PROPOSED PACKAGE INSERT FOR CIPLASYL PLUS 4 TABLETS:
SCHEDULING STATUS:

S3

PROPRIETARY NAME (and dosage form):
CIPLASYL PLUS 4 TABLETS (tablet)

COMPOSITION:
Active ingredient:
Each tablet contains 4 mg perindopril tert-butylamine and 1,25 mg indapamide. Sugar-free.
Inactive ingredients:
Lactose anhydrous, sodium hydrogen carbonate, colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose.

PHARMACOLOGICAL CLASSIFICATION:
A 7.1.3 Other hypotensives

PHARMACOLOGICAL ACTION:
Pharmacodynamics:
CIPLASYL PLUS 4 TABLETS is a combination of perindopril tert-butylamine salt, (an angiotensin converting enzyme (ACE) inhibitor) and indapamide, an indole derivative of chlorosulphonamide (the chlorosulphamoyl diuretic).

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

Perindopril inhibits angiotensin-converting enzyme (ACE) activity. It inhibits the conversion of the relatively inactive angiotensin I to the active angiotensin II.
Angiotensin II is a potent vasoconstrictor and stimulates the release of aldosterone. Decreased angiotensin II levels result in a decrease in vasopressor activity and a reduction in aldosterone secretion, which may result in small increases in serum potassium.
It is also thought that ACE inhibition may inhibit degradation of bradykinin, leading to increased bradykinin levels.

Indapamide has an antihypertensive action causing a drop in systolic, diastolic and mean blood pressure. The extra-renal mechanism of action has also been demonstrated by the maintenance of anti-hypertensive effect in functionally anephric patients. The extra-renal action is thought to be due to the inhibition of transmembrane ionic influx, essentially calcium, and the stimulation of synthesis of the vasodilatory hypotensive prostaglandin PGE2.

Pharmacokinetics:
Perindopril:
Given orally the peak concentration of perindoprilat, the active metabolite is reached within 3 to 4 hours and peak pharmacological activity is obtained within 4 to 6 hours. In terms of trough versus peak blood pressure effect, the trough effect ranges between 75 – 100 % of peak effects.
Perindopril and perindoprilat both have a low volume of distribution and plasma protein binding is weak.
Perindopril is metabolised to perindoprilat and to five other inactive metabolites.
Perindoprilat is about 10 % to 20 % bound to plasma proteins. Perindoprilat binds to angiotensin converting enzyme at both plasma and tissue levels.
About 75 % of an oral dose of perindopril is excreted in the urine as unchanged perindopril, as perindoprilat and as other metabolites, the remainder is excreted in the faeces.
The elimination of perindoprilat is biphasic with a distribution half-life of about 5 hours and an elimination half-life of about 25 hours. Elimination of perindoprilat is less in the patients with cardiac or renal failure and in the elderly patients. In these cases dosage adjustment should be applied in relation to the degree of reduction in creatinine clearance.

Indapamide:
Indapamide is rapidly and completely absorbed from the gastrointestinal tract. Elimination is biphasic with a half-life in whole blood of about 14 hours.
Indapamide is strongly bound to red blood cells. It is extensively metabolised. Only about 5 to 7 % is excreted unchanged in the urine. Indapamide is not removed by haemodialysis but does not accumulate in patients with renal impairment.

INDICATIONS:
CIPLASYL PLUS 4 TABLETS is indicated for the treatment of:
Essential hypertension in patients where blood pressure is not adequately controlled and where fixed combination is considered more appropriate than monotherapy.

CONTRAINDICATIONS:
- Hypersensitivity to perindopril, indapamide, sulphonamides or to any of the components of **CIPLASYL PLUS 4 TABLETS**.
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs): Such patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Severe renal function impairment (creatinine clearance less than 30 ml/min).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis.
- Concomitant therapy with potassium salts or potassium sparing diuretics such as spironolactone, triamterene, amiloride, may lead to hyperkalaemia which may be severe and lead to cardiac conduction abnormalities, dysrhythmias and cardiac arrest.
- Porphyria.
- Lithium therapy: Concomitant administration with **CIPLASYL PLUS 4 TABLETS** may lead to toxic blood concentrations of lithium.
- Severe hepatic impairment, patients with hepatic encephalopathy or severe liver disorder.
- Hyperkalaemia.
- Cardiac failure (uncompensated).
- Pregnancy and lactation (see **PREGNANCY AND LACTATION** and **WARNINGS**).
- It is inadvisable to use **CIPLASYL PLUS 4 TABLETS** in combination with non anti-dysrhythmic agents causing *torsades de pointes* and certain medicines which can cause heart rhythm disorders (see **INTERACTIONS**).

