Module 1.3.1.1 Professional Information for

CIPLASYL 2 / 4 / 8 (Tablets)

SCHEDULING STATUS:

S3

PROPRIETARY NAME (AND DOSAGE FORM):

CIPLASYL 2 (Tablets)

CIPLASYL 4 (Tablets)

CIPLASYL 8 (Tablets)

COMPOSITION:

CIPLASYL 2: Each film-coated tablet contains: perindopril erbumine monohydrate equivalent to 2 mg perindopril erbumine

CIPLASYL 4: Each film-coated tablet contains: perindopril erbumine monohydrate equivalent to 4 mg perindopril erbumine

CIPLASYL 8: Each film-coated tablet contains: perindopril erbumine monohydrate equivalent to 8 mg perindopril erbumine

Inactive ingredients:

Hypromellose 6 CPS, hypromellose (HPMC E-15), magnesium stearate, Opadry AMB OY-B-28920, polyethylene Glycol-6000, siliconised Talc 3 %, sodium carbonate anhydrous, sodium starch glycollate.

CIPLASYL 2 mg: Contains sugar (43,318 mg mannitol per tablet).

CIPLASYL 4 mg: Contains sugar (86,637 mg mannitol per tablet).

CIPLASYL 8 mg: Contains sugar (173,274 mg mannitol per tablet).

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.3 Other hypotensives.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Perindopril acts through its active metabolite perindoprilat. The other metabolites of perindopril show no inhibition of ACE activity *in vitro.* Perindopril inhibits angiotensin I-converting enzyme (ACE) activity. It inhibits the conversion of the relatively inactive angiotensin I to the active angiotensin II. The converting enzyme, or kinase, is an exopeptidase that allows conversion of angiotensin I into angiotensin II. It also causes the degradation of the vasodilator bradykinin into an inactive heptapeptide. 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.

Since ACE inactivates bradykinin, inhibition of ACE also results in an increased activity of circulating and local kallikreinkinin systems (and therefore also activation of the prostaglandin system). This mechanism possibly contributes to

the blood pressure lowering action of ACE inhibitors and is partially responsible for certain of their side-effects (e.g. cough). It is also thought that ACE inhibition may inhibit degradation of bradykinin, leading to increased bradykinin levels.

A reduction in diastolic and systolic blood pressures in both standing and supine positions is observed. The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours. The trough effect ranges between 75 - 100 % of peak effects in terms of trough versus peak blood pressure effect. The decrease in blood pressure occurs rapidly. Normalisation is achieved within a month in responding patients and persists without the occurrence of tachyphylaxis. Discontinuation of treatment does not lead to a rebound effect. A reduction in peripheral resistance with no significant changes in heart rate or glomerular filtration rate accompanies a reduction in blood pressure in patients treated with perindopril. An increase in the compliance of large arteries was also observed, which suggests a direct effect on arterial smooth muscle. As a rule, renal blood flow increases, while the glomerular filtration rate (GFR) is usually unchanged.

Clinical efficacy and safety:

Hypertension

Perindopril is active in all grades of hypertension: mild, moderate, severe; a reduction in diastolic and systolic blood pressures in both standing and supine positions is observed.

Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. Consequently, peripheral blood flow increases, with no effect on heart rate.

The glomerular filtration rate (GFR) is usually unchanged while renal blood flow increases as a rule.

The anti-hypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 87-100% of peak effects.

Decrease in blood pressure occurs rapidly. Normalisation is achieved within a month and persists without the occurrence of tachyphylaxis in responding patients.

Discontinuation of treatment does not lead to a rebound effect.

Perindopril reduces left ventricular hypertrophy.

Perindopril has been confirmed to demonstrate vasodilatory properties in man. It improves large artery elasticity and decreases the media: lumen ratio of small arteries.

Adjunctive therapy with a thiazide diuretic produces an additive type of synergy. The combination of an ACE inhibitor and a thiazide also decreases the risk of hypokalaemia induced by the diuretic treatment.

Paediatric population:

The safety and efficacy of perindopril in children and adolescents aged below 18 years have not been established.

Heart failure:

Cardiac work is reduced by perindopril by a decrease in pre-load and after-load.

Studies in patients with heart failure have demonstrated:

- decreased left and right ventricular filling pressures
- reduced total peripheral vascular resistance.

