ACERTIL® PLUS 5mg/1.25mg
雅施達® 加利 5mg/1.25mg

Perindopril arginine / indapamide
film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

ACERTIL PLUS 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, ACERTIL PLUS 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
Oral route.
One ACERTIL PLUS 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. ACERTIL PLUS 5mg/1.25mg film-coated tablet should be used when blood pressure is not adequately controlled on ACERTIL PLUS 2.5mg/0.625mg film-coated tablet (where available). When clinically appropriate, direct change from monotherapy to ACERTIL PLUS 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.
Children and adolescents
ACERTIL PLUS 5mg/1.25mg should not be used in children and adolescents as the efficacy and tolerability of perindopril in children and adolescents, alone or in combination, have not been established.

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

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 ACERTIL PLUS 5mg/1.25mg;
- Hypersensitivity to any of the excipients

Due to the lack of sufficient therapeutic experience, ACERTIL PLUS 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:
Risk of neutropenia/agranulocytosis in immunosuppressed patients: The risk of neutropenia appears to be dose and type related and is dependent on patient's clinical status. It is rarely seen in uncomplicated patients but may occur in patients with some degree of renal impairment especially when it is associated with collagen vascular disease e.g. systemic lupus erythematosus, scleroderma and therapy with immunosuppressive agents. It is reversible after discontinuation of the ACE inhibitor. Strict compliance with the predetermined dose seems to be the best way to prevent the onset of these events. However, if an angiotensin converting enzyme inhibitor is to be administered to this type of patient, the risk/benefit ratio should be evaluated carefully.
Angioedema (Quincke's oedema): Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients receiving treatment with angiotensin converting enzyme inhibitors, including perindopril. In such cases, treatment with perindopril should be stopped immediately and the patient should be monitored until the oedema has disappeared.
When the oedema only affects the face and the lips, the effect generally recedes without treatment, even though anti-histamines may be used to relieve symptoms.
Angioedema combined with laryngeal oedema may be fatal. Involvement of tongue, glottis or larynx may lead to an obstruction of the airways. A subcutaneous injection of adrenaline at 1:1000

(0.3 ml to 0.5 ml) should be administered quickly and other appropriate measures taken. The prescription of an angiotensin converting enzyme inhibitor should not subsequently be considered in these patients (see section 4.3).

Patients with a previous history of Quincke's oedema which was not linked to taking an angiotensin converting enzyme inhibitor have an increased risk of Quincke's oedema with an angiotensin converting enzyme inhibitor.

Anaphylactoid reactions during desensitization:

There have been isolated reports of patients experiencing sustained, life-threatening anaphylactoid reactions while receiving ACE inhibitors during desensitization 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 desensitization.

Anaphylactoid reactions druing membrane exposure:

There have been reports of patients experiencing sustained, life-threatening anaphylactoid reactions while receiving ACE inhibitors during dialysis with high-flux membranes or low-density lipoprotein apheresis with dextran sulphate adsorption. ACE inhibitors should be avoided in patients undergoing dialysis with high-flux membranes or LDL apheresis with dextran sulphate adsorption. 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 LDL apheresis.

Potassium-sparing diuretics, potassium salts:

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

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.

Sultopride:

The combination of indapamide and sultopride is usually not recommended (see section 4.5).

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 reestablishment 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: ACERTIL PLUS 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 characterized by its persistence and by its disappearance when treatment is withdrawn. An iatrogenic aetiology should be considered in the event of this symptom. If the prescription of an angiotensin converting enzyme inhibitor is still preferred, continuation of treatment may be considered.

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

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

Marked stimulation of the renin-angiotensin-aldosterone system has been observed particularly during marked water and electrolyte depletions (strict sodium-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 revascularization. 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 ACERTIL PLUS 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.

Anaemia: Anaemia has been observed in patients who have had a kidney transplant or have been undergoing dialysis. The reduction in haemoglobin levels is more apparent as initial values were high. This effect does not seem to be dose-dependent but may be linked to the mechanism of action of angiotensin converting enzyme inhibitors.

This reduction in haemoglobin is slight, occurs within 1 to 6 months, and then remains stable. It is reversible when treatment is stopped. Treatment can be continued with regular haematological testing.

Surgery: 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 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. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, uncontrolled diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended. The drug is usually not recommended in case of raised plasma levels of potassium.

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 umol/l for an adult).

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

$$\text{Clcr} = \frac{(140 - \text{age}) \times \text{body weight}}{0.814 \times \text{plasma creatinine level}}$$

with: age expressed in years, body weight in kg, plasma creatinine level in micromol/l

This formula is suitable for an elderly male and should be adapted for women by multiplying the result by 0.85. Hypovolaemia, resulting from the loss of water and sodium caused by the diuretic at the start of treatment, causes a reduction in glomerular filtration. It may result in an increase in blood urea and creatinine levels. This transitory functional renal insufficiency is of no adverse consequence in patients with normal renal function but may however worsen a pre-existing renal impairment.

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

4.5 Interaction with other medicinal products and other forms of interaction

Common to perindopril and indapamide:

Concomitant use not recommended:

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

Concomitant use which requires special care:

- Baclofen: Potentiation of antihypertensive effect. Monitoring of blood pressure and renal function, and dose adaptation of the antihypertensive if necessary.
- Non-steroidal anti-inflammatory medicinal products (included acetylsalicylic acid at high doses) : the administration of non-steroidal anti-inflammatory medicinal product may reduce the diuretic, natriuretic and antihypertensive effects in some patients. In elderly patients and patients who may be dehydrated there is a risk of acute renal failure, therefore monitoring of renal function at the initiation of treatment is recommended. Patients should be well hydrated.