WARNINGS:
Should a woman become pregnant while receiving CIPLASYL PLUS 4 TABLETS, the treatment must be stopped promptly and changed to a different medicine.
If a woman is contemplating pregnancy, a different class of medicine should be used (see PREGNANCY AND LACTATION).

Related to Perindopril*:*
- Cerebrovascular disease or ischaemic heart disease – Reduction in blood pressure could aggravate these conditions and may result in myocardial infarction and cerebrovascular incidence.
- Volume depleted patients (e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting) – Although it may occur in normovolaemic patients, hypotension is more likely in volume depleted patients. A sudden reduction in angiotensin II may result in sudden and severe hypotension. There is also an increased risk of perindopril induced renal failure, especially in those with congestive heart failure.
- Patients at a high risk of symptomatic hypotension e.g. patients with salt or volume depletion with or without hyponatraemia should have these conditions corrected before therapy with **CIPLASYL PLUS 4 TABLETS**. Monitoring is required after initiating therapy.
- Autoimmune disease, especially systemic lupus erythematosus, other collagen vascular disease or scleroderma, increase the risk for development of neutropenia or agranulocytosis.
- In acute myocardial infarction, treatment with **CIPLASYL PLUS 4 TABLETS** should not be initiated in patients with evidence of renal dysfunction (serum creatinine concentrations exceeding 177 µmol/l or proteinuria exceeding 500 mg/24 hours). If renal dysfunction develops during treatment (serum creatinine concentrations exceeding 177 µmol/l or doubling of the pre-treatment value) then perindopril may need to be withdrawn (see **CONTRAINDICATIONS**).
- In acute myocardial infarction, patients may develop persistent hypotension and/or impaired renal function.
- Hypotension in acute myocardial infarction - Treatment with **CIPLASYL PLUS 4 TABLETS** must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator. These include patients with systolic blood pressure of 100 mmHg or lower or cardiogenic shock. During the first 3 days following the infarction, the dose should be reduced if the systolic blood pressure is 120 mmHg or lower. **CIPLASYL PLUS 4 TABLETS** should be discontinued if systolic blood pressure is 100 mmHg or lower.
  If hypotension persists (systolic blood pressure less than 90 mmHg or more in 1 hour) then **CIPLASYL PLUS 4 TABLETS** should be withdrawn.
- Bone marrow depression – Increased risk of agranulocytosis and neutropenia.
- Diabetes mellitus – Increased risk of hyperkalaemia, as well as hypoglycaemia may occur.
- Hyperkalaemia – perindopril may cause an increase in serum potassium levels.
- Renovascular disease – **CIPLASYL PLUS 4 TABLETS** should not be used in patients with renovascular disease or suspected renovascular disease but it may be used cautiously in severe resistant hypertension in such patients. In this instance **CIPLASYL PLUS 4 TABLETS** should only be used under specialist supervision. The elderly, patients with peripheral vascular diseases or generalised atherosclerosis may have asymptomatic renovascular disease (see **DOSAGE AND DIRECTIONS FOR USE**).
- Renal artery stenosis, bilateral or in one kidney or renal transplant – **CIPLASYL PLUS 4 TABLETS** is contraindicated due to an increased risk of renal function impairment and an increase in blood urea and serum creatinine concentrations.
- Renal function impairment – Decreased elimination of perindopril resulting in an increased risk of hyperkalaemia. These patients may require lower doses. Also see **CONTRAINDICATIONS**: Severe renal function impairment.
- Anaphylactoid reactions have occurred in patients using ACE inhibitors including **CIPLASYL PLUS 4 TABLETS** during desensitising protocols involving for example, hymenoptera venom.
- Anaphylactoid reactions have been reported in patients exposed to either high-flux membrane dialysis or low-density lipoprotein aphaeresis with dextran sulphate absorption.
- Hypersensitivity / angioedema - If angioedema of the face, extremities, lips, tongue, glottis and/or larynx is observed in patients treated with **CIPLASYL PLUS 4 TABLETS**, treatment should be discontinued promptly. These patients should be monitored to ensure complete resolution of symptoms.
- Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, it is likely to cause airway obstruction, and appropriate emergency therapy should be administered. This may include the administration of epinephrine (adrenaline) and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred. **These patients should never receive any CIPLASYL PLUS 4 TABLETS, any other ACE-inhibitor or angiotensin-receptor blocker again.**
- Perindopril causes a higher rate of angioedema in black patients than in non-black patients.
- Safety and efficacy in children has not been established.

