PRODUCT MONOGRAPH

PrARCOSYL® PLUS LD
2.5 mg / 0.625 mg film-coated tablets

PrARCOSYL® PLUS
5 mg / 1.25 mg film-coated tablets
10 mg / 2.5 mg film-coated tablets

(perindopril arginine / indapamide)

Angiotensin converting enzyme inhibitor / Diuretic

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Table of Contents

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(perindopril arginine/ indapamide)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non Medicinal Ingredients
Oral	Film-coated tablet: 2.5 mg / 0.625 mg 5 mg / 1.25 mg 10 mg / 2.5 mg	Glycerol, Hypromellose, Lactose monohydrate, Macrogol 6000, Magnesium stearate, Maltodextrin, Silica colloidal anhydrous, Sodium starch glycolate, Titanium dioxide

INDICATIONS AND CLINICAL USE

ARCOSYL® PLUS LD (perindopril arginine/ indapamide) is indicated for the initial treatment of mild to moderate essential hypertension.

ARCOSYL® PLUS (perindopril arginine/ indapamide) is indicated in the treatment of mild to moderate essential hypertension in patients for whom combination therapy is appropriate.

ARCOSYL® PLUS is not indicated for initial therapy. Patients in whom perindopril and indapamide are initiated simultaneously can develop symptomatic hypotension (see DRUG INTERACTIONS – Drug-Drug Interactions – Concomitant ACE Inhibitor and Diuretic Therapy).

Patients should be titrated on the individual drugs. If the fixed combination represents the dosage determined by this titration, the use of ARCOSYL® PLUS may prove to be more convenient in the management of patients. If during maintenance therapy dosage adjustment is necessary, it is advisable to use individual drugs (see DOSAGE AND ADMINISTRATION).

The safety and efficacy of ARCOSYL® PLUS LD/ ARCOSYL® PLUS in renovascular hypertension and in congestive heart failure have not been established and therefore, their use in this condition is not recommended.

Geriatrics (> 65 years of age)
Although the blood pressure response and safety profile of ARCOSYL® PLUS LD/ ARCOSYL® PLUS in patients > 65 years old were comparable to those of the younger adult patients, greater sensitivity of some elderly patients cannot be ruled out.

Pediatrics
The safety and effectiveness of ARCOSYL® PLUS LD/ ARCOSYL® PLUS in children have not been established. Its use in this age group, therefore, is not recommended.

CONTRAINDICATIONS

ARCOSYL® PLUS (perindopril arginine 10 mg/ indapamide 2.5 mg) is contraindicated in patients with moderate renal impairment (GFR = 30-59 ml/min/1.73m^2).

ARCOSYL® PLUS LD/ ARCOSYL® PLUS (perindopril arginine/ indapamide) are contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation. For a complete listing, see Dosage Forms, Composition and Packaging.
- Patients who are hypersensitive to other sulfonamide derivatives.
- Patients with hereditary/ idiopathic angioedema or a history of angioedema related to previous treatment with an angiotensin converting enzyme (ACE) inhibitor (see WARNINGS and PRECAUTIONS, General).
- Women who are pregnant, intend to become pregnant, or of childbearing potential who are not using adequate contraception (see WARNINGS and PRECAUTIONS, Special Populations, Pregnant Women).
- Nursing women (see WARNINGS AND PRECAUTIONS, Special Populations, Nursing Women).
- Patients with severe renal impairment (GFR < 30 ml/min/1.73m^2).
- Patients with hypokalemia.
- Patients with severe hepatic impairment.
- Patients with hepatic encephalopathy.
- Combination with anti-arrhythmic agents causing torsade de pointes (see DRUG INTERACTIONS – Drug-Drug Interactions).
- Patients with hereditary problems of galactose intolerance, glucose-galactose malabsorption, or the Lapp lactase deficiency as ARCOSYL® PLUS LD/ ARCOSYL® PLUS contain lactose (see WARNINGS AND PRECAUTIONS, Sensitivity/ Resistance)
- Combination with sacubitril / valsartan due to an increased risk of angioedema.
- Combination with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment (GFR < 60 ml/min/1.73m^2) (see WARNINGS and PRECAUTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) and Renal, and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ACE inhibitors, ARBs or aliskiren-containing drugs).
- Patients with extracorporeal treatments leading to contact of blood with negatively charged surfaces (see DRUG INTERACTIONS).

- Patients with bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney (see WARNINGS AND PRECAUTIONS, Renal).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
When used in pregnancy, angiotensin converting enzyme (ACE) inhibitors can cause injury or even death of the developing fetus.
When pregnancy is detected, ARCOSYL® PLUS LD/ ARCOSYL® PLUS should be discontinued as soon as possible.

General

Driving a vehicle or performing other hazardous tasks
Perindopril can have minor or moderate influence on the ability to drive and use machines. If patients suffer from dizziness, headache, fatigue, weariness or nausea, the ability to react may be impaired. Caution is recommended with ARCOSYL® PLUS especially at the start of treatment.

Head and neck angioedema
Life-threatening angioedema has been reported with ACE inhibitors. The overall incidence is approximately 0.1-0.2%. The aetiology is thought to be non-immunogenic and may be related to accentuated bradykinin activity. Usually, the angioedema is non-pitting edema of the skin mucuous membrane and subcutaneous tissue.

Angioedema involving the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors, including perindopril. Angioedema associated with laryngeal involvement may be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, ARCOSYL® PLUS LD/ ARCOSYL® PLUS should be discontinued immediately, the patient treated appropriately in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment, although anti-histamines may be useful in relieving symptoms.