Pharmacokinetics:

Absorption:

The absorption of perindopril is rapid following oral administration (peak concentration is attained within 1 hour), and relatively complete (plasma-availability above 75 %). The plasma half-life of perindopril is 1 hour. The bioavailability of the active metabolite, perindoprilat, is 27 %. Apart from the active metabolite perindoprilat, perindopril is also converted to 5 other metabolites. These are all inactive. The peak concentration of perindoprilat, is reached within 3 to 4 hours and peak pharmacological activity is obtained within 4 to 6 hours. Conversion to perindoprilat and hence bioavailability is decreased with the ingestion of food. Perindopril should therefore be administered orally as a single daily dose in the morning before breakfast. A linear relationship exists between the dose of perindopril and its plasma exposure.

The trough blood pressure effect ranges between 75 -100 % of the peak blood pressure effect.

Distribution:

Both perindopril and perindoprilat have a low volume of distribution. The volume of distribution for unbound perindoprilat is approximately 0,2 ℓ/kg. Plasma protein binding of both is weak, but is concentration dependant (binding of perindoprilat to plasma proteins is 20 %, principally to angiotensin converting enzyme). Perindoprilat binds to angiotensin converting enzyme (ACE) in the plasma and in the tissues.

Elimination:

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

Special populations:

As elimination of perindoprilat is slower in patients with cardiac failure or renal failure, as well as in the elderly, dosage adjustment should be applied in these patients based on the degree of reduction in creatinine clearance. Dialysis clearance of perindoprilat is equal to 70 ml/min. Perindopril kinetics is modified in patients with cirrhosis: hepatic clearance of the parent molecule is reduced by half. The quantity of perindoprilat formed is not reduced and no dosage adjustment is therefore required.

Reduction in blood pressure in patients treated with perindopril may be

accompanied by a reduction in peripheral resistance with no significant changes in heart rate or glomerular filtration rate. An increase in the compliance of large arteries may also occur.

INDICATIONS:

CIPLASYL is indicated in:

- Mild to moderate hypertension.
- Congestive heart failure not adequately controlled by conventional therapy with diuretics and digitalis, and in whom vasodilatation is indicated.
- Reduction of risk of cardiovascular events in patients with stable coronary artery disease and without heart failure.

CONTRA-INDICATIONS:

- Hypersensitivity to any of the ingredients of **CIPLASYL** or to any other ACE-inhibitor.
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs). These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Aortic stenosis.
- 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.
- Concomitant therapy with potassium-sparing diuretics, such as spironolactone, triamterene, amiloride (see **"INTERACTIONS"**).
- Porphyria.
- Pregnancy and lactation (see **"HUMAN REPRODUCTION"**).
- Concomitant use of CIPLASYL with aliskiren-containing products (see **"WARNINGS AND SPECIAL PRECAUTIONS"** and **"INTERACTIONS"**).
- Lithium therapy: concomitant administration with **CIPLASYL** may lead to toxic blood concentrations of lithium (see **"INTERACTIONS"**).
- Concomitant use of fluoroquinolones with ACE inhibitors is contra-indicated in patients with moderate to severe renal impairment.

The safety of **CIPLASYL** in children has not been established (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

WARNINGS AND SPECIAL PRECAUTIONS:

Should a woman become pregnant while receiving **CIPLASYL**, the treatment must be stopped immediately and changed to a different class of antihypertensive medicine (see **"CONTRA-INDICATIONS"** and **"HUMAN REPRODUCTION"**).

If a woman is contemplating pregnancy, a different class of medicine should be used (see **"HUMAN REPRODUCTION"**).

CIPLASYL should be used with caution in the following conditions:

- Severe autoimmune disease, especially systemic lupus erythematosus, other collagen vascular diseases or scleroderma, increase the risk for development of neutropenia or agranulocytosis.
- In acute myocardial infarction, patients may develop persistent hypotension and/or impaired renal function.
- In acute myocardial infarction, treatment with **CIPLASYL** should not be initiated in patients with evidence of renal dysfunction (serum creatinine concentrations exceeding 177 micromol/L or proteinuria exceeding 500 mg/24 hours). If renal dysfunction develops during treatment (serum creatinine concentrations exceeding 177 micromol/L or doubling of the pretreatment value) then **CIPLASYL** may need to be withdrawn (see **"CONTRA-INDICATIONS"**).
- Hypotension in acute myocardial infarction – treatment with **CIPLASYL** 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 mm Hg 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 mm Hg or lower. Maintenance doses should be reduced to 4 mg or temporarily to 2 mg if systolic blood pressure is 100 mm Hg or lower. If hypotension persists (systolic blood pressure less than 90 mm Hg for more than 1 hour) then **CIPLASYL** should be withdrawn.