Related to Indapamide*:*
When liver function is impaired, indapamide may cause hepatic encephalopathy particularly in the case of electrolyte imbalance. Administration of **CIPLASYL PLUS 4 TABLETS** should be stopped immediately if this occurs.
Photosensitivity reactions have been reported with indapamide.

INTERACTIONS:
Related to CIPLASYL PLUS 4 TABLETS:
- **Lithium**
  See **CONTRAINDICATIONS**.
- **Antidiabetic agents (insulin, hypoglycaemic sulphonamides)**
  The use of ACE-inhibitors as in **CIPLASYL PLUS 4 TABLETS** may increase the hypoglycaemic effect in diabetics receiving treatment with insulin or with hypoglycaemic sulphonamides.
- **Baclofen**
  Potentiation of antihypertensive effect.
- **NSAIDs e.g. aspirin (systemic route), high dose salicylates**
  Acute renal insufficiency in dehydrated patients (reduction in glomerular filtration). The patient should be well hydrated; renal function should be monitored at the start of treatment.
  Reduction in the antihypertensive effects of perindopril. Blood pressure monitoring should be increased when any NSAID is added or discontinued in a patient treated with **CIPLASYL PLUS 4 TABLETS**.
- **Imipramine-like antidepressants (tricyclics), neuroleptics**
  Increased antihypertensive effect and increased risk of orthostatic hypotension (addictive effect).
- **Corticosteroids, tetracosactide**
  Reduction in antihypertensive effect (salt and water retention due to corticosteroids).

Related to Perindopril:
- Alcohol and hypotension-producing medications – The antihypertensive effect is additive. Dosage adjustments may be necessary during concurrent use or when one medicine is discontinued.
- 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 **CIPLASYL PLUS 4 TABLETS**.
- Potassium supplements or potassium sparing diuretics such as spironolactone, triamterene or amiloride (see **CONTRAINDICATIONS**). Potassium-sparing medicines should not be combined with indapamide, except when potassium levels are low.

Related to Indapamide:
- **Non anti-dysrhythmic agents which prolong the QT interval or cause *torsades de pointes* (erythromycin, halofantrine, pentamidine,):**
  Torsades de pointes (low potassium levels are a risk, as are bradycardia and pre-existing long QT interval).
- **Potassium-lowering medicines: amphotericin B (IV route), glucocorticoids and mineralocorticoids, tetracosactide, stimulant laxatives:**
  Increased risk of low potassium levels (additive effect). Monitoring of potassium levels and correction if necessary.
- **Cardiac glycosides:**
  Low potassium levels favour the toxic effects of cardiac glycosides. Potassium levels and ECG should be monitored and treatment reconsidered if necessary.
- **Anti-dysrhythmic medicines, which produce *torsades de pointes*; Class IA anti dysrhythmic agents (quinidine, hydroquinidine, disopyramide), amiodarone, sotalol:**
  Torsades de pointes (low potassium levels are a risk factor, as are bradycardia and pre-existing long QT interval). Prevention of low potassium levels and correction if necessary: monitoring of the QT interval.
- **Metformin*:***
  Lactic acidosis due to metformin caused by possible functional renal insufficiency linked to diuretics and in particular 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 indapamide, 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 iodated compound is administered.
- **Calcium (salts):**
  Risk of increased levels of calcium due to the 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.
- **Corticosteroids, tetracosactide (systemic route):**
  Reduction in antihypertensive effect (salt and water retention due to corticosteroids).

PREGNANCY AND LACTATION:
CIPLASYL PLUS 4 TABLETS is contraindicated during pregnancy and lactation. Indapamide can cause foetal morbidity and death (see **WARNINGS**). Safety in lactation has not been established.

CIPLASYL PLUS 4 TABLETS passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. Oligohydramnios, as well as hypotension, oliguria and anuria in newborns have been reported after
administration of **CIPLASYL PLUS 4 TABLETS** in the second and third trimesters. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur. In addition, use of **CIPLASYL PLUS 4 TABLETS** during the first trimester of pregnancy has been associated with an increased risk of birth defects, in particular of the cardiovascular and the central nervous system (see **CONTRAINDICATIONS** and **WARNINGS**).

DOSAGE AND DIRECTIONS FOR USE:
The recommended dosage is one tablet per day as a single dose, preferably to be taken in the morning, before a meal. This dosage regimen depends upon the individual requirements of the patient and is at the discretion of the medical doctor.