Where there is involvement of the tongue, glottis or larynx, angioedema may be fatal due to airway obstruction, appropriate therapy (including but not limited to 0.3-0.5 ml of subcutaneous epinephrine solution 1:1000 and oxygen) should be administered promptly (see ADVERSE REACTIONS).

Treatment of progressive angioedema should be aggressive. Failing a rapid response to medical therapy, mechanical methods to secure an airway should be undertaken before massive oedema complicates oral or nasal intubation.

Patients who respond to medical treatment should be observed carefully for a possible rebound phenomenon. The onset of angioedema associated with the use of ACE inhibitors may be delayed for weeks or months.

Patients may have multiple episodes of angioedema with long symptom-free intervals. Angioedema may occur with or without urticaria. The incidence of angioedema during ACE inhibitor therapy has been reported to be higher in black than in non-black patients.

There are reports that switching a patient to another ACE inhibitor could be followed by a recurrence of angioedema. Because of the potential severity of this rare event, another ACE inhibitor should not be used in patients with a history of angioedema (see CONTRAINDICATIONS).

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

Concomitant use of mTOR inhibitors, DPP-IV inhibitors and NEP inhibitors
Patients taking a concomitant mTOR inhibitor (e.g. sirolimus, everolimus, temsirolimus), DPP-IV inhibitor (e.g. sitagliptin) or neutral endopeptidase (NEP) inhibitor may be at increased risk for angioedema. Caution should be used when initiating ACE inhibitor therapy in patients already taking an mTOR, DPP-IV or NEP inhibitor or vice versa (see DRUG INTERACTIONS).

Intestinal Angioedema
Intestinal angioedema has been reported 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 history of facial angioedema and C-1 esterase levels were normal.

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.

Cardiovascular

Hypotension
Perindopril can cause symptomatic hypotension. Perindopril has been associated with hypotension in 0.3% of uncomplicated hypertensive patients in U.S. placebo-controlled trials. Symptoms related to orthostatic hypotension were reported in another 0.8% of patients. It is more likely to occur after the first or second dose or when the dose was increased and in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhoea, vomiting or with impaired renal function. Volume and/or salt depletion should be corrected before initiation of therapy with perindopril (see DOSAGE AND ADMINISTRATION). In patients with ischemic heart or cerebrovascular disease and/or severe congestive heart failure, with or without associated renal insufficiency, ACE inhibitors may cause an excessive fall in blood pressure which could result in syncope, myocardial infarction, neurological deficits, oliguria

and/or progressive azotemia and, rarely, in acute renal failure and/or death (see ADVERSE REACTIONS).

Because of the potential fall in blood pressure in these patients, therapy with ARCOSYL® PLUS LD/ ARCOSYL® PLUS should be started under very close medical supervision. Such patients should be followed closely for the first 2 weeks of treatment.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of 0.9% sodium chloride. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion. If hypotension recurs, treatment with ARCOSYL® PLUS LD/ ARCOSYL® PLUS should be discontinued.

Aortic or Mitral Valve Stenosis/ Hypertrophic Cardiomyopathy
As with other ACE inhibitors, ARCOSYL® PLUS LD/ ARCOSYL® PLUS should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy. There is concern on theoretical grounds that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators including ACE inhibitors because they do not develop as much afterload reduction. Vasodilators may tend to drop diastolic pressure, and hence coronary pressure, without producing the concomitant reduction in myocardial oxygen demand that normally accompanies vasodilation.

Dual blockade of the Renin-Angiotensin System (RAS)

There is evidence that co-administration of angiotensin converting enzyme (ACE) inhibitors, such as the perindopril arginine component of ARCOSYL® PLUS LD/ ARCOSYL® PLUS, or of angiotensin receptor antagonists (ARBs) with aliskiren increases the risk of hypotension, syncope, stroke, hyperkalemia and deterioration of renal function, including renal failure, in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment (GFR < 60 ml/min/1.73m^2). Therefore, the use of ARCOSYL® PLUS LD/ ARCOSYL® PLUS in combination with aliskiren-containing drugs is contraindicated in these patients (see CONTRAINDICATIONS).

Further, co-administration of ACE inhibitors, including the perindopril arginine component of ARCOSYL® PLUS LD/ ARCOSYL® PLUS, with other agents blocking the RAS, such as ARBs or aliskiren-containing drugs, is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia.

Primary aldosteronism
Patients with primary aldosteronism generally will not respond to anti-hypertensive drugs acting through inhibition of the RAS. Therefore, the use of ARCOSYL® PLUS LD/ ARCOSYL® PLUS is not recommended in these patients.

Hematologic

Neutropenia/ Agranulocytosis/ Thrombocytopenia/ Anaemia

Neutropenia/ agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Perindopril should be used with extreme caution in patients with collagen vascular disease such as systemic lupus erythematosus or scleroderma, and those on multiple drug therapy with agents known to be nephrotoxic or myelosuppressive (immunosuppressant therapy, treatment with allopurinol or procainamide), or a combination of these complicating factors, especially if there is pre-existing impaired renal function.

Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If perindopril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (see Monitoring and Laboratory Tests, Hematological Monitoring and DRUG INTERACTIONS, Drug-Drug Interactions).

Hepatic

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.

Immune

Anaphylactoid Reactions during Membrane Exposure (hemodialysis patients)

Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g. polyacrylonitrile [PAN]) and treated concomitantly with an ACE inhibitor. Dialysis should be stopped immediately if symptoms such as nausea, abdominal cramps, burning, angioedema, shortness of breath and severe hypotension occur. Symptoms are not relieved by anti-histamines. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Anaphylactoid Reactions during LDL Apheresis

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

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. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld for at least 24 hours, but they reappeared upon inadvertent re-challenge.

