

**SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET**

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BIPRETERAX 5mg/1.25mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 3.395 mg perindopril corresponding to 5 mg perindopril arginine and 1.25 mg indapamide.

Excipient : 71.33 mg lactose monohydrate
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
White, rod-shaped film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension, BIPRETERAX 5mg/1.25mg film-coated tablet is indicated in patients whose blood pressure is not adequately controlled on perindopril alone.

4.2 Posology and method of administration

Posology

One BIPRETERAX 5mg/1.25mg film-coated tablet per day as a single dose, preferably to be taken in the morning, and before a meal.

When possible individual dose titration with the components is recommended. BIPRETERAX 5mg/1.25mg film-coated tablet should be used when blood pressure is not adequately controlled on PRETERAX 2.5mg/0.625mg film-coated tablet (where available). When clinically appropriate, direct change from monotherapy to BIPRETERAX 5mg/1.25mg film-coated tablet may be considered.

Elderly (see section 4.4)

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

Patients with renal impairment (see section 4.4)

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

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

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

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

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

In severe hepatic impairment, treatment is contraindicated.

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

Paediatric population

The safety and efficacy of perindopril arginine/indapamide in the paediatric population have not yet been established.

BIPRETERAX 5mg/1.25mg should not be used in children and adolescents.

Method of administration

Oral route

4.3 Contraindications

Linked to perindopril:

- Hypersensitivity to perindopril or any other ACE inhibitor
- History of angioedema (Quincke's oedema) associated with previous ACE inhibitor therapy
- Hereditary/idiopathic angioedema
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)

Linked to indapamide:

- Hypersensitivity to indapamide or to any other sulphonamides
- Severe renal impairment (creatinine clearance below 30 ml/min)
- Hepatic encephalopathy
- Severe hepatic impairment
- Hypokalaemia
- As a general rule, this medicine is inadvisable in combination with non antiarrhythmic agents causing torsades de pointes (see section 4.5)
- Lactation (see section 4.6).

Linked to BIPRETERAX 5mg/1.25mg:

- Hypersensitivity to any of the excipients

Due to the lack of sufficient therapeutic experience, BIPRETERAX 5mg/1.25mg should not be used in :

- Dialysis patients
- Patients with untreated decompensated heart failure.

4.4 Special warnings and precautions for use

Special warnings

Common to perindopril and indapamide:

Lithium:

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

Linked to perindopril:

Neutropenia/agranulocytosis:

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Perindopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy. If perindopril is used in such patients, periodical monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (e.g. sore throat, fever).

Hypersensitivity/angioedema:

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with angiotensin converting enzyme inhibitors, including perindopril. This may occur at any time during treatment. In such cases perindopril should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. In those instances where swelling has been confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

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

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

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

Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Anaphylactoid reactions during desensitisation:

There have been isolated reports of patients experiencing sustained, life-threatening anaphylactoid reactions while receiving ACE inhibitors during desensitisation treatment with hymenoptera (bees, wasps) venom. ACE inhibitors should be used with caution in allergic patients treated with desensitisation, and avoided in those undergoing venom immunotherapy. However these reactions could be prevented by temporary withdrawal of ACE inhibitor for at least 24 hours before treatment in patients who require both ACE inhibitors and desensitisation.

Anaphylactoid reactions during LDL apheresis:

Rarely, patients receiving ACE inhibitors during low density lipoprotein (LDL)-apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each apheresis.

Haemodialysis patients:

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g., AN 69®) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Potassium-sparing diuretics, potassium salts:

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

Pregnancy:

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

Linked to indapamide:

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

Photosensitivity:

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

Precautions for use

Common to perindopril and indapamide:

Renal impairment:

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

In certain hypertensive patients without pre-existing apparent renal lesions and for whom renal blood tests show functional renal insufficiency, treatment should be stopped and possibly restarted either at a low dose or with one constituent only.

In these patients usual medical follow-up will include frequent monitoring of potassium and creatinine, after two weeks of treatment and then every two months during therapeutic stability period. Renal failure has been reported mainly in patients with severe heart failure or underlying renal failure including renal artery stenosis.

The drug is usually not recommended in case of bilateral renal artery stenosis or a single functioning kidney.