- Bone marrow depression – increased risk of agranulocytosis and neutropenia.
- Renovascular disease – **CIPLASYL** 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** 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 – increased risk of renal function impairment with increases in blood urea and serum creatinine concentrations, which may be reversible upon discontinuation of therapy. There is also an increased risk of agranulocytosis and neutropenia when immunosuppressants are concurrently administered.
- Concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see **"CONTRA-INDICATIONS"**). Renal function should be assessed before initiating treatment, and monitored during treatment, with fluoroquinolones or ACE inhibitors/renin-angiotensin receptor blockers.

Stable coronary artery disease:

If an episode of unstable angina pectoris (major or not) occurs during the first month of perindopril treatment, a careful appraisal of the benefit/risk should be performed before treatment continuation.

Hypotension:

ACE inhibitors may cause a fall in blood pressure. This usually occurs in patients on multiple or high-dose diuretics with hypovolaemia, hyponatraemia, pre-existing hypotension, patients with unstable cardiac failure and renal impairment. Volume-depleted patients (e.g., by diuretic therapy, dietary salt restriction, dialysis, diarrhoea vomiting or who have severe renin-dependant hypertension) – although it may occur in normovolaemic patients, hypotension is more likely in volume-depleted patients. Hypotension may also occur with those on high-dose vasodilator therapy and patients aged 70 years and over. Symptomatic hypotension has been observed in patients with symptomatic heart failure, with or without associated renal insufficiency. This is most likely to occur in those patients with more severe degrees of heart failure and is reflected by the use of high doses of loop diuretics, functional renal impairment or hyponatraemia. Initiation of therapy and dose adjustment should be closely monitored in patients with an increased risk of symptomatic hypotension. Myocardial infarction and cerebrovascular accidents may occur due to severe falls in blood pressure in high risk patients, e.g. those with ischaemic heart disease or cerebrovascular disease. Reduction in blood pressure could aggravate these conditions and may result in myocardial infarction and cerebrovascular accidents. In volume-depleted

patients or patients with ischaemic heart disease or cerebrovascular disease, therapy should be monitored especially when the dose of CIPLASYL or diuretic is adjusted. A sudden reduction in angiotensin II may result in sudden and severe hypotension. There is also an increased risk of **CIPLASYL**-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**. Monitoring is required after initiating therapy. In the event of hypotension, the patient should be placed in the supine position, and, if necessary, receive an intravenous infusion of 0,9 % saline. A transient hypotensive response is not a contra-indication to further doses. Once the blood pressure has increased after volume expansion, further doses can be given usually without difficulty. Additional lowering of systemic blood pressure may occur with **CIPLASYL** in some patients with congestive heart failure, who have normal or low blood pressure. This effect is anticipated and is usually not a reason to discontinue treatment. A reduction of the dose or discontinuation of perindopril may be necessary if hypotension becomes symptomatic.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy:

CIPLASYL should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle, such as hypertrophic cardiomyopathy or aortic stenosis.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS):

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hyperkalaemia, hypotension, and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of **CIPLASYL** and aliskiren is therefore contraindicated (see **"CONTRA-INDICATIONS"**). **CIPLASYL** should not be used concomitantly with aliskiren (see **"CONTRAINDICATIONS"**). Dual blockade of RAAS through the combined use of angiotensin II receptor blockers and CIPLASYL, is not recommended (see **"INTERACTIONS"**). If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Impaired renal function:

Decreased elimination of **CIPLASYL** resulting in an increased risk of hyperkalaemia. These patients may require lower doses. With creatinine clearance < 60 ml/min, the initial **CIPLASYL** dosage should be adjusted according to the patient's creatinine clearance and then as a function of the patient's response to treatment (see **"Renal impairment"**). Routine monitoring of creatinine and potassium are part of normal medical practice for these patients. Hypotension following the initiation of therapy with ACE-inhibitors may lead to

some further impairment in renal function in patients with symptomatic heart failure. In this situation, acute renal failure has been reported.

In patients with stenosis of the artery to a solitary kidney or bilateral renal artery stenosis, and who have been treated with ACE-inhibitors, increases, in serum creatinine and blood urea may occur. This is usually reversible upon discontinuation of therapy.

