bring about a mild and transient increase in calcaemia. Considerable hypercalcaemia may be linked to undiagnosed hyperparathyroidism. In such cases the treatment should be stopped before investigating the parathyroid function.

Glycaemia:
Monitoring of glycaemia is important in diabetic patients, particularly when potassium levels are low.

Uric acid:
Hyperuricaemic patients may have an increased tendency to attacks of gout.

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

In the elderly the creatinine value should be adjusted to take account of the age, weight and sex of the patient, according to the Cockcroft formula:
cl_{cr} = (140 - age) x body weight/0.814 x creatinine
with: age expressed in years
body weight in kg
creatinine level in µmol/l.

This formula is valid for elderly male subjects 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 plasma urea and creatinine levels. This transitory functional renal insufficiency is of no consequence in subjects with normal renal function but may however worsen a pre-existing renal insufficiency.

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

4.5 Interaction with other drugs and other forms of interaction

Common to perindopril and indapamide
Combinations which are not recommended

Lithium: reversible increases in serum lithium concentrations and in its toxicity have been reported during concomitant administration of lithium with ACE inhibitors. The concomitant use of thiazide diuretics may increase plasma lithium and increase the risk of lithium toxicity with ACE inhibitors. The use of perindopril associated with indapamide with lithium is not recommended, but if the association proves necessary, close monitoring of plasma lithium should be carried out (see section 4.4).

Combinations requiring special care
Baclofen: potentiation of the antihypertensive effect. Monitoring of blood pressure and renal function and dose adaptation of the antihypertensive if necessary.
Non steroidal anti-inflammatory drugs (NSAIDs) (including high-dose acetylsalicylic acid):
The administration of NSAIDs may reduce the diuretic, natriuretic and antihypertensive effects in some patients. In elderly patients or those that might be dehydrated, the risk of acute renal insufficiency exists: it is therefore recommended to monitor renal function at the start of treatment. The patients should be well hydrated.

Associations to take into account
Imipramine antidepressants (tricyclics), neuroleptics: increased antihypertensive effect and increased risk of orthostatic hypotension (additive effect).
Corticosteroids, tetracosactide: reduction in antihypertensive effect (sodium and water retention due to corticosteroids).
Other antihypertensive agents: the concomitant use of other antihypertensive agents with perindopril/indapamide can result in an additional effect on blood pressure reduction.

Linked to perindopril
Combinations which are not recommended
Potassium-sparing diuretics (spironolactone, triamterene, alone or in combination), potassium (salts): ACE inhibitors attenuate the loss of potassium induced by the diuretics.

Potassium-sparing diuretics (for ex.: spironolactone, triamterene or amiloride), potassium supplements or salt substitutes containing potassium can lead to a significant (potentially lethal) increase in kalaemia. If a concomitant use is indicated due to proven hypokalaemia, these medicinal products must be used with care and with a frequent control of kalaemia and of the ECG.

Combinations requiring special care
Antidiabetic agents (insulin, sulfonylureas): reported with captopril and enalapril. The use of angiotensin-converting enzyme inhibitors may increase the hypoglycaemic effect in diabetics receiving treatment with insulin or with sulfonylureas. The onset of hypoglycaemic episodes is very rare (improvement in glucose tolerance with a resulting reduction in insulin requirements).

Associations to take into account
Allopurinol, cytostatic or immunosuppressant agents, corticosteroids (systemic route) or procainamide: concomitant administration with angiotensin-converting enzyme inhibitors may lead to an increased risk of leucopaenia.
Anaesthetics: angiotensin-converting enzyme inhibitors may increase the hypotensive effects of certain anaesthetic products.
Diuretics (thiazide or loop diuretics): previous high-dose diuretic treatment may result in blood volume depletion and a risk of hypotension during initiation of perindopril treatment.
Gold compounds: nitritoid reactions (symptoms including facial flush, nausea, vomiting and hypotension) have been reported rarely in patients receiving gold compound injections (sodium aurothiomalate) and an ACE inhibitor (including perindopril) concomitantly.