Hypotension and water and electrolyte depletion:

There is a risk of sudden hypotension in the presence of pre-existing sodium depletion (in particular in individuals with renal artery stenosis). Therefore systematic testing should be carried out for clinical signs of water and electrolyte depletion, which may occur with an intercurrent episode of diarrhoea or vomiting. Regular monitoring of plasma electrolytes should be carried out in such patients.

Marked hypotension may require the implementation of an intravenous infusion of isotonic saline.

Transient hypotension is not a contraindication to continuation of treatment. After re-establishment of a satisfactory blood volume and blood pressure, treatment can be started again either at a reduced dose or with only one of the constituents.

Potassium levels:

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

Excipients:

BIPRETERAX 5mg/1.25mg should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

Linked to perindopril:

Cough:

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

Paediatric population:

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

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

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

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

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

Elderly:

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

Patients with known atherosclerosis:

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

Renovascular hypertension:

The treatment for renovascular hypertension is revascularisation. Nonetheless, angiotensin converting enzyme inhibitors can be beneficial in patients presenting with renovascular hypertension who are awaiting corrective surgery or when such a surgery is not possible.

If BIPRETERAX 5mg/1.25mg is prescribed to patients with known or suspected renal artery stenosis, treatment should be started in a hospital setting at a low dose and renal function and potassium levels should be monitored, since some patients have developed a functional renal insufficiency which was reversed when treatment was stopped.

Other populations at risk:

In patients with severe cardiac insufficiency (grade IV) or in patients with insulin dependent diabetes mellitus (spontaneous tendency to increased levels of potassium), treatment should be started under medical supervision with a reduced initial dose. Treatment with beta-blockers in hypertensive patients with coronary insufficiency should not be stopped : the ACE inhibitor should be added to the beta-blocker.

Diabetic patients:

The glycaemia levels should be closely monitored in diabetic patients previously treated with oral antidiabetic drugs or insulin, namely during the first month of treatment with an ACE inhibitor.

Ethnic differences:

As with other angiotensin converting enzyme inhibitors, perindopril is apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Surgery / anaesthesia:

Angiotensin converting enzyme inhibitors can cause hypotension in cases of anaesthesia, especially when the anaesthetic administered is an agent with hypotensive potential.

It is therefore recommended that treatment with long-acting angiotensin converting enzyme inhibitors such as perindopril should be discontinued where possible one day before surgery.

Aortic or mitral valve stenosis / hypertrophic cardiomyopathy:

ACE inhibitors should be used with caution in patient with an obstruction in the outflow tract of the left ventricle.

Hepatic failure:

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

Hyperkalaemia:

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

Linked to indapamide:

Water and electrolyte balance:

Sodium levels:

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

Potassium levels:

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

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

In all cases more frequent testing of potassium levels is necessary. The first measurement of plasma potassium levels should be carried out during the first week following the start of treatment.

If low potassium levels are detected, correction is required.

Calcium levels:

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

Blood glucose:

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

Uric acid:

Tendency to gout attacks may be increased in hyperuricaemic patients.

Renal function and diuretics:

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

In the elderly the value of plasma creatinine levels should be adjusted to take account of the age, weight and sex of the patient, according to the Cockcroft formula:

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

with: age expressed in years

body weight in kg

plasma creatinine level in micromol/l

This formula is suitable for an elderly male and should be adapted for women by multiplying the result by 0.85.

Hypovolaemia, resulting from the loss of water and sodium caused by the diuretic at the start of treatment, causes a reduction in glomerular filtration. It may result in an increase in blood urea and creatinine levels. This transitory functional renal insufficiency is of no adverse consequence in patients with normal renal function but may however worsen a pre-existing renal impairment.

Athletes:

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

4.5 Interaction with other medicinal products and other forms of interaction

Common to perindopril and indapamide:

Concomitant use not recommended:

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

Concomitant use which requires special care:

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

Concomitant use which requires some care:

- Imipramine-like antidepressants (tricyclics), neuroleptics: Increased antihypertensive effect and increased risk of orthostatic hypotension (additive effect).
- Corticosteroids, tetracosactide: Reduction in antihypertensive effect (salt and water retention due to corticosteroids).
- other antihypertensive agents : use of other antihypertensive medicinal products with perindopril/indapamide could result in additional blood pressure lowering effect.