It is especially likely in patients with renal impairment. There is an increased risk of severe hypotension and renal insufficiency in the presence of renovascular hypertension. Treatment should be started under close medical supervision with low doses and careful dose titration in these patients. Treatment with diuretics may be a contributory factor to the above and should be discontinued, and renal function should be monitored during the first weeks of **CIPLASYL** therapy.

Clinical laboratory test findings:

A fall in haemoglobin may occur at the start of treatment. A rise in plasma potassium has been reported.

Increases in blood urea and serum creatinine have been seen in patients with no apparent pre-existing vascular disease, usually minor and transient, especially when **CIPLASYL** has been given concomitantly with a diuretic. This is more likely

to occur in patients with pre-existing renal impairment. Dosage reduction or discontinuation of **CIPLASYL** or the diuretic may be required.

Haemodialysis patients:

Anaphylactoid reactions have been reported in patients exposed to highflux membrane dialysis and treated concomitantly with an ACE-inhibitor. Consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent in these patients.

Kidney transplantation:

There is no experience regarding the administration of **CIPLASYL** in patients with a recent kidney transplant.

Hypersensitivity/Angioedema:

If angioedema of the face, extremities, lips, tongue, glottis, mucous membranes and/or larynx is observed in patients treated with **CIPLASYL, CIPLASYL** should be discontinued promptly. This may occur at any time during therapy. These patients should be monitored to ensure complete resolution of symptoms. In cases where swelling was confined to the lips and face, antihistamines have been useful in relieving symptoms, although the condition generally resolved without treatment.

Signs of facial or extremity swelling or difficulty in swallowing or breathing, requires immediate medical attention, because of the risk of angioedema. Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate emergency therapy should be administered. This may include the administration of 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 CIPLASYL, any other ACE inhibitors or angiotensin-receptor blockers again.**

Patients with a history of angioedema which is not related to ACE-inhibitor therapy may be at increased risk of angioedema while receiving an ACE-inhibitor.

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.

Concomitant use of mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) – patients taking concomitant mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see **"INTERACTIONS"**).

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis:

Life-threatening anaphylactoid reactions have less frequently been reported in patients exposed to low-density lipoprotein apheresis with dextran sulphate absorption. By temporarily withholding ACE-inhibitors therapy prior to each apheresis, these reactions were avoided.

Anaphylactic reactions during desensitization:

Anaphylactoid reactions have occurred in patients using ACE-inhibitors, including **CIPLASYL** during desensitising protocols involving for example, hymenoptera venom. These reactions were avoided when the ACE-inhibitors were temporarily withheld, but they reappeared upon re-challenge.

Hepatic failure:

ACE-inhibitors have been associated with a syndrome that starts with cholestatic jaundice which could suddenly progresses to hepatic necrosis and even death. The mechanism of this syndrome is not understood. Patients receiving ACE-

inhibitors who develop marked elevations of hepatic enzymes or jaundice should discontinue the **CIPLASYL** and receive appropriate medical follow-up.

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia:

Neutropenia, agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE-inhibitors. Neutropenia rarely occurs in patients with normal renal function with no other complicating factors.

CIPLASYL should be used with extreme caution in patients with immunosuppressant therapy, collagen vascular disease, treatment with procainamide or allopurinol, 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 **CIPLASYL**, is used in such patients, patients should be instructed to report any sign of infection and periodic monitoring of the white blood cell count is advised.

Race:

CIPLASYL causes a higher rate of angioedema in black patients than in non-black patients. **CIPLASYL** may be less effective in lowering blood pressure in black people than in other ethnic groups. The reason could be a higher prevalence of low-renin levels in the black hypertensive population.

Cough:

Cough, which is non-productive, persistent and resolves after discontinuation of therapy, has been reported with the use of ACE-inhibitors. ACE-inhibitors induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anaesthesia:

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, **CIPLASYL** may block angiotensin II formation secondary to compensatory renin release. The treatment should be discontinued one day prior to the surgery. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia:

CIPLASYL may cause an increase in serum potassium levels. Patients at risk for the development of hyperkalaemia include those with, renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, inter-current events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium supplements, potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene or amiloride), or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin and co-trimoxazole). 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. Hyperkalaemia can cause serious, sometimes fatal arrhythmias. Caution in use of the above agents and regular monitoring of serum potassium is recommended if concomitant use of these agents is deemed necessary (see "**INTERACTIONS**").