Nitritoid Reactions-Gold

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting, and symptomatic hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including ARCOSYL® PLUS LD/ ARCOSYL® PLUS (see DRUG INTERACTIONS).

Metabolism

Calcium excretion is decreased by diuretics pharmacologically related to indapamide. However, after 6-8 weeks of indapamide 1.25 mg treatment and in long-term studies of hypertensive patients with higher doses of indapamide, serum concentrations of calcium increased only slightly with indapamide. Prolonged treatment with drugs pharmacologically related to indapamide may in rare instances be associated with hypercalcemia and hypophosphatemia secondary to physiologic changes in the parathyroid gland; however, the common complications of hyperparathyroidism, such as renal lithiasis, bone resorption, and peptic ulcer, have not been seen.

Treatment should be discontinued before tests for parathyroid function are performed. Like the thiazides, indapamide may decrease serum PBI levels without signs of thyroid disturbance. The antihypertensive effect of the drug may be enhanced in the patient post-sympathectomy.

Other Metabolic Parameters
Blood urea nitrogen (BUN), uric acid, and glucose levels should also be assessed during therapy.

Hyperuricemia may occur during administration of indapamide. Rarely gout has been reported. Blood uric acid levels should be monitored, particularly in patients with a history of gout who should continue to receive appropriate treatment.

Peri-Operative Considerations

ACE inhibitors may augment the hypotensive effects of anaesthetics and analgesics. In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, perindopril may block the angiotensin II formation that could otherwise occur secondary to compensatory renin release. The treatment should be discontinued 1 day prior to the surgery. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion (see DRUG INTERACTIONS, Drug-Drug Interactions).

Renal

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), changes in renal function may be anticipated in susceptible individuals.

Use of ARCOSYL® PLUS LD/ ARCOSYL® PLUS should include appropriate assessment of renal function.

The use of ACE inhibitors, including the perindopril arginine component of ARCOSYL® PLUS LD / ARCOSYL® PLUS, or ARBs with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR < 60 ml/min/1.73m^2). (See CONTRAINDICATIONS and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ACE inhibitors, ARBs or aliskiren-containing drugs).

In patients with severe renal impairment (GFR < 30 ml/min/1.73m^2), all dosages are contraindicated (see CONTRAINDICATIONS).

In patients with moderate renal impairment (GFR = 30-59 ml/min/1.73m^2), ARCOSYL® PLUS (10 mg / 2.5 mg) is contraindicated (see CONTRAINDICATIONS), and the initial dosage of ARCOSYL® PLUS LD (2.5 mg/ 0.625 mg) / ARCOSYL® PLUS (5 mg/ 1.25 mg) should be adjusted according to the patient's creatinine clearance and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients.

In patients whose renal function may depend on the activity of the RAAS, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk.

Hypertensive Patients with Renal Artery Stenosis

In clinical trials in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen (BUN) and serum creatinine were observed in 20% of patients. Experience with ACE inhibitors suggests that these increases are usually reversible upon discontinuation of the drug. In such patients, renal function should be monitored during the first few weeks of therapy. ACE inhibitors should be avoided in patients with known or suspected renal artery stenosis.

When an ACE inhibitor is given to a patient with stenosis of the renal artery supplying a solitary kidney, or bilateral artery stenosis, acute renal insufficiency may occur. ACE inhibition may also cause a decrease in renal function in patients with stenosis of the artery supplying a transplanted kidney. It is believed that renal artery stenosis reduces the pressure in the afferent glomerular arteriole, and transglomerular hydrostatic pressure is then maintained by angiotensin II–induced

constriction of the efferent arteriole. When an ACE inhibitor is given, the efferent arteriole relaxes, glomerular filtration falls, and renal failure may result. The thrombotic occlusion of a stenosed renal artery can be precipitated by ACE inhibitors.

Some hypertensive patients without apparent pre-existing renal vascular disease have developed increases in BUN and serum creatinine, usually minor and transient. These increases are more likely to occur in patients treated concomitantly with a diuretic and in patients with pre-existing renal impairment. Reduction of dosages of perindopril, the diuretic or both may be required. In some cases, discontinuation of either or both drugs may be necessary. Evaluation of hypertensive patients should always include an assessment of renal function (see DOSAGE AND ADMINISTRATION). If deterioration in renal function has occurred after treatment with one ACE inhibitor, then it is likely to be precipitated by another and in these patients usage of another class of antihypertensive agent would be preferable. Patients with unilateral renal artery disease present a special problem as deterioration of function may not be apparent from measurement of blood urea and serum creatinine.

Proteinuria
Some ACE inhibitors have been associated with the occurrence (up to 0.7%) of proteinuria (< 1 gram / 24 hours) and/or decline in renal function in patients with one or more of the following characteristics: old age, pre-existing renal disease, concomitant treatment with potassium-sparing diuretics or high doses of other diuretics, limited cardiac reserve, or treatment with a non-steroidal anti-inflammatory drug. Perindoprilat, the active form of perindopril, is dialysable with a clearance of 70 ml/min.

Fluid and Electrolyte Imbalance
Electrolyte changes observed with indapamide may be severe. The recommended maximum daily dose of 2.5 mg/day should not be exceeded.

Hypokalemia may occur with consequent weakness, cramps and cardiac dysrhythmias. Hypokalemia is a particular hazard in digitalized patients; dangerous or fatal cardiac arrhythmias may be precipitated. Hypokalemia occurs commonly with diuretics; electrolyte monitoring is essential particularly in patients who would be at increased risk from hypokalemia, such as patients with cardiac arrhythmias or those who are receiving concomitant cardiac glycosides.

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.