Elderly
It is recommended to start the treatment with only one of the active constituents.

Patients with renal failure
In cases of severe renal failure (creatinine clearance below 30 ml/min), treatment is contraindicated. In patients with a creatinine clearance greater than or equal to 30 ml/min and less than 60 ml/min, it is recommended to start the treatment with only one of the active constituents. It is not necessary to change the dose when the creatinine clearance is greater than 60 ml/min.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:
Side effects:
Blood and the lymphatic system disorders:
Less frequent: Neutropenia, agranulocytosis, haemoglobin and haematocrit, bone marrow depression, anaemia, thrombocytopenia, haemolytic anaemia, granulocytopenia, leucopenia, aplastic anaemia

Immune system disorders:
Less frequent: Hypersensitivity/angioedema reactions: angioedema of the face, which may be fatal, extremities, lips, tongue, glottis and/or larynx and intestinal angioedema. Possible aggravation of pre-existing acute systemic lupus erythematosus. Toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme, hypersensitivity reactions (mainly dermatological) in subjects with a predisposition to allergic and asthmatic reactions, purpura, cases of photosensitivity reactions have been reported.
Metabolism and nutrition disorders:
Less frequent: Hyperkalaemia, hyponatraemia, hypokalaemia
The following have been reported but the frequency is unknown:
Increases in uric acid, blood urea, blood glucose levels and serum creatinine

Nervous system disorders:
Frequent: Headache
Less frequent: Dizziness, fatigue, asthenia, mood alterations, paraesthesia, sleep disturbances
The following have been reported but the frequency is unknown:
Mental confusion, vertigo, yellow vision

Cardiac disorders:
Less frequent: Orthostatic effects (including hypotension), chest pain
The following have been reported but the frequency is unknown:
Myocardial infarction, cerebrovascular accident, palpitations, tachycardia

Respiratory, thoracic and mediastinal disorders:
Frequent: Dry cough
The following have been reported but the frequency is unknown:
Bronchospasm, rhinitis, and sinusitis

Gastrointestinal disorders:
Frequent: Constipation, dry mouth, nausea, epigastric pain, anorexia (loss of appetite), abdominal pain, taste disturbances
Less frequent: Diarrhoea, pancreatitis, indigestion
The following have been reported but the frequency is unknown:
Vomiting, stomatitis

Hepatobiliary disorders:
Less frequent: Hepatic encephalopathy
The following have been reported but the frequency is unknown:
Hepatitis (hepatocellular or cholestatic) jaundice, increases in liver enzymes, increases in serum bilirubin

Skin and subcutaneous tissue disorders:
Frequent: Rash, pruritus, maculopapular eruptions
Less frequent: Urticaria, diaphoresis, alopecia, psoriasis, severe skin disorders including pemphigus

Musculoskeletal, connective tissue and bone disorders:
Less frequent: Muscle cramps

Renal and urinary disorders:
Less frequent: Renal insufficiency, acute renal failure
The following have been reported but the frequency is unknown:
Uraemia, oligouria, anuria, renal dysfunction, impotence, proteinuria

General disorders:
Less frequent: A symptom complex has been reported which may include: fever, vasculitis, myalgia, arthritis/arthralgia, a positive antinuclear antibodies (ANA), elevated erythrocyte sedimentation rate, eosinophilia and leucocytosis, sweating

Special precautions:
CIPLASYL PLUS 4 TABLETS should be used with caution in the following circumstances:
- disorders of electrolyte balance, diabetes, gout, hypotension or strict sodium- free diets,
- heart or kidney failure, atherosclerosis (artery narrowing), renal artery stenosis (stricture),
- elderly, surgery.

The treatment may be monitored by blood tests. The normal medical practice includes periodic testing for creatinine and potassium. A dry cough may occur. In such cases, medical advice is necessary for assessing whether the treatment should be continued.

Angioneurotic oedema of the face, extremities, lips, tongue and glottis or larynx has been reported with ACE-inhibitors. In such cases, **CIPLASYL PLUS 4 TABLETS** should be discontinued and appropriate medical measures taken immediately (see **WARNINGS**).

Related to CIPLASYL PLUS 4 TABLETS:
Renal insufficiency:
In cases of severe renal insufficiency (creatinine clearance < 30 ml/min), treatment is contraindicated. In certain hypersensitive patients without pre-existing apparent renal lesions and for whom renal blood tests show functional renal insufficiency, treatment should be stopped and possibly restarted with one active constituent only. In these patients usual medical follow-up will include frequent monitoring of plasma-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.