Diabetic patients:

Diabetes mellitus – increased risk of hyperkalaemia, as well as hypoglycaemia may occur. In diabetic patients treated with oral insulin or antidiabetic agents, glycaemic control should be closely monitored during the first month of treatment with ACE-inhibitors (see **"INTERACTIONS"**).

Lithium:

The combination of lithium and **CIPLASYL** is generally not recommended (see **"INTERACTIONS"**).

Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes:

Concomitant therapy with potassium-sparing diuretics, such as spironolactone, triamterene, amiloride and eplerenone may lead to hyperkalaemia, which may be severe and lead to cardiac conduction abnormalities, dysrhythmias and cardiac arrest. The concomitant use of **CIPLASYL** and potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes is generally not recommended (see **"INTERACTIONS").**

Effect on ability to drive and use machines:

Caution when driving or performing tasks requiring alertness because of possible dizziness.

Mannitol:

Contains mannitol, which may have an effect on the glycaemic control of patients with diabetes mellitus.

Special populations:

Dosage should be adjusted in the elderly (see **"DOSAGE AND DIRECTIONS FOR USE"**).

Safety and efficacy in children has not been established.

INTERACTIONS:

Concomitant use of **CIPLASYL** with:

- Angiotensin II receptor blockers or aliskiren – clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-

acting agent (see **“CONTRA-INDICATIONS”** and **“WARNINGS AND SPECIAL PRECAUTIONS”**).

- Diuretics, alcohol, and hypotension-producing medications – the antihypertensive effect is additive. The possibility of hypotensive effects can be reduced by discontinuing the diuretic, and by increasing volume or salt intake before initiating therapy with low and increasing doses of perindopril. Dosage adjustments may be necessary during concurrent use or when one medicine is discontinued.
- Loop, thiazide or related diuretics – “first dose hypotension” may occur (see **"DOSAGE AND DIRECTIONS FOR USE"**).

Non-steroidal anti-inflammatory medicines (NSAID’s) including aspirin > 3 g/day:

Indomethacin and non-steroidal anti-inflammatory medicines (NSAID’s) – reduce the antihypertensive effects of **CIPLASYL.** In addition, NSAIDs and ACE-inhibitors exert an additive effect on the increase in serum potassium and may result in a deterioration of renal function, but these effects are usually reversible. Acute renal failure may occur, particularly in patients with compromised renal function like dehydrated patients or the elderly. 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 at the beginning of the treatment and periodically thereafter. Blood

pressure monitoring should be increased when any NSAID is added or discontinued in a patient treated with **CIPLASYL**.

Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes:

Hyperkalaemia may occur in some patients treated with **CIPLASYL.** Potassium supplements, potassium-sparing diuretics (such as spironolactone, triamterene, eplerenone or amiloride) or potassium-containing salt substitutes – concurrent administration may result in hyperkalaemia. The combination of CIPLASYL with above-mentioned medicines is therefore not recommended (see "**WARNINGS AND SPECIAL PRECAUTIONS"**). If concomitant use is indicated with confirmed hypokalaemia, they should be used with caution and serum potassium should frequently be monitored. For use of spironolactone in heart failure, see below.

Lithium:

Lithium (see **"CONTRA-INDICATIONS"**) – Reversible increases in lithium concentrations and toxicity have been reported. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE-inhibitors.

Antihypertensive agents and vasodilators:

Concomitant use of these agents may increase the hypotensive effects of **CIPLASYL** and concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

Antidiabetic agents:

Epidemiological studies have suggested that administration of ACE-inhibitors and antidiabetic medicines (oral hypoglycaemic agents, insulins) may cause an increased blood-glucose lowering effect with the risk of hypoglycaemia. This phenomenon appeared to be more likely in patients with renal impairment and during the first weeks of combined treatment.

Acetylsalicylic acid, thrombolytics and betablockers:

CIPLASYL may be used with acetylsalicylic acid (when used as a thrombolytic), thrombolytics and betablockers.

Tricyclic antidepressants/antipsychotics/anaesthetics:

Concomitant use of certain anaesthetic medicines, tricyclic antidepressants and antipsychotics with ACE-inhibitors, may result in further reducing the blood pressure.