Patients with renal insufficiency receiving ARCOSYL® PLUS LD/ ARCOSYL® PLUS should be carefully monitored. If increased azotemia and oliguria occur during treatment, ARCOSYL® PLUS LD/ ARCOSYL® PLUS should be discontinued.

Patients receiving indapamide should be carefully observed for signs and symptoms of electrolyte imbalance, namely hypokalemia, hyponatremia and hypochloremia, and their serum electrolytes should be closely monitored. Hypokalemia will be more common in association with concomitant steroid or ACTH therapy and with inadequate electrolyte intake. Serum potassium

should be determined at regular intervals. The first measurement of plasma potassium levels should be carried out during the first week following the start of treatment. Potassium supplementation should be instituted when indicated.

The signs of electrolyte imbalance are: dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscle fatigue, hypotension, oliguria, gastrointestinal disturbances such as nausea and vomiting, tachycardia and ECG changes.

Potassium Balance

Hypokalemia

In clinical trials with the perindopril / indapamide combination, hypokalemia (serum potassium < 3.4 mmol/L) occurred in an apparent dose-related fashion. Potassium supplementation should be given.

Hyperkalemia

In clinical trials with perindopril/ indapamide combination, hyperkalemia (serum potassium > 5.5 mmol/L) occurred in approximately 1% of hypertensive patients. In most cases, these were isolated values which resolved despite continued therapy. Risk factors for development of hyperkalemia may include renal insufficiency, worsening of renal function, diabetes mellitus, elderly patients, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and the concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements, potassium–containing salt substitutes or any drugs associated with increases in serum potassium (e.g. aliskiren, NSAIDs, heparin, cyclosporine, tacrolimus, trimethoprim and fixed dose combination with sulfamethoxazole, angiotensin receptor blockers) which should be used cautiously, if at all, with perindopril/ indapamide. The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalemia can cause serious, sometimes fatal arrhythmias (see DRUG INTERACTIONS – Drug-Drug Interactions).

Renovascular hypertension:

There is an increased risk of hypotension and renal insufficiency when patient with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors (see CONTRAINDICATIONS). Treatment with diuretics may be a contributory factor. Loss of renal function may occur with only minor changes in serum creatinine even in patients with unilateral renal artery stenosis.

Respiratory

Cough

A dry persistent irritating cough, which usually disappears only after withdrawal or lowering of the dose of perindopril has been reported. Such possibility should be considered as part of the differential diagnosis of the cough.

The cough is often worse when lying down or at night, and has been reported more frequently in women (who account for 2/3 of the reported cases). Patients who cough may have increased

bronchial reactivity compared with those who do not. The observed higher frequency of this side-effect in non-smokers may be due to a higher level of tolerance of smokers to cough.

The cough is most likely due to stimulation of the pulmonary cough reflex by kinins (bradykinin) and/or prostaglandins, which accumulate because of ACE inhibition. Once a patient has developed intolerable cough, an attempt may be made to switch the patient to another ACE inhibitor; the reaction may recur but this is not invariably the case. A change to another class of drugs may be required in severe cases.

Sensitivity/ Resistance

Due to the presence of lactose, patients with hereditary problems of galactose intolerance, glucose-galactose malabsorption or the Lapp lactase deficiency should not take ARCOSYL® PLUS LD/ ARCOSYL® PLUS (see CONTRAINDICATIONS).

Photosensitivity

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

Skin

Dermatological reactions

Dermatological reactions characterised by maculo-papular pruritic rashes and sometimes photosensitivity have been reported with ACE inhibitors. Rare and sometimes severe skin reactions (lichenoid eruptions, psoriasis, pemphigus like rash, rosacea, Stevens-Johnson syndrome, etc.) have occurred.

Patients who develop a cutaneous reaction with one ACE inhibitor might not when switched to another drug of the same class, but there are reports of cross-reactivity.

Severe dermatological adverse reactions, some accompanied by systemic manifestations, have been rarely reported with the use of indapamide. In the majority of cases, the condition subsided within 14 days following discontinuation of indapamide therapy (see ADVERSE REACTIONS).

Lupus Erythematosus

Sulfonamide derivatives have been reported to exacerbate or activate systemic lupus erythematosus. These possibilities should be kept in mind with the use of indapamide although no case has been reported to date.

Special populations

Pregnant women

ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is detected, ARCOSYL® PLUS LD/ ARCOSYL® PLUS should be discontinued as soon as possible (see CONTRAINDICATIONS).

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death.

Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function, associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development.

Prematurity and patent ductus arteriosus and other structural cardiac malformations, as well as neurologic malformations, have also been reported following exposure in the first trimester of pregnancy.

Infants with a history of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for impaired renal function; however, limited experience with those procedures has not been associated with significant clinical benefit. Perindoprilat, the active form of perindopril, can be removed from the body by hemodialysis (see ACTION AND CLINICAL PHARMACOLOGY, Special populations and conditions – Renal insufficiency).

Animal data: see Part II - Scientific information – TOXICOLOGY, Teratology studies.

Nursing women

The presence of concentrations of ACE inhibitor have been reported in human milk. Use of ARCOSYL® PLUS LD/ ARCOSYL® PLUS is contraindicated during breast-feeding (see CONTRAINDICATIONS).

Diabetic patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycemic control should be closely monitored during the first month of treatment with an ACE inhibitor.

Pediatrics

The safety and effectiveness of ARCOSYL® PLUS LD/ ARCOSYL® PLUS in children have not been established. Its use in this age group, therefore, is not recommended.

Geriatrics (> 65 years of age)
Although the blood pressure response and safety profile of ARCOSYL® PLUS LD/ ARCOSYL® PLUS in patients > 65 years old were comparable to those of the younger adult patients, greater sensitivity of some elderly patients cannot be ruled out.