Linked to indapamide
Combinations requiring special care
Medicinal products inducing torsades de pointe: due to the risk of hypokalaemia, indapamide must be used with care when it is combined with medicinal products inducing torsades de pointe, such as class IA antiarrythmics (quinidine, hydroquinidine, disopyramide), class III antiarrythmics (amiodarone, dofetilide, ibutilide, bretylium, sotalol); certain 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, mizolastin, moxifloxacin, pentamidine, sparfloxacin, IV vincamine, methadone, astemizole, terfenadine. Prevention of hypokalaemia and correction if required: 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 kalaemia, and correction if necessary; particular consideration required in cases of treatment with digitalis glycosides. Non stimulant laxatives should be used.
Digitalis glycosides: low potassium levels favour the toxic effects of digitalis glycosides. Kalaemia and ECG should be monitored and treatment reconsidered if necessary.

Associations to take into account
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 calcaemia due to reduced elimination of calcium in the urine.
Ciclosporin: risk of increased creatinine levels with no change in circulating levels of ciclosporin, even when there is no sodium and water depletion.

4.6 Pregnancy and lactation

Pregnancy
PRETERAX must not be used during the first trimester of pregnancy. If a pregnancy is envisaged or confirmed, an alternative treatment must be initiated as soon as possible. There have been no controlled studies with ACE inhibitors in humans, but in a limited number of cases of exposure during the first trimester no malformations occurred that could correspond to human foetotoxicity, as described hereafter.

PRETERAX is contraindicated during the second and third trimesters of pregnancy (see section 4.3).

Prolonged exposure to an ACE inhibitor during the second and third trimesters is known for inducing foetotoxicity (reduction in renal function, oligohydramnios, delayed ossification of the vault of the cranium) and neonatal toxicity (renal insufficiency, hypotension, hyperkalaemia) (see section 5.3).

Prolonged exposure to thiazide diureticzs during the third trimester of pregnancy can reduce the maternal plasmatic volume and the utero-placental blood flow which may lead to foeto-placental ischaemia and delayed growth. Furthermore, some rare cases of neonatal hypoglycaemia and thrombocytopaenia have been reported following exposure close to term.

In the event of exposure to PRETERAX during the second trimester of pregnancy, an ultrasound of renal function and of vault of the cranium is recommended.

Lactation
PRETERAX is contraindicated during breastfeeding.
The excretion of perindopril into maternal milk is unknown.
Indapamide is excreted into maternal milk. Indapamide is tightly linked to thiazide diuretics that are implicated in the reduction or even the suppression of milk during breastfeeding. Hypersensitivity to sulphonamide-derived products, hypokalaemia and nuclear icterus of the neonate can occur.
These two substances can bring about serious undesirable effects in breastfed neonates, that is why a solution must be envisaged, either stop breastfeeding or stop the treatment while taking into account the importance of this treatment for the mother.

4.7 Effects on ability to drive and use machines

Linked to perindopril, indapamide and PRETERAX
Neither the two drug substances taken separately or combined in PRETERAX affect aptitude to drive vehicles and use machines but individual reactions related to low blood pressure may occur in some patients, particularly at the start of treatment or in combination with another antihypertensive medication. As a result the ability to drive or operate machinery may be impaired.

4.8 Undesirable effects

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

The following undesirable effects have been observed during treatment and are classed according to the following frequencies:
Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1000, <1/100), rare (>1/10 000, <1/1000), very rare (<1/10 000), unknown (cannot be estimated from available data).

Blood disorders and lymphatic system
Very rare:
Thrombocytopaenia, leucopaenia/neutropaenia, agranulocytosis, aplastic anaemia, haemolytic anaemia.
Anaemia (see section 4.4) has been reported with angiotensin-converting enzyme inhibitors in specific circumstances (kidney transplants, haemodialysis).

Psychiatric disorders
Uncommon: mood or sleep disorders.

Nervous system disorders
Common: paraesthesia, headache, asthenia, dizziness, vertigo.
Very rare: confusion.

Eye disorders
Common: vision disorders.

Ear and labyrinth disorders
Common: tinnitus.

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

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

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

Gastro-intestinal disorders
Common: constipation, dry mouth, nausea, vomiting, abdominal pains, taste disturbance, dyspepsia, diarrhoea.
Very rare: pancreatitis.

Hepato-biliary disorders
Very rare: cytolytic or cholestatic hepatitis (see section 4.4).
Unknown: in the event of liver failure, the occurrence of hepatic encephalopathy is possible (see sections 4.3 and 4.4).