Linked to perindopril:

Concomitant use not recommended:

- Potassium-sparing diuretics (spironolactone, triamterene, alone or in combination), potassium (salts): ACE inhibitors attenuate diuretic induced potassium loss. Potassium sparing diuretics e.g. spironolactone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium (potentially lethal). If concomitant use is

indicated because of documented hypokalemia they should be used with caution and with frequent monitoring of serum potassium and by ECG.

Concomitant use which requires special care:

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

Concomitant use which requires some care:

- Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids or procainamide: Concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia.
- Anaesthetic drugs: ACE inhibitors may enhance the hypotensive effects of certain anaesthetic drugs.
- Diuretics (thiazide or loop diuretics): Prior treatment with high dose diuretics may result in volume depletion and in a risk of hypotension when initiating therapy with perindopril.
- Gold : Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including perindopril.

Linked to indapamide:

Concomitant use which requires special care:

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

Concomitant use which requires some care:

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

4.6 Pregnancy and lactation

Given the effects of the individual components in this combination product on pregnancy and lactation, BIPRETERAX 5mg/1.25mg is not recommended during the first trimester of pregnancy. BIPRETERAX 5mg/1.25mg is contraindicated during the second and third trimesters of pregnancy.

BIPRETERAX 5mg/1.25mg is contraindicated during lactation. A decision should therefore be made whether to discontinue nursing or to discontinue BIPRETERAX 5mg/1.25mg 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:

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

Breastfeeding :

BIPRETERAX 5mg/1.25mg is contraindicated during lactation.

Linked to perindopril :

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

Linked to indapamide:

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

4.7 Effects on ability to drive and use machines

Linked to perindopril, indapamide and BIPRETERAX 5mg/1.25mg:

Neither the two active substances nor BIPRETERAX 5mg/1.25mg affect alertness but individual reactions related to low blood pressure may occur in some patients, particularly at the start of treatment or in combination with another antihypertensive medication.

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

4.8 Undesirable effects

The administration of perindopril inhibits the renin-angiotensin-aldosterone axis and tends to reduce the potassium loss caused by indapamide. Four percent of the patients on treatment with BIPRETERAX 5mg/1.25mg experience hypokalaemia (potassium level < 3.4 mmol/l).

The following undesirable effects could be observed during treatment and ranked under the following frequency:

Very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1000$, $< 1/100$); rare ($\geq 1/10000$, $< 1/1000$), very rare ($< 1/10000$), not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders:

Very rare:

- Thrombocytopenia, leucopenia/neutropenia, agranulocytosis, aplastic anaemia, haemolytic anaemia.
- Anaemia (see section 4.4) has been reported with angiotensin converting enzyme inhibitors in specific circumstances (patients who have had kidney transplants, patients undergoing haemodialysis).

Psychiatric disorders:

Uncommon: mood or sleep disturbances.

Nervous system disorders:

Common: Paresthesia, headache, asthenia, feelings of dizziness, vertigo.

Very rare : Confusion.

Not known: Syncope

Eye disorders:

Common: Vision disturbance.

Ear and labyrinth disorders:

Common: Tinnitus.

Cardiac disorders:

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

Not known: Torsade de pointes (potentially fatal) (see sections 4.4 and 4.5)

Vascular disorders:

Common: Hypotension whether orthostatic or not (see section 4.4).

Respiratory, thoracic and mediastinal disorders:

Common: A dry cough has been reported with the use of angiotensin converting enzyme inhibitors. It is characterised by its persistence and by its disappearance when treatment is withdrawn. An iatrogenic aetiology should be considered in the presence of this symptom. Dyspnoea.

Uncommon: Bronchospasm.

Very rare: Eosinophilic pneumonia, rhinitis.

Gastrointestinal disorders:

Common : Constipation, dry mouth, nausea, epigastric pain, anorexia, vomiting, abdominal pain, taste disturbance, dyspepsia, diarrhoea.

Very rare: Pancreatitis.

Hepato-biliary disorders:

Very rare: Hepatitis either cytolytic or cholestatic (see section 4.4).