Patients with Impaired Liver Function
Hepatitis (hepatocellular and/or cholestatic), elevations of liver enzymes and/or serum bilirubin have occurred during therapy with ACE inhibitors, in patients with or without pre-existing liver abnormalities. In most cases, the changes were reversed upon discontinuation of the drug.

Elevations of liver enzymes and/or serum bilirubin have been reported with perindopril (see ADVERSE REACTIONS). Should the patient receiving ARCOSYL® PLUS LD/ ARCOSYL® PLUS experience any unexplained symptoms, particularly during the first weeks or months of treatment, it is recommended that a full set of liver function tests and any other necessary investigation be carried out. Discontinuation of ARCOSYL® PLUS LD/ ARCOSYL® PLUS should be considered when appropriate.

ARCOSYL® PLUS LD/ ARCOSYL® PLUS should be used with particular caution in patients with pre-existing liver abnormalities. In such patients, baseline liver function tests should be obtained before administration of the drug and close monitoring of response and metabolic effects should apply.

ARCOSYL® PLUS LD/ ARCOSYL® PLUS are contraindicated in patients with severe hepatic impairment since diuretics may induce metabolic alkalosis in cases of potassium depletion which may precipitate episodes of hepatic encephalopathy (see CONTRAINDICATIONS).

Monitoring and Laboratory Tests

Hematological Monitoring
Perindopril should be used with extreme caution and periodic monitoring of white blood cell counts is advised in patients with collagen vascular disease such as systemic lupus erythematosus or scleroderma, and those on multiple drug therapy with agents known to be nephrotoxic or myelosuppressive (immunosuppressant therapy, treatment with allopurinol or procainamide), or a combination of these complicating factors, especially if there is pre-existing impaired renal function (see WARNINGS AND PRECAUTIONS, Hematologic, Neutropenia/ Agranulocytosi / Thrombocytopenia/ Anaemia and DRUG INTERACTIONS, Drug-Drug Interactions).

Renal Function Monitoring
Routine monitoring of potassium and creatinine is part of normal medical practice for renal impairment patients (GFR = 30-59 ml/min/1.73m^2).
Particularly careful monitoring is required in hypertensive patients with renal artery stenosis. In such patients, renal function should be monitored during the first few weeks of therapy.

Potassium Monitoring
If concomitant use of potassium-sparing diuretics, potassium supplements, potassium-containing

salt substitutes, drugs associated with increase in serum potassium, or other RAAS inhibitors is deemed appropriate, regular monitoring of serum potassium and urea is recommended.

Sodium Monitoring
Sodium levels 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 ADVERSE REACTIONS and OVERDOSAGE).

Doping Tests
Athletes should note that this product contains indapamide which may cause a positive reaction in doping tests.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In controlled trials, the overall incidence of adverse events (AEs) reported with perindopril erbumine 2 mg/ indapamide 0.625 mg and perindopril erbumine 4 mg/ indapamide 1.25 mg were comparable to placebo. The overall incidence of AEs reported with perindopril erbumine 8 mg/ indapamide 2.5 mg were comparable to perindopril erbumine 4 mg/ indapamide 1.25 mg. AEs were generally mild and transient and did not require discontinuation of therapy.

The most frequent clinical adverse drug reactions reported in patients treated with:

- Perindopril erbumine 2 mg/ indapamide 0.625 mg: cough (3.7%), headache (1.8%), asthenia (1.3%), dizziness (0.9%) and nausea/vomiting (0.8%).
- Perindopril erbumine 4 mg/ indapamide 1.25 mg: cough (3.0%), headache (2.1%), asthenia (1.6%), nausea / vomiting (1.5%) and dizziness (1.2%).
- Perindopril erbumine 8 mg/ indapamide 2.5 mg in the 2 long-term trials (137 patients): cough (3.9%) and headache (1.7%).

The most serious adverse drug reactions were isolated cases of worsening of heart failure due to atrial fibrillation, hyperglycaemia with renal failure, loss of consciousness, renal colic and transient cerebral ischemia.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Perindopril erbumine 2 mg/ indapamide 0.625 mg was evaluated for safety in 1974 patients with 1898 patients from controlled clinical trials. Long-term safety was assessed in 745 patients: 659 were treated for 3 months, 597 for 6 months and 385 for ≥ 1 year.

Perindopril erbumine 4 mg/ indapamide 1.25 mg was evaluated for safety in 1029 patients in controlled clinical trials. Long-term safety was assessed in 492 patients: 444 were treated for 3 months, 420 for 6 months and 245 for ≥ 1year.

Perindopril erbumine 8 mg/ indapamide 2.5 mg was evaluated for safety in 199 patients in controlled clinical trials. Long-term safety was assessed in 137 patients in two 52-week trials for a mean duration of exposure of 6 ½ months.

ARCOSYL® PLUS LD and ARCOSYL® PLUS (5 mg/ 1.25 mg)

Discontinuation of therapy due to adverse drug reactions was required in 2.3% of patients treated with perindopril erbumine 2 mg/ indapamide 0.625 mg and in 2.5% of patients treated with perindopril erbumine 4 mg/ indapamide 1.25 mg, versus 1.5% of patients treated with placebo.
The main reasons for discontinuation of perindopril erbumine 2 mg/ indapamide 0.625 mg and perindopril erbumine 4 mg/ indapamide 1.25 mg were cough (0.5% and 0.6%), headache (0.4% and 0.5%) and nausea/vomiting (0.4% and 0.4%), respectively.

AEs reported in ≥ 1.0% of hypertensive patients treated with 1 tablet daily of perindopril erbumine 2 mg/ indapamide 0.625 mg or perindopril erbumine 4 mg/ indapamide 1.25 mg in short-term controlled trials are listed by body system in the following table. Their occurrence was always low and they correspond to those previously reported with perindopril and indapamide when used separately for the treatment of hypertension.