Sympathomimetics:

Sympathomimetics may reduce the antihypertensive effects of **CIPLASYL.**

Medicines inducing hyperkalaemia:

Some therapeutic classes or medicinal products may increase the occurrence of hyperkalaemia: ACE inhibitors, angiotensin-II receptors antagonists, aliskiren, potassium salts, potassium-sparing diuretics, NSAIDs, heparins, immunosuppressant agents such as ciclosporin or tacrolimus and trimethoprim. The combination of these drugs increases the risk of hyperkalaemia.

Co-trimoxazole (trimethoprim/sulfamethoxazole):

Concomitant use of co-trimoxazole (trimethoprim/sulfamethoxazole) increases risk for hyperkalaemia (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Aliskiren:

Concomitant use contraindicated (see **"CONTRA-INDICATIONS"**):

In renal impaired or diabetic patients, worsening of renal function, risk of hyperkalaemia and cardiovascular morbidity and mortality increase.

Concomitant use not recommended (see **"WARNINGS AND SPECIAL PRECAUTIONS")**: In patients other than diabetic or impaired renal patients, risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increase.

Concomitant therapy with ACE inhibitor and angiotensin-receptor blocker:

The literature reports that in patients with established heart failure, atherosclerotic disease, or with diabetes with end organ damage, concomitant

therapy with ACE inhibitor and angiotensin-receptor blocker is associated with a higher frequency of hypotension, hyperkalaemia, syncope, and worsening renal function (including acute renal failure) as compared to use of a single renin-angiotensin-aldosterone system agent. Dual blockade (e.g. by combining an ACE-inhibitor with an angiotensin II receptor antagonist) should be limited to individually defined cases with close monitoring of renal function, blood pressure and potassium levels.

Racecadotril:

ACE inhibitors (e.g. perindopril) are known to cause angioedema. Concomitant use with racecadotril (used against acute diarrhoea) may elevate this risk.

***mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus)*:**

Patients taking concomitant mTOR inhibitors therapy may be at increased risk for angioedema (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Estramustine:

The risk of adverse effects such as angioneurotic oedema (angioedema) is increased.

Baclofen:

The antihypertensive effect is increased. Blood pressure needs to be monitored and antihypertensive dosage adjusted if necessary.

Non-potassium sparing diuretics:

Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating therapy with low and progressive doses of perindopril.

When prior diuretic therapy can have caused salt/volume depletion in arterial hypertension, either the diuretic must be discontinued before initiating the ACE inhibitor, with reintroduction of a non-potassium-sparing diuretic thereafter, or the ACE inhibitor must be initiated with a low dosage and progressively increased.

In congestive heart failure treated with a diuretic, the ACE inhibitor should be initiated at a very low dosage, possibly after reducing the dosage of the associated non-potassium-sparing diuretic.

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

Potassium-sparing diuretics (eplerenone, spironolactone):

With spironolactone or eplerenone at doses between 12.5 mg to 50 mg by day and with low doses of ACE inhibitors: In the treatment of class II-IV heart failure

(NYHA) with an ejection fraction < 40%, and previously treated with loop diuretics and ACE inhibitors, there is a risk of hyperkalaemia, potentially lethal, especially in case of non-observance of the prescription recommendations on this combination.

Check the absence of hyperkalaemia and renal impairment before initiating the combination.

Close monitoring of the creatinaemia and kalaemia and is recommended in the first month of the treatment once a week at the beginning and, monthly thereafter.

Gliptins (linagliptin, saxagliptin, sitagliptin, vildagliptin):

In patients co-treated with an ACE inhibitor, there is an increased risk of angioedema, due to dipeptidyl peptidase IV (DPP-IV) decreased activity by the gliptin.

Gold:

Nitritoid reactions (symptoms include nausea, facial flushing, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including perindopril.

Fluoroquinolones:

Concomitant use of fluoroquinolones and ACE inhibitors/reninangiotensin receptor blockers may precipitate acute kidney injury (see **"CONTRA-INDICATIONS"**).

This adverse effect could be attributed to ciprofloxacin alone, to infection or a combined effect. Although the mechanism is unclear, interstitial nephritis of other pathology due to a fluoroquinolone could be a trigger for ACE-inhibitor related acute kidney injury.

HUMAN REPRODUCTION:

The use of **CIPLASYL** is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take **CIPLASYL** during pregnancy (see **"CONTRA-INDICATIONS"**). 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 **CIPLASYL** should be stopped immediately and if appropriate, alternative therapy should be started. Foetal exposure to ACE inhibitors during the first trimester of pregnancy has been reported to be associated with an increased risk of malformations of the cardiovascular (atrial and/or ventricular septal defect, pulmonic stenosis, patent ductus arteriosus) and central nervous system (microcephaly spins bifida) and of kidney malformations.