Not known: In case of hepatic insufficiency, there is a possibility of onset of hepatic encephalopathy (see sections 4.3 and 4.4).

Skin and subcutaneous tissue disorders:

Common: Rash, pruritus, maculopapular eruptions.

Uncommon:

- Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see section 4.4).
- Hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions.
- Purpura.
- Possible aggravation of pre-existing acute disseminated lupus erythematosus.

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

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

Musculoskeletal, connective tissue and bone disorders:

Common: Cramps.

Renal and urinary disorders:

Uncommon: Renal insufficiency.

Very rare: Acute renal failure.

Reproductive system and breast disorders:

Uncommon: Impotence.

General disorders and administration site conditions:

Common: Asthenia.

Uncommon: Sweating.

Investigations:

Not known:

- Electrocardiogram QT prolonged (see sections 4.4 and 4.5)
- - Blood glucose increased and blood uric acid increased during treatment .
- Slight increase in urea and in plasma creatinine levels, reversible when treatment is stopped. This increase is more frequent in cases of renal artery stenosis, arterial hypertension treated with diuretics, renal insufficiency.
- Elevated liver enzyme levels.

Metabolism and nutrition disorder:

Rare : Hypercalcemia

Not known:

- Potassium depletion with particularly serious reduction in levels of potassium in some at risk populations (see section 4.4).
- Increased levels of potassium, usually transitory.
- Hyponatraemia with hypovolaemia responsible for dehydration and orthostatic hypotension.

4.9 Overdose

The most likely adverse reaction in cases of overdose is hypotension, sometimes associated with nausea, vomiting, cramps, dizziness, sleepiness, mental confusion, oliguria which may progress to anuria (due to hypovolaemia). Salt and water disturbances (low sodium levels, low potassium levels) may occur.

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

If marked hypotension occurs, this can be treated by placing the patient in a supine position with the head lowered. If necessary an intravenous infusion of isotonic saline may be given, or any other method of volaemic expansion may be used.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: perindopril and diuretics, ATC code: C09BA04

BIPRETERAX 5mg/1.25mg is a combination of perindopril arginine 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.

Mechanism of action

Linked to BIPRETERAX 5mg/1.25mg:

BIPRETERAX 5mg/1.25mg produces an additive synergy of the antihypertensive effects of the two components.

Linked to perindopril:

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

This results in:

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

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

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

Perindopril reduces the work of the heart :

- by a vasodilatory effect on veins, probably caused by changes in the metabolism of prostaglandins : reduction in 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 BIPRETERAX 5mg/1.25mg:

In hypertensive patients regardless of age, BIPRETERAX 5mg/1.25mg exerts a dose-dependent antihypertensive effect on diastolic and systolic arterial pressure whilst supine or standing. This antihypertensive effect lasts for 24 hours. The reduction in blood pressure is obtained in less than one month without tachyphylaxis ; stopping treatment has no rebound effect. During clinical trials, the concomitant administration of perindopril and indapamide produced antihypertensive effects of a synergic nature in relation to each of the products administered alone.

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

In PICXEL, hypertensive patients with LVH (defined as left ventricular mass index (LVMI) > 120 g/m² in male and > 100 g/m² in female) were randomised either to perindopril 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) and 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)/indapamide 0.625mg (versus 20% with Enalapril 10mg).

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

A better effect on LVMI was reached with higher perindopril/indapamide doses than those licensed for PRETERAX 2.5mg/0.625mg and BIPRETERAX 5mg/1.25mg.

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

Linked to perindopril:

Perindopril is active in all grades of hypertension : mild to moderate or severe. A reduction in systolic and diastolic arterial pressure is observed in the lying and standing position.

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

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

In patients who respond, normalised blood pressure is reached after one month and is maintained without tachyphylaxis.

Withdrawal of treatment has no rebound effect on hypertension.

Perindopril has vasodilatory properties and restores elasticity of the main arterial trunks, corrects histomorphometric changes in resistance arteries and produces a reduction in left ventricular hypertrophy.

If necessary, the addition of a thiazide diuretic leads to an additive synergy.