Table 1 - Drug-related adverse experience reported in ≥ 1% of patients (%)

Adverse drug reaction	Perindopril erbumine 2 mg/ indapamide 0.625 mg (n=789) %	perindopril erbumine 4 mg/ indapamide 1.25 mg (n=1029) %	Placebo (n=717) %
Body as a whole			
Asthenia	1.0	1.9	2.0
Gastrointestinal			
Dyspepsia	0.5	1.1	0.6
Nausea, vomiting	0.1	1.5	0.4
Musculoskeletal			
Joint pain	1.1	0.4	0.6
Nervous			
Headache	2.5	3.7	5.7
Dizziness	1.3	1.6	0.6
Respiratory			
Cough	5.4	3.4	2.1
Rhinopharyngitis	1.8	0.1	1.5
Upper respiratory influenzal infection	0.9	1.5	1.4
Bronchitis	1.0	0.7	0.7

The safety profile of perindopril erbumine 2 mg/ indapamide 0.625 mg in patients > 65 years old was comparable to that in the younger adult patients. This was demonstrated in a specific 3-month placebo-controlled study involving 193 patients treated with perindopril erbumine 2 mg/ indapamide 0.625 mg and in a sub-population analysis on 618 elderly patients who received perindopril erbumine 2 mg/ indapamide 0.625 mg in all short-term studies combined, and confirmed in a 1 year follow-up study on 253 elderly patients (215 treated for 3 months, 177 for 6 months and 140 for ≥ 1 year).

The safety profile of perindopril erbumine 4 mg/ indapamide 1.25 mg in patients > 65 years old was comparable to that in the younger adult patients. This was demonstrated in a sub-population analysis on 197 elderly patients who received perindopril erbumine 4 mg/ indapamide 1.25 mg in all short term studies combined, and in a sub-population analysis on 87 elderly patients who received perindopril erbumine 4 mg/ indapamide 1.25 mg in a 1 year study.

AEs reported in ≥1.0% of hypertensive patients treated with perindopril erbumine 8 mg/ indapamide 2.5 mg corresponded to those previously reported with perindopril erbumine 4 mg/ indapamide 1.25 mg and with perindopril and indapamide when used separately for the treatment of hypertension. In a long-term study including 492 patients (444 were treated for 3 months, 420 for 6 months and 245 for ≥ 1 year), the nature and frequency of AEs were similar to those listed in Table 1.

The safety profile of perindopril erbumine 8 mg/ indapamide 2.5 mg in patients >65 years old was comparable to that in the younger adult patients. This was demonstrated in a sub-population analysis in the elderly patients who received perindopril erbumine 8 mg/ indapamide 2.5 mg in the short-term and the 2 long-term studies.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

AEs reported in <1.0% of patients treated with perindopril erbumine / indapamide in controlled clinical trials include the following:

Body as a Whole: bloating, chest pain, oedema, epistaxis, malaise, pallor and flushing, poisoning, pyrexia, tetany, weight loss;

Cardiovascular: abnormal ECG, angina pectoris, heart rate and rhythm disorders, hypertension, orthostatic hypotension, palpitations, Raynaud's syndrome, syncope and collapse, tachycardia, venous insufficiency;

Dermatological: contact dermatitis, dermatomycosis, eczema, herpes zoster, local infection of skin/ subcutaneous tissues, pruritus, rash;

Ear/ Nose/ Throat: coryza, impacted cerumen, otitis media, laryngitis, pharyngitis, rhinitis, sinusitis, tonsillitis, tinnitus, tracheitis, upper respiratory tract infections;

Gastrointestinal: abdominal pain, colitis, constipation, diarrhoea, esophageal reflux, esophagitis, functional digestive disorders, gastritis, gastroduodenitis, infective and non-infective gastroenteritis, intestinal infection, nausea, periapical abscess, salivary secretion disturbance, vomiting;

Genitourinary: dysuria, enuresis, female genital neoplasm, penis disorders, polyuria, prostate hyperplasia, urinary frequency, urinary tract infection, cystitis, uremia;

Hematological: blood creatinine increased;

Metabolic and Nutritional: gout, liver and biliary system disorders;

Musculoskeletal: backache, cervicalgia, cervicobrachial syndrome, enthesopathy of elbow region, injury, pain in limb, symptoms referable to limbs, lumbago, muscle/ ligament/ fascia disorders, localized osteoarthrosis, periarthritis/ fibrositis of shoulder, sciatica, sprains of ankle/ knee/ leg;

Neurologic: anxiety, depression, drowsiness, fall, migraine, nervousness, sleep disturbance, somnolence, peripheral vertigo, smell and taste disturbances, skin sensation disturbances;

Ophthalmologic: conjunctivitis, visual disturbances;

Respiratory: allergic rhinitis, asthma, pharynx diseases, respiratory insufficiency;

Sexual Function: frigidity, impotence.

Abnormal Hematologic and Clinical Chemistry Findings

Serum electrolytes
The administration of perindopril inhibits the renin-angiotensin-aldosterone (RAAS) axis and tends to reduce the potassium loss caused by indapamide.

During 12-week studies, 1.8% of patients treated with 1 tablet daily of perindopril erbumine 2 mg/ indapamide 0.625 mg and 3.9% of patients treated with 1 tablet daily of perindopril erbumine 4 mg/ indapamide 1.25 mg experienced hypokalemia (potassium level < 3.4 mmol/L, versus 0.3% in placebo-treated patients). These percentages were statistically significantly lower than in patients treated with indapamide alone at the usual therapeutic dose of 1.25 mg. The mean reduction of potassium level was 0.10 mmol/L with 1 tablet of perindopril erbumine 2 mg/ indapamide 0.625 mg and 0.20 mmol/L with 1 tablet of perindopril erbumine 4 mg/ indapamide 1.25 mg (versus 0.03 mmol/L with placebo).