Concomitant use which requires some care:

- Imipramine-like antidepressants (tricyclics), neuroleptics: Increased antihypertensive effect and increased risk of orthosatatic 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, triamterence, 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 with 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 perindorpril.

Linked to indapamide:

Concomitant use not recommended:

- Sultopride: Increased risk of ventricular arrhythmia, especially torsades de pointes (hypokaliema favours the occurrence of this adverse event)(see section 4.4).

Concomitatn 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, tiapride), butyrophenones (droperidol, haloperidol), other neuroleptics (pimozide); other substances such as bepridil, cisapride, diphemanil, IV erythromycin, halofantrine, mizolastine, moxifloxacin, pentamidine, sparfloxacin, IV vincamine, methoadone, 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

Pregnancy: ACERTIL PLUS 5mg/1.25mg should not be used during the first trimester of pregnancy. When a pregnancy is planned or confirmed the switch to an alternative treatment should be initiated as soon as possible. Controlled studies with ACE inhibitors have not been done in humans, but in a limited number of cases with first trimester exposure there do not appear to have been any malformations consistent with human fetotoxicity as described below.

ACERTIL PLUS 5mg/ 1.25mg is contraindicated during the second and third trimesters of pregnancy (see section 4.3).

Prolonged ACE inhibitors exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, retardation of skull ossification) and neonatal toxicity (renal failure, hypotension, hyperkalemia) (see section 5.3).

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

Should exposure to ACERTIL PLUS 5mg/1.25mg have occurred from the second trimester of pregnancy, an ultrasound check of renal function and the skull is recommended.

Lactation: ACERTIL PLUS 5mg/1.25mg is contraindicated during lactation.

The excretion of perindopril into breast milk is unknown. 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.

As, with both drugs, serious adverse reactions might occur in nursing infants, a decision should be made whether to discontinue nursing or to discontinue therapy taking account the importance of this therapy for the mother.

4.7 Effects on ability to drive and use machines

Linked to perindopril, indapamide and ACERTIL PLUS 5mg/1.25mg:

Neither the two active substances nor ACERTIL PLUS 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 ACERTIL

PLUS 5mg/1.25mg experience hypokalaemia (potassium level < 3.4 mmol/l).

Blood and the lymphatic system disorders:

Very rare (<1/10,000):

- *Thrombocytopenia, leucopenia, 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).

Nervous system disorders:

Uncommon (>1/1,000, <1/100):

- Paresthesia, headache, asthenia, feelings of dizziness, mood disturbances and/or sleep disturbances.

Vascular disorders:

Uncommon (>1/1,000, <1/100):

- Hypotension whether orthostatic or not (see section 4.4).

Respiratory, thoracic and mediastinal disorders:

Common (>1/100,<1/10):

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

Gastrointestinal disorders:

Common (>1/100, <1/10):

- Constipation, dry mouth, nausea, epigastric pain, anorexia, abdominal pains, taste disturbance

Very rare (<1/10,000):

- pancreatitis

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:

Uncommon (>1/1,000, <1/100):

- Hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions
- Maculopapular eruptions, purpura, possible aggravation of pre-existing acute disseminated lupus erythematosus
- Skin rash

Very rare (<1/10,000):

- Angioedema (Quincke's oedema) (see section 4.4)

Musculoskeletal, connective tissue and bone disorders:

Uncommon (>1/1,000, <1/100):

- Cramps.

Investigations:

- Potassium depletion with particularly serious reduction in levels of potassium in some at risk populations (see section 4.4).
- Reduced sodium levels with hypovolaemia causing dehydration and orthostatic hypotension.
- Increase in uric acid levels and in blood glucose levels during treatment.
- Slight increase in urea and in plasma creatinine levels, reversible when treatment is stopped. This increase is more frequent in cases of renal artery stenosis, arterial hypertension treated with diuretics, renal insufficiency.
- Increased levels of potassium, usually transitory.

Rare (>1/10,000, <1/1,000):

- raised plasma calcium levels.

4.9 Overdose

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

The first measures to be taken consist of rapidly eliminating the product(s) ingested by gastric lavage and/or administration of activated charcoal, then restoring fluid and electrolyte balance in a specialized 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, ATD code: C09BA04

ACERTIL PLUS 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.

Pharmacological mechanism of action

Linked to ACERTIL PLUS 5mg/1.25mg:

ACERTIL PLUS 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.

Characteristics of antihypertensive action

Linked to ACERTIL PLUS 5mg/1.25mg:

In hypertensive patients regardless of age, ACERTIL PLUS 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.

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, normalized 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 ACERTIL PLUS 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 70ml/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

ACERTIL PLUS 5mg/1.25mg has slightly increased toxicity than that of its components. Renal manifestations do not seems to be potentiated in the rat. However, the combination produces gastro-intestinal toxicity in the dog and the toxic effects on the mother seems 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 Storage conditions

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

Keep out of the reach and sight of children.

Do not use this drug after the expiry date printed on the box.

Store below 30^{o}C.

This leaflet was last approved on February 2007.

SERVIER

Les Laboratoires Servier – France

Manufacturer:

Les Laboratoires Servier Industrie
45520 Gidy - France