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

Linked to indapamide:

Indapamide, as monotherapy, has an antihypertensive effect which lasts for 24 hours. This effect occurs at doses at which the diuretic properties are minimal.

Its antihypertensive action is proportional to an improvement in arterial compliance and a reduction in total and arteriolar peripheral vascular resistance.

Indapamide reduces left ventricular hypertrophy.

When a dose of thiazide diuretic and thiazide-related diuretics is exceeded, the antihypertensive effect reaches a plateau, whereas the adverse effects continue to increase. If the treatment is ineffective, the dose should not be increased.

Furthermore, it has been shown that in the short-term, mid-term and long-term in hypertensive patients, indapamide :

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

5.2 Pharmacokinetic properties

Linked to BIPRETERAX 5mg/1.25mg:

The co-administration of perindopril and indapamide does not change their pharmacokinetic properties by comparison to separate administration.

Linked to perindopril:

After oral administration, the absorption of perindopril is rapid and the peak concentration is achieved within 1 hour. The plasma half-life of perindopril is equal to 1 hour.

Perindopril is a prodrug. Twenty seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.

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

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

The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Protein binding of perindoprilat to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration-dependent.

Perindoprilat is eliminated in the urine and the terminal half-life of the unbound fraction is approximately 17 hours, resulting in steady-state within 4 days.

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

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

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

Perindopril kinetics are modified in patients with cirrhosis: hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required (see sections 4.2 and 4.4).

Linked to indapamide:

Indapamide is rapidly and completely absorbed from the digestive tract.

The peak plasma level is reached in humans approximately one hour after oral administration of the product. Plasma protein binding is 79 %.

The elimination half-life is between 14 and 24 hours (average 18 hours). Repeated administration does not produce accumulation. Elimination is mainly in the urine (70 % of the dose) and faeces (22 %) in the form of inactive metabolites.

The pharmacokinetics are unchanged in patients with renal insufficiency.

5.3 Preclinical safety data

BIPRETERAX 5mg/1.25mg has slightly increased toxicity than that of its components. Renal manifestations do not seem to be potentiated in the rat. However, the combination produces gastro-intestinal toxicity in the dog and the toxic effects on the mother seem to be increased in the rat (compared to perindopril).

Nonetheless, these adverse effects are shown at dose levels corresponding to a very marked safety margin by comparison to the therapeutic doses used.

Preclinical studies performed separately with perindopril and indapamide did not show genotoxic, carcinogenic or teratogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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 polypropylene white container equipped with a low density polyethylene flow reducer and a low density polyethylene white opaque 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

No special requirements.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

{CARTON}

1. NAME OF THE MEDICINAL PRODUCT

BIPRETERAX 5mg/1.25mg film-coated tablets
perindopril arginine/indapamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One film-coated tablet contains 3.395 mg perindopril corresponding to 5 mg perindopril arginine and 1.25 mg indapamide

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
20 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
56 film-coated tablets
60 film-coated tablets
90 film-coated tablets
100 film-coated tablets
500 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Keep the container tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

To be completed nationally
For RMS (France):
Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex

12. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

BIPRETERAX 5mg/1.25mg

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

{CONTAINER}

1. NAME OF THE MEDICINAL PRODUCT

BIPRETERAX 5mg/1.25mg film-coated tablets
perindopril arginine/indapamide
oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

LOT {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Container of 14, 20, 28, 30 or 50 tablets

6. OTHER

Abbreviations for days of the week

MON

TUE

WED

THU

FRI

SAT

SUN

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

BIPRETERAX 5mg/1.25mg film-coated tablets perindopril arginine/indapamide

Read all of this leaflet carefully before you start taking this medicine.

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

In this leaflet:

1. What BIPRETERAX 5mg/1.25mg is and what it is used for
2. Before you take BIPRETERAX 5mg/1.25mg
3. How to take BIPRETERAX 5mg/1.25mg
4. Possible side effects
5. How to store BIPRETERAX 5mg/1.25mg
6. Further information

1. WHAT BIPRETERAX 5mg/1.25mg IS AND WHAT IT IS USED FOR

What is BIPRETERAX 5mg/1.25mg ?

BIPRETERAX 5mg/1.25mg is a combination of two active ingredients, perindopril and indapamide. It is an anti-hypertensive and is used in the treatment of high blood pressure (hypertension).