During the 52-week studies, the maximum mean reduction of potassium level with perindopril erbumine 8 mg/ indapamide 2.5 mg was 0.16 mmol/L (*versus* 0.11 mmol/L with perindopril

erbumine 4 mg/ indapamide 1.25 mg and *versus* 0.07 mmol/L with perindopril erbumine 2 mg/ indapamide 0.625 mg).

The incidence of potassium levels < 3.4 mmol/L during long-term treatment was not significantly different from that observed during short-term studies and the probability to have potassium levels below this limit did not depend on the extent of exposure.

Of the 137 patients treated with perindopril erbumine 8 mg/ indapamide 2.5 mg in two 52-week trials, 9 (6.6%) presented with an emergent hypokalemia. (see WARNINGS AND PRECAUTIONS).

Increases in potassium levels > 5.5 mmol/L occurred in 0.8% of patients treated with 1 tablet daily of perindopril erbumine 2 mg/ indapamide 0.625 mg and 1.0% of patients treated with 1 tablet daily of perindopril erbumine 4 mg/ indapamide 1.25 mg (versus 0.7% with placebo) (see WARNINGS AND PRECAUTIONS). Similar percentages of potassium levels variations were observed in elderly patients.

Blood Urea/ Serum Creatinine Levels

Elevations of blood urea (> 10 mmol/L) or serum creatinine (> 160 µmol/L) have been observed in 3.5% and 0.5% of patients treated with 1 tablet daily of perindopril erbumine 2 mg/ indapamide 0.625 mg and in 2.3% and 0.3% of patients treated with 1 tablet daily of perindopril erbumine 4 mg/ indapamide 1.25 mg (versus 1.5% and 0.14% with placebo), respectively. The mean increases in blood urea levels and serum creatinine levels were 0.4 mmol/L and 1.1 µmol/L in patients treated with 1 tablet of perindopril erbumine 2 mg/ indapamide 0.625 mg, 0.5 mmol/L and 2.1 µmol/L in patients treated with 1 tablet daily of perindopril erbumine 4 mg/ indapamide 1.25 mg (versus 0.1 mmol/L and 0.9 µmol/L with placebo), respectively. The serum creatinine level was stable in patients with mild to moderate renal failure after 12 weeks of treatment.

Mean increases in blood urea levels and serum creatinine were observed in patients treated with perindopril erbumine 8 mg/ indapamide 2.5 mg, larger than the increases seen with perindopril erbumine 4 mg/ indapamide 1.25 mg.

Blood Uric Acid

Increases of uric acid level (> 600 µmol/L) have been observed in 0.7% of patients treated with 1 tablet daily of perindopril erbumine 2 mg/ indapamide 0.625 mg and in 0.5% of patients treated with 1 tablet of perindopril erbumine 4 mg/ indapamide 1.25 mg (versus 0.1% with placebo). Uric acid level remained stable during the long-term studies including patients treated ≤ 1 year.

As with perindopril erbumine 4 mg/ indapamide 1.25 mg, increases of uric acid level were observed in patients treated with perindopril erbumine 8 mg/ indapamide 2.5 mg.

Calcium

Calcium excretion is decreased by diuretics pharmacologically related to indapamide (see WARNINGS AND PRECAUTIONS). Serum concentrations of calcium increased only slightly with indapamide.

Hematology
Minor decreases in haemoglobin (mean decrease of approximately 1g/L) occurred in hypertensive patients treated with perindopril erbumine 2 mg/ indapamide 0.625 mg or perindopril erbumine 4 mg/ indapamide 1.25 mg (versus 0.1 g/L with placebo), but were rarely of clinical importance. In clinical trials, hematocrit was unaffected by treatment and no patients discontinued therapy due to anemia.

Minor changes in haemoglobin occurred in hypertensive patients treated with perindopril erbumine 8 mg/ indapamide 2.5 mg, but were not of clinical relevance. In clinical trials, haematocrit was mostly unaffected by treatment.

Liver Function
Rarely, elevations of liver enzymes have been reported (see WARNINGS AND PRECAUTIONS).

Potential Adverse Events Reported with ACE inhibitors

Taste disturbances (dysgeusia)
Taste disturbances were reported to be common (prevalence up to 12.5%) with high doses of an ACE inhibitor.

Taste disturbance with ACE inhibitors have been described as suppression of taste or a metallic sensation in the mouth. Any dysgeusia usually occurs in the first weeks of treatment and may disappear in most cases within 1-3 months.

Post-Market Adverse Drug Reactions

Among the less common suspected adverse reactions, the following have been reported:

Blood and lymphatic system disorders: aplastic anemia, hemolytic anemia, leucopenia agranulocytosis, neutropenia, thrombocytopenia, anemia that has been reported with ACE inhibitors in specific circumstances (patients who have had kidney transplants, patients undergoing haemodialysis), eosinophilia

Cardiac disorders: arrhythmia, including bradycardia, ventricular tachycardia, atrial fibrillation, torsade de pointes (potentially fatal), angina pectoris, myocardial infarction, palpitations

Ear and labyrinth disorders: tinnitus;

Endocrine disorders: syndrome of inappropriate antidiuretic hormone secretion (SIADH);

Eye disorders: cataract, acute myopia, visual impairment, blurred vision;

Gastrointestinal disorders: pancreatitis, epigastric pain, anorexia, constipation, dry mouth, nausea, vomiting, abdominal pain, taste disturbance, dyspepsia, diarrhea;