Foetal exposure after the first trimester can cause foetal morbidity and death. **CIPLASYL** crosses the placenta and can be presumed to cause disturbances in foetal blood pressure regulatory mechanisms. Exposure to ACE-inhibitor therapy during the second and third trimesters is known to induce foetotoxicity (decreased renal function, oligohydramnios and skull ossification retardation), and can cause hypotension, anuria, oligohydramnios (may occur resulting in pulmonary hypoplasia, limb contractures and craniofacial deformation) and oliguria in new-borns. Renal failure, skull hypoplasia and hyperkalaemia have also been reported. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur (see **"CONTRA-INDICATIONS"**).

Infants who have been exposed *in utero* to **CIPLASYL** should be closely monitored. Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and the skull are recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see **"CONTRA-INDICATIONS"** and **"WARNINGS AND SPECIAL PRECAUTIONS"**). Peritoneal dialysis may be of some benefit in the clearance of **CIPLASYL** from the neonatal circulation.

Safety in lactation has not been established. It is not known whether perindopril is excreted into human breast milk. The use of ACE-inhibitors is contra-indicated during lactation.

DOSAGE AND DIRECTIONS FOR USE:

The tablets should be taken before meals.

Mild to moderate hypertension:

Recommended dosage: 4 mg once daily in the morning before breakfast. After one month of treatment the dose can be increased to a single dose of 8 mg, if necessary.

A substantially lower dosage should be used in elderly patients and in cardiac failure because of reduced clearance.

Diabetics (both insulin and non-insulin dependent) can be treated with normal doses.

Congestive heart failure:

Treatment in these patients should be initiated under close medical supervision. Initial dose of 2 mg once daily in the morning. In most instances, this can be increased to 4 mg (once it has been demonstrated that the blood pressure is acceptable).

Reduction of risk of cardiovascular events:

In patients with stable coronary artery disease, **"CIPLASYL"** should be

introduced at a dose of 4 mg once daily for two weeks. The dose should then be increased to 8 mg once daily, depending on renal function. Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 mg once daily depending on renal function (see table **"Renal impairment"** for dosage adjustment).

Concomitant diuretic therapy in hypertension:

Caution is recommended in patients who are already on diuretic treatment. Diuretic therapy should be discontinued prior to initiating therapy with **CIPLASYL**, as the effects of ACE-inhibitors may be potentiated in potential hypovolaemic situations. When **CIPLASYL** is combined with a diuretic, prescription of a potassium salt or a potassium-sparing agent is not recommended before the blood potassium has been determined, and attention should be paid to potential overdosage of the diuretic.

Renal impairment:

In patients with renal impairment, the dosage of **CIPLASYL** must be adjusted based on the severity of the impairment. The following dosages may be recommended:

Creatinine clearance:	**Recommended dosage:**
30 - 60 ml/min	2 mg daily
15 - 30 ml/min	2 mg on alternate days
< 15 ml/min	2 mg on day of dialysis

Perindopril is dialysable at a rate of 70 ml/min. For patients on haemodialysis, the dose should be taken after the dialysis.

Hepatic impairment:

No dosage adjustment is necessary in patients with hepatic impairment.

SIDE-EFFECTS:

Blood and lymphatic system disorders:

Less frequent: Decreases in white blood cell count/neutropenia, decreases in haemoglobin and haematocrit, thrombocytopenia, haemolytic anaemia, (in patients with congenital deficiency of G-6PDH), agranulocytosis, pancytopenia or eosinophilia.

The following side-effects have been reported and frequencies are unknown:

Bone marrow depression, 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. A symptom complex has been reported which may include fever, vasculitis, myalgia, arthritis/arthralgia, positive antinuclear antibodies (ANA), elevated erythrocyte sedimentation rate,

eosinophilia and leucocytosis. Rash, photosensitivity or other dermatological manifestations may occur.

Metabolism and nutrition disorders:

Less frequent: Fever, hyperuricaemia or gout, hypoglycaemia, hyperkalaemia (reversible upon discontinuation), hyponatraemia.

Nervous system disorders:

Frequent: Dizziness, headache, vertigo and paresthesia.

Less frequent: Mental confusion, somnolence, syncope, mood alterations, sleep disturbances.