What is BIPRETERAX 5mg/1.25mg used for ?

Perindopril belongs to a class of medicines called ACE inhibitors. These work by widening the blood vessels, which makes it easier for your heart to pump blood through them. Indapamide is a diuretic. Diuretics increase the amount of urine produced by the kidneys. However, indapamide is different from other diuretics, as it only causes a slight increase in the amount of urine produced. Each of the active ingredients reduces blood pressure and they work together to control your blood pressure.

2. BEFORE YOU TAKE BIPRETERAX 5mg/1.25mg

Do not take BIPRETERAX 5mg/1.25mg

- if you are allergic to perindopril or any other ACE inhibitor, or to indapamide or any other sulphonamides or any of the other ingredients of BIPRETERAX 5mg/1.25mg,
- if you have experienced symptoms such as wheezing, swelling of the face or tongue, intense itching or severe skin rashes with previous ACE inhibitor treatment or if you or a member of your family have had these symptoms in any other circumstances (a condition called angioedema),
- if you have severe liver disease or suffer from a condition called hepatic encephalopathy (degenerative disease of the brain),
- if you have a severe kidney disease or if you are receiving dialysis,
- if you have low or high blood potassium,
- if you are suspected of having untreated decompensated heart failure (severe water retention, difficulty in breathing),
- if you are more than 3 months pregnant (It is also better to avoid BIPRETERAX 5mg/1.25mg in early pregnancy - see "Pregnancy and Breast-feeding"),
- if you are breastfeeding.

Take special care with BIPRETERAX 5mg/1.25mg

If any of the following apply to you please talk to your doctor before taking BIPRETERAX 5mg/1.25mg:

- if you have aortic stenosis (narrowing of the main blood vessel leading from the heart) or hypertrophic cardiomyopathy (heart muscle disease) or renal artery stenosis (narrowing of the artery supplying the kidney with blood),
- if you have any other heart problems or problems with your kidneys,
- if you have liver problems,
- if you suffer from a collagen disease (skin disease) such as systemic lupus erythematosus or scleroderma,
- if you have atherosclerosis (hardening of the arteries),
- if you suffer from hyperparathyroidism (overactive parathyroid gland),
- if you suffer from gout,
- if you have diabetes,
- if you are on a salt restricted diet or use salt substitutes which contain potassium,
- if you take lithium or potassium-sparing diuretics (spironolactone, triamterene) as their use with BIPRETERAX 5mg/1.25mg should be avoided (see “Taking other medicines”).

You must tell your doctor if you think that you are (or might become) pregnant. BIPRETERAX 5mg/1.25mg is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see “Pregnancy and breastfeeding”).

When you are taking BIPRETERAX 5mg/1.25mg, you should also inform your doctor or the medical staff:

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

Athletes should be aware that BIPRETERAX 5mg/1.25mg contains an active ingredient (indapamide) which may give a positive reaction in drug tests.

BIPRETERAX 5mg/1.25mg should not be given to children.

Taking other medicines

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

You should avoid BIPRETERAX 5mg/1.25mg with:

- lithium (used to treat depression),
- potassium-sparing diuretics (spironolactone, triamterene), potassium salts.

Treatment with BIPRETERAX 5mg/1.25mg can be affected by other medicines. Make sure to tell your doctor if you are taking any of the following medicines as special care may be required:

- other medicines for treating high blood pressure,
- procainamide (for the treatment of an irregular heart beat),
- allopurinol (for the treatment of gout),
- terfenadine or astemizole (antihistamines for hay fever or allergies),
- corticosteroids used to treat various conditions including severe asthma and rheumatoid arthritis,
- immunosuppressants used for the treatment of auto-immune disorders or following transplant surgery to prevent rejection (e.g. ciclosporin),
- medicines for the treatment of cancer,
- erythromycin by injection (an antibiotic),
- halofantrine (used to treat certain types of malaria),