Cutaneous and tissue disorders
Common: rash, pruritus, maculo-papulous eruptions.
Uncommon: angioedema of the face, the extremities, lips, mucous membranes, tongue, glottis and/or of the larynx, urticaria (see section 4.4)
Hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions,
Purpura
Possible aggravation of pre-existing systemic lupus erythematosus

Very rare: erythema multiforme, toxic epidermic necrosis, Steven Johnson syndrome.

Cases of photosensitivity have been reported (see section 4.4).

Muscular-, connective tissue and bone disorders
Common: muscle cramps.

Kidney and urinary tract disorders
Uncommon: renal insufficiency.
Very rare: acute renal insufficiency.

Reproductive organs and breast disorders
Uncommon: impotence.

General disorders
Common: asthenia.
Uncommon: sweating.

Laboratory parameters
Potassium depletion with considerable reduction in kalaemia in some at-risk populations (see section 4.4).
Hyponatraemia with hypovolaemia causing dehydration and orthostatic hypotension.
Increase in uricaemia and glycaemia during treatment.
Slight increase in urea and in plasma creatinine, reversible when treatment is stopped. This increase is more frequent in cases of renal artery stenosis, hypertension treated with diuretics, renal insufficiency.
Increased plasma levels of potassium, usually transitory.

Rare: increased calcaemia.

4.9 Overdose
The most likely event in the case of overdose is hypotension, sometimes associated with nausea, vomiting, cramps, vertigo, drowsiness, confusional states, oliguria which may progress to anuria (due to hypovolaemia). Hydroelectrolytic disorders (hyponatraemia, hypokalaemia) may occur.

The first measures to be taken consist of a rapidly eliminating the product(s) ingested by gastric lavage and/or administration of activated charcoal, then restoring hydroelectrolytic balance in a specialised centre until they return to normal.

If marked hypotension occurs, this can be treated by placing the patient in the decubitus position with the head lowered. If necessary an IV infusion of isotonic saline may be given, or any other method of expanding blood volume may be used.

Perindoprilate, 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 is a combination of perindopril tert-butylamine salt, an angiotensin-converting enzyme inhibitor, and indapamide, a chlorosulphamoyl diuretic. Its pharmacological properties are derived from those of each of the components taken separately, in addition to those due to the additive synergic action of the two products when combined.
Pharmacological mechanism of action
Linked to PRETERAX
PRETERAX produces an additive synergy of the antihypertensive effects of the two components.

Linked to perindopril
Perindopril is an inhibitor of the converting enzyme of angiotensin I into angiotensin II, a vasoconstricting substance; which also stimulates the secretion of aldosterone by the adrenal cortex and 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 resistances with a preferential action on the muscular and renal territories, with no accompanying sodium 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, perindoprilate. The other metabolites are inactive.

Perindopril reduces the work of the heart:

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

Studies carried out on patients with heart failure 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 nucleus, pharmacologically related to the thiazide group of diuretics. Indapamide inhibits the reabsorption of sodium in the cortical dilution segment. It increases the urinary excretion of sodium and chlorides and, to a lesser extent, the excretion of potassium and magnesium, thereby increasing urine output and having an antihypertensive action.

Characteristics of the antihypertensive activity

Linked to PRETERAX

In hypertensive patients regardless of age, PRETERAX 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 escape beats; 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, controlled study versus enalapril assessed, via echocardiography, the effects of the perindopril/indapamide combination in monotherapy on left ventricular hypertrophy (LVH).

In the PICXEL study, hypertensive patients with LVH (defined by a left ventricular mass index (LVMI) >120 g/m² in men and >100 g/m² in women) were randomised into 2 groups for one year of treatment: perindopril 2 mg/indapamide 0.625 mg or enalapril 10 mg, in one administration per day. Dose could be adjusted according to blood pressure control up to perindopril 8 mg/indapamide 2.5 mg or enalapril 40 mg in one administration per day. Only 34% of subjects remained treated with perindopril 2 mg/indapamide 0.625 mg (versus 20% with enalapril 10 mg).

At the end of treatment, LVMI was significantly more reduced in the perindopril/indapamide group (-10.1 g/m²) than in the enalapril group (-1.1 g/m²) in the total population of randomised patients. The difference in LVMI variation between the two groups was –8.3 g/m² (CI95% (-11.5, -5.0), p<0.0001).