The following side-effects have been reported and frequencies are unknown:

Fatigue.

Cardiac disorders:

Frequent: Hypotension and effects related to hypotension.

Less frequent: Peripheral oedema, chest pain, myocardial infarction and cerebrovascular accident, (possibly secondary to excessive hypotension in high-risk patients), arrhythmia, angina pectoris, palpitations, tachycardia, vasculitis.

The following side-effects have been reported and frequencies are unknown:

Orthostatic effects (including hypotension).

Respiratory, thoracic and mediastinal disorders:

Frequent: Cough and dyspnoea.

Less frequent: Eusinophilic pneumonia, bronchospasm and rhinitis.

The following side-effects have been reported and frequencies are unknown:

Sinusitis.

Gastrointestinal disorders:

Frequent: Nausea, vomiting, abdominal pain, taste disturbances, indigestion, diarrhoea and constipation.

Less Frequent: Dry mouth, pancreatitis, anorexia, stomach upset.

Hepato-biliary disorders:

Less frequent: Cholecystitis, hepatic function impairment, hepatitis, (cytolytic, hepatocellular or cholestatic)

The following side-effects have been reported and frequencies are unknown:

Jaundice, increases in liver enzymes, increases in serum bilirubin.

Skin and subcutaneous tissue disorders:

Frequent: Rash, pruritus.

Less frequent: Angioedema of face, lips, mucous membranes, tongue, glottis and/or larynx, extremities, urticaria, erythema multiforme,

photosensitivity reactions, phemigoid, diaphoresis, psoriasis aggravation.

The following side-effects have been reported and frequencies are unknown:

Alopecia, psoriasis, severe skin disorders, including pemphigus, toxic epidermal necrolysis, Stevens-Johnson syndrome.

Musculoskeletal, connective tissue and bone disorders:

Frequent: Muscle cramps

Less frequent: Joint pain, myalgia.

The following side-effects have been reported and frequencies are unknown:

Asthenia.

Renal and urinary disorders:

Less frequent: Renal insufficiency, acute renal failure.

The following side-effects have been reported and frequencies are unknown:

Uraemia, oliguria, anuria, renal dysfunction.

Reproductive system and breast disorders:

Less frequent: Impotence.

Investigations:

Less frequent: Increases in blood urea, increases in serum creatinine, blood bilirubin increased, hepatic enzyme increased.

Eye disorders:

Frequent: Visual disturbances.

Ear and labyrinth disorders:

Frequent: Tinnitus.

General disorders and administration site conditions:

Frequent: Asthenia

Less frequent: Sweating, chest pain, malaise, oedema peripheral, pyrexia.

Injury and poisoning:

Less frequent: Fall.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

(See **"SIDE-EFFECTS"** and **"WARNINGS AND SPECIAL PRECAUTIONS"**.)

Limited data are available for overdosage in humans.

Symptoms of overdose:

Severe hypotension, electrolyte disturbances renal failure, circulatory shock, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough.

Treatment of overdose:

Treatment is symptomatic and supportive. Activated charcoal may be given in severe overdosage if the patient presents within 1 hour of ingestion. Treatment consists of volume expansion to correct hypotension and treating dehydration and electrolyte imbalances. The recommended treatment of an overdose is an intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. Treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered if available. Pacemaker therapy is indicated for therapy-resistant bradycardia. Serum electrolytes, vital signs and creatinine concentrations should be monitored continuously. Expected signs and symptoms would be linked to hypotension. **CIPLASYL** is removable by haemodialysis.

IDENTIFICATION:

CIPLASYL 2:	White to off-white, circular, biconvex film-coated tablets plain on both sides
CIPLASYL 4:	White to off white, barrel shaped, biconvex coated tablet with a central break line on both the sides

CIPLASYL 8:	White to off white, barrel shaped, biconvex film-coated tablet with a central break line on both the sides

PRESENTATION:

CIPLASYL 2:	Aluminium blister pack of 30 tablets.
CIPLASYL 4:	Aluminium blister pack of 30 tablets.
CIPLASYL 8:	Aluminium blister pack of 30 tablets.

STORAGE INSTRUCTIONS:

Store at or below 25°C.

Keep the blisters in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

CIPLASYL 2: 41/7.1.3/0670

CIPLASYL 4: 41/7.1.3/0671

CIPLASYL 8: 41/7.1.3/0672

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION:

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