- pentamidine (used to treat pneumonia),
- injectable gold (used to treat rheumatoid polyarthritis),
- vincamine (used to treat symptomatic cognitive disorders in elderly including memory loss),
- bepridil (used to treat angina pectoris),
- sultopride (for the treatment of psychoses),
- medicines used for heart rhythm problems (e.g. quinidine, hydroquinidine, disopyramide, amiodarone, sotalol),
- digoxin or other cardiac glycosides (for the treatment of heart problems),
- baclofen (to treat muscle stiffness occurring in diseases such as multiple sclerosis),
- medicines to treat diabetes such as insulin or metformin,
- calcium including calcium supplements,
- stimulant laxatives (e.g. senna),
- non-steroidal anti-inflammatory drugs (e.g. ibuprofen) or high dose salicylates (e.g. aspirin),
- amphotericin B by injection (to treat severe fungal disease),
- medicines to treat mental disorders such as depression, anxiety, schizophrenia...(e.g. tricyclic antidepressants, neuroleptics),
- tetracosactide (to treat Crohn's disease).

Taking BIPRETERAX 5mg/1.25mg with food and drink

It is preferable to take BIPRETERAX 5mg/1.25mg before a meal.

Pregnancy and breast-feeding

Pregnancy

You must tell your doctor if you think that you are (or might become) pregnant.

Your doctor will normally advise you to stop taking BIPRETERAX 5mg/1.25mg before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of BIPRETERAX 5mg/1.25mg. BIPRETERAX 5mg/1.25mg is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breast-feeding

You must not take BIPRETERAX 5mg/1.25mg if you are breast-feeding.

Tell your doctor immediately if you are breast-feeding or about to start breast-feeding.

See your doctor immediately.

Driving and using machines

BIPRETERAX 5mg/1.25mg usually does not affect alertness but different reactions such as dizziness or weakness in relation to the decrease in blood pressure may occur in certain patients. If affected, your ability to drive or to operate machinery may be impaired.

Important information about some of the ingredients of BIPRETERAX 5mg/1.25mg

BIPRETERAX 5mg/1.25mg contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE BIPRETERAX 5mg/1.25mg

Always take BIPRETERAX 5mg/1.25mg exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose is one tablet once a day. Your doctor may decide to modify the dosage regimen if you suffer from renal impairment. Take your tablet preferably in the morning and before a meal. Swallow the tablet with a glass of water.

If you take more BIPRETERAX 5mg/1.25mg than you should

If you take too many tablets, contact your doctor or nearest hospital casualty immediately. The most likely effect in case of overdose is low blood pressure. If marked low blood pressure occurs (symptoms such as dizziness or faintness), lying down with the legs raised can help.

If you forget to take BIPRETERAX 5mg/1.25mg

It is important to take your medicine every day as regular treatment is more effective. However, If you forget to take a dose of BIPRETERAX 5mg/1.25mg, take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

If you stop taking BIPRETERAX 5mg/1.25mg

As the treatment for high blood pressure is usually life-long, you should discuss with your doctor before stopping this medicinal product.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, BIPRETERAX 5mg/1.25mg can cause side effects, although not everybody gets them.

If you experience any of the following, stop taking the medicinal product at once and tell your doctor immediately :

- swelling of the face, lips, mouth, tongue or throat, difficulty in breathing,
- severe dizziness or fainting,
- unusual fast or irregular heart beat.

In decreasing order of frequency, side effects can include:

- Common (occur in fewer than 1 in 10 users but in more than 1 in 100 users): headache, feelings of dizziness, vertigo, pins and needles, vision disturbances, tinnitus (sensation of noises in the ears), light-headedness due to low blood pressure, cough, shortness of breath, gastro-intestinal disorders (nausea, epigastric pain, anorexia, vomiting, abdominal pain, taste disturbances, dry mouth, dyspepsia or difficulty of digestion, diarrhoea, constipation), allergic reactions (such as skin rashes, itching), cramps, feeling of tiredness
- Uncommon (occur in fewer than 1 in 100 users but in more than 1 in 1000 users): mood swings, sleep disturbances, bronchospasm (tightening of the chest, wheezing and shortness of breath), angioedema (symptoms such as wheezing, swelling of the face or tongue), urticaria, purpura (red pinpoints on skin), kidney problems, impotence, sweating.
- Very rare (occur in fewer than 1 in 10,000 users): confusion, cardiovascular disorders (irregular heart beat, angina, heart attack), eosinophilic pneumonia (a rare type of pneumonia), rhinitis (blocked up or runny nose), severe skin manifestations such as erythema multiforme. If you suffer from systemic lupus erythematosus (a type of collagen disease), this might get worse. Cases of photosensitivity reactions (change in skin appearance) after exposure to the sun or artificial UVA have also been reported.
- Not known (frequency cannot be estimated from the available data): fainting, life-threatening irregular beat (Torsade de Pointes), abnormal ECG heart tracing, increased levels of liver enzymes.