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 with only one of the constituents.

Potassium levels:
The combination of perindopril and indapamide as in **CIPLASYL PLUS 4 TABLETS** does not prevent the onset of hypokalaemia particularly in diabetic patients or in patients with renal failure. Regular monitoring of plasma potassium levels should be carried out.

Related to perindopril:
Cough:
A dry cough has been reported with the use of ACE-inhibitors such as **CIPLASYL PLUS 4 TABLETS**. It is characterised by its persistence and by its disappearance when treatment is withdrawn. An iatrogenic aetiology should be considered in the event of this symptom. If the prescription of an ACE-inhibitor like **CIPLASYL PLUS 4 TABLETS** is still preferred, continuation of treatment may be considered.

Children:
The efficacy and safety of perindopril, alone or in combination, has not been established.

Risk of arterial hypotension and/or renal insufficiency (in cases of cardiac insufficiency, water and electrolyte depletion, etc.):
Blocking the renin-angiotensin-aldosterone system with an ACE-inhibitor may cause, particularly at the time of the first administration and during the first two weeks of treatment, sudden drop in blood pressure and/or 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 with only one of the constituents and increased progressively.
If hypotension occurs, the patient should be placed in the supine position and if necessary receive an intravenous infusion of 0,9 % saline.

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 with only one of the constituents.
Renovascular hypertension:
The treatment of renovascular hypertension is revascularisation. Nonetheless, ACE-inhibitors can be beneficial in patients presenting with renovascular hypertension who are awaiting corrective surgery or when such a surgery is not possible. Treatment should be started in a hospital setting with only one of the constituents 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 only one of the constituents. 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 if initial values were high. This reduction 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:
Perindopril may precipitate hypotension during general anaesthesia. It is therefore recommended that treatment with perindopril should be discontinued where possible two days before surgery.

Related to Indapamide:
Water and electrolyte balance:
Potassium levels:
Potassium depletion with hypokalaemia is a major risk with indapamide. 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 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 should be carried out during the first week following the start of treatment. If low potassium levels are detected, correction is required.

Sodium levels:
These should be tested before treatment is started, then at regular intervals. Diuretic treatment can cause a reduction in sodium levels, which may have serious consequences. Reduction in sodium levels can initially be asymptomatic and regular testing is therefore essential. Testing should be more frequent in the elderly and cirrhotic patients.

Calcium levels:
Indapamide may reduce the 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.

Uric acid:
Tendency to gout attacks may be increased in hyperuricaemic patients.

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

Renal function and indapamide:
Indapamide is 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 into account the age, weight and sex of the patient:
Cl_{cr} = (140 - age) x body weight / 0,814 x plasma creatinine level with: age expressed in years, bodyweight in kg, plasma creatinine level in µmol/l.
This formula is suitable for an elderly male and should be adapted for women by multiplying the result by 0,85.

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

Athletes:
Athletes should be aware that **CIPLASYL PLUS 4 TABLETS** contains an active ingredient which may give a positive reaction in drug tests.

Lactose:
CIPLASYL PLUS 4 TABLETS contain lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption should not take **CIPLASYL PLUS 4 TABLETS**.

Effect on ability to drive and operate machines*:*
Individual reactions related to a reduction in blood pressure and side-effects such as dizziness may occur in some patients. As a result, the ability to drive or operate machinery may be impaired.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
The most likely adverse event in case of overdose is hypotension, sometimes associated with nausea, vomiting, cramps, dizziness, sleepiness, mental confusion, polyuria or 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 patients in a supine position with the head lowered. If necessary an IV infusion of isotonic saline may be given, or any other method of volaemic expansion may be used.
Perindoprilat, the active form of perindopril, is removable by haemodialysis.

IDENTIFICATION:
White to off white oblong shaped, flat faced beveled edge tablet with a median line on both sides.

PRESENTATION:
CIPLASYL PLUS 4 TABLETS are packed into either:
- Transparent PVC/PVDC aluminium blister strips containing 10 tablets. Three blisters (3 x 10) are packed into a laminated aluminium pouch.
- Alu/Alu blister strip containing 10 tablets. Three blisters (3 x 10) are packed into a cardboard carton.

STORAGE INSTRUCTIONS:
Store at or below 25 °C in a dry place.
Keep the blister strips in the outer carton or pouch until required for use.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:
44/7.1.3/0503

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:
Zydus Healthcare SA (Pty) Ltd.
Southdowns Office Park,
22 Karee Street
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