A more considerable effect on LVMI was achieved with doses of perindopril/indapamide greater than those recorded for PRETERAX and BIPRETERAX.

Concerning blood pressure, the estimated average differences between the 2 groups in the randomised population was, respectively, -5.8 mmHg (CI95% (-7.9, -3.7), p<0.0001) for systolic blood pressure and –2.3 mmHg (CI95% (-3.6, -0.9), p=0.0004) for diastolic blood pressure, in favour of the perindopril/indapamide group.

Linked to perindopril

Perindopril is active at all stages of hypertension: mild to moderate or severe. A reduction in systolic and diastolic pressures is observed in decubitus and in orthostatism.

The antihypertensive activity after a single administration is maximal at between 4 and 6 hours and is maintained over 24 hours.

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

In responder patients, normalised blood pressure is reached after one month and is maintained without escape beats.

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-type synergy.

The combination of an angiotensin-converting enzyme inhibitor with a thiazide diuretic decreases the hypokalaemia risk induced by the diuretic alone.

Linked to indapamide
Indapamide, in monotherapy, has an antihypertensive effect which lasts for 24 hours. This effect occurs at doses at which the diuretic properties are minimal.
Its antihypertensive activity is proportional to an improvement in arterial compliance and a reduction in total and arteriolar peripheral vascular resistances.
Indapamide reduces left ventricular hypertrophy.
When a dose of thiazide diuretics and related substances is exceeded, the antihypertensive effect reaches a plateau, whereas the adverse effects continue to increase. If the treatment is ineffective, the doses should not be increased.
Furthermore, it has been shown that in the short-, medium- and long-term in hypertensive patients, indapamide:

- has no effect on lipid metabolism: triglycerides ,LDL-cholesterol and HDL-cholesterol,
- has no effect on carbohydrate metabolism, even in diabetic hypertensive patients.

5.2 Pharmacokinetic properties

Linked to PRETERAX
The co-administration of perindopril and indapamide does not change their pharmacokinetic parameters in relation to their separate administration.

Linked to perindopril
Perindopril is rapidly absorbed by the oral route and peak concentration is achieved in 1 hour. The plasma half-life of perindopril is 1 hour.

Perindopril is a prodrug. Twenty-seven per cent of perindopril administered reaches the blood circulation as active metabolite, perindoprilate. In addition to active perindoprilate, perindopril is at the origin of 5 other metabolites, all inactive. The plasma concentration peak of perindoprilate is reached in 3 to 4 hours.

As food intake lowers transformation into perindoprilate, and therefore its bioavailability, perindopril tert-butylamine must be administered by the oral route, in a single daily administration in the morning before a meal.

A linear relation between the administered perindopril dose and plasma exposure has been shown.

The distribution volume is approximately 0.2 l/kg for the free form of perindoprilate. Binding of perindoprilate to plasma proteins is 20%, mainly to the angiotensin-converting enzyme, but is concentration-dependant.

Perindoprilate is eliminated by the urinary route and the terminal half-life of the unbound fraction is around 17 hours, making it possible to obtain steady state in 4 days.

Elimination of perindoprilate is reduced in elderly subjects as well as in those with heart failure or renal insufficiency. Dose adjustment in the event of renal insufficiency is advisable as a function of the degree of impairment (creatinine clearance).
The clearance of perindopril by dialysis is 70 ml/min.

In cirrhotic patients, the kinetics of perindopril are modified: hepatic clearance of the parent substance is reduced by half. However, the quantity of perindoprilate formed is not reduced and dose adjustment is therefore not necessary (see sections 4.2 and 4.4).

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

5.3 Preclinical safety data

PRETERAX 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 maternotoxic effects seem to be increased in rats (compared to perindopril).
Nonetheless, these adverse effects occur at dose levels that are markedly higher than the therapeutic doses used.
Preclinical studies performed separately with perindopril and indapamide have not shown any genotoxic, carcinogenic or teratogenic potential.

6. PHARMACEUTICAL DATA

6.1 List of excipients

Lactose monohydrate, magnesium stearate (E470B), anhydrous colloidal silica (E551), microcrystalline cellulose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years in blister strips overwrapped in a sachet.
2 months after opening the sachet overwrap.

6.4 Special precautions for storage

Store in the original packaging.
Store below 30°C.

DATE OF REVISION OF THE TEXT:

May 2008