Disorders of the blood, kidney, liver or pancreas and changes in laboratory parameters (blood tests) can occur. Your doctor may need to give you blood tests to monitor your condition.

In cases of hepatic insufficiency (liver problems), there is a possibility of onset of hepatic encephalopathy (degenerative disease in the brain).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE BIPRETERAX 5mg/1.25mg

Keep out of the reach and sight of children.

Do not use BIPRETERAX 5mg/1.25mg after the expiry date which is stated on the carton and container. The expiry date refers to the last day of that month.

Keep the container tightly closed in order to protect from moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What BIPRETERAX 5mg/1.25mg contains

- The active substances are perindopril arginine and indapamide. One film-coated tablet contains 5mg perindopril arginine (corresponding to 3.395 mg perindopril) and 1.25 mg indapamide.
- The other ingredients in the tablet core are: lactose monohydrate, magnesium stearate (E470B), maltodextrin, anhydrous colloidal silica (E551), sodium starch glycolate (type A), and in the tablet film-coating: glycerol (E422), hypromellose (E464), macrogol 6000, magnesium stearate (E470B), titanium dioxide (E171).

What BIPRETERAX 5mg/1.25mg looks like and contents of the pack

BIPRETERAX 5mg/1.25mg tablets are white, rod-shaped film-coated tablets. One film-coated tablet contains 5 mg perindopril arginine and 1.25 mg indapamide.

The tablets are available in containers of 14, 20, 28, 30, 50, 56, 60, 90, 100 or 500 tablets.

Not all pack sizes may be available.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder :

For RMS (France):

Les Laboratoires Servier

50, rue Carnot

92284 Suresnes cedex - France

Manufacturer:

Les Laboratoires Servier Industrie

905 route de Saran

45520 Gidy - France

and

Servier (Ireland) Industries Ltd

Gorey Road

Arklow - Co. Wicklow – Ireland

and

ANPHARM Przedsiębiorstwo Farmaceutyczne S.A.

ul. Annopol 6B

03-236 Warszawa – Poland

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria	BI_PRETERAX-ARGININ
Belgium	Preterax 5 mg/1,25 mg
Cyprus	Coversyl Plus arginine 5mg/1.25mg
Denmark	COVERSYL COMP NOVUM
Estonia	NOLIPREL FORTE ARGININE
Finland	COVERSYL COMP NOVUM
France	BIPRETERAX 5 mg/1,25 mg
Germany	BI PRETERAX N 5 mg / 1,25 mg filmtabletten
Greece	PRETERAX 5 mg/1,25 mg
Hungary	NOLIPREL ARGININ FORTE
Ireland	COVERSYL ARGININE PLUS 5mg/1.25mg Film-coated tablets
Italy	PRETERAX 5 mg/1,25 mg
Latvia	NOLIPREL FORTE ARGININE
Lithuania	Noliprel forte 5 mg/1,25 mg tabletès
Luxembourg	Preterax 5 mg/1,25 mg
Malta	BIPRETERAX Arginine 5 mg /1.25 mg
The Netherlands	Coversyl Plus arg 5mg/1,25mg
Poland	TERTENSIF KOMBI (5/1.25)
Portugal	PRETERAX 5 mg/1,25 mg
Romania	NOLIPREL ARG FORTE 5 mg/ 1,25 mg
Slovakia	NOLIPREL FORTE A
Slovenia	BIONOLIPREL 5mg/1.25mg filmsko obložene tablete
Spain	Bipreterax 5 mg/1,25 mg comprimidos
United Kingdom	Coversyl Arginine Plus 5 mg / 1.25 mg

This leaflet was last approved in {18/07/2012}.