General disorders and administration site conditions: fever, sweating, asthenia, chest pain, malaise, oedema peripheral;

Hepato-biliary disorders: hepatitis either cytolytic or cholestatic; in case of hepatic insufficiency, there is a possibility of onset of hepatic encephalopathy;

Injury, Poisoning and Procedural Complications: fall;

Immune system disorders: hypersensitivity;

Investigations: electrocardiogram QT prolonged, blood glucose increase, blood uric acid increase, elevated liver enzymes, slight increase in urea and in plasma creatinine levels (reversible when treatment is stopped);

Metabolism and nutrition disorders: hyperosmolar coma, metabolic alkalosis, dehydration, hypokalemia, hyperkalemia (usually transitory), hypercalcemia, hyponatremia with hypovolaemia responsible for dehydration and orthostatic hypotension;

Musculoskeletal, connective tissue and bone disorders: rhabdomyolysis, cramps, arthralgia, myalgia;

Nervous system disorders: paresthesia, optic neuritis, stroke, headache, dizziness, vertigo, confusion, syncope, somnolence;

Psychiatric disorders: mood disturbances, sleep disturbance;

Renal and urinary disorders: interstitial nephritis, acute renal failure, renal insufficiency;

Reproductive system and breast disorders: impotence;

Respiratory / Thoracic and Mediastinal disorders: bronchospasm, eosinophilic pneumonia,dry cough, dyspnea, rhinitis;

Skin and sub-cutaneous tissue disorders: rash, pruritus, hypersensitivity reactions (mainly dermatological), Stevens-Johnson syndrome, bullous eruption, maculopapular eruption, photosensitivity, erythroderma, purpura, toxic epidermal necrolysis, erythema multiforme, angioedema, possible aggravation of pre-existing acute disseminated lupus erythematosus, pemphigoid, pemphigus, psoriasis aggravation;

Vascular disorders: hypotension whether orthostatic or not, vasculitis.

DRUG INTERACTIONS

Overview

The combined use of perindopril and indapamide in ARCOSYL® PLUS LD or ARCOSYL® PLUS does not expose to any additional interactions with concomitant drugs other than those known for each of these components.

Drug-Drug Interactions

Table 2 - Established or potential concomitant drug-drug interactions

Proper name	Ref	Effect	Clinical Comment
Agents affecting sympathetic activity	CTC	Beta adrenergic blocking drugs add further antihypertensive effect to perindopril.	Agents affecting sympathetic activity (e.g. ganglionic blocking agents or adrenergic neuron blocking agents) may be used with caution. Beta adrenergic blocking drugs add further antihypertensive effect to perindopril/indapamide.
Agents causing renin release	CTC	The antihypertensive effect of perindopril is augmented by antihypertensive agents that cause renin release (e.g. diuretics).	
Agents increasing serum potassium	CT	Since perindopril decreases aldosterone production, elevation of serum potassium may occur.	Potassium-sparing diuretics such as spironolactone, eplerenone, triamterene or amiloride, or potassium supplements, potassium-containing salt substitutes, or any drugs associated with increase of serum potassium (aliskiren, NSAIDs heparin, cyclosporine, tacrolimus, trimethoprim, angiotensin receptor blockers and others) should be given only for documented hypokalemia and with caution and frequent monitoring of serum potassium, since they may lead to a significant increase in serum potassium. Salt substitutes which contain potassium should also be used with caution (see WARNINGS AND PRECAUTIONS, Renal, Potassium Balance).
Alcohol, barbiturates, narcotics		In the presence of indapamide, potentiation of orthostatic hypotension may occur.	
Allopurinol		Concomitant treatment with indapamide may increase the incidence of hypersensitivity reactions to allopurinol.	Use with caution when ARCOSYL® PLUS LD / ARCOSYL® PLUS is co-administered with allopurinol.

Table 2 - Established or potential concomitant drug-drug interactions

Proper name	Ref	Effect	Clinical Comment
Anti-hypertensive agents and vasodilators		Concomitant use of these agents may increase the hypotensive effects of perindopril. Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.	
Anti-diabetic agents		Epidemiological studies have suggested that concomitant administration of ACE inhibitors and anti-diabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood-glucose lowering effect with risk of hypoglycaemia.	This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.
Concomitant ACE inhibitor and diuretic therapy		Patients concomitantly taking ACE inhibitors and diuretics, and especially those in whom diuretic therapy was recently instituted, and who are volume and/or salt depleted, may experience an excessive reduction of blood pressure after initiation of therapy.	The possibility of hypotensive effects after the first dose of perindopril / indapamide can be minimized by either increasing the volume or salt intake prior to initiation of treatment or reducing the starting dose of the combination. In this case, the patient should be closely observed for several hours following the initial dose and until blood pressure has stabilized (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).
Digoxin	C	A pharmacokinetic study has shown no effect on plasma digoxin concentration when co-administered with perindopril but an effect of digoxin on the plasma concentration of perindopril / perindoprilat has not been excluded.	
DDP-IV inhibitors (linagliptin, saxagliptin, sitagliptin)		Increased risk of angio-oedema in patients co-treated with an ACE inhibitor	Caution should be used when initiating ARCOSYL® PLUS LD / ARCOSYL® PLUS in patients already taking a DPP-IV inhibitor or *vice versa* (see WARNINGS AND PRECAUTIONS, General, Head and Neck Angioedema).
Dual blockade of the Renin-Angiotensin-System (RAS) with ACE inhibitors, ARBs or aliskiren-containing drugs	CT	Dual Blockade of the Renin-Angiotensin-System (RAS) with ACE inhibitors, ARBs or aliskiren-containing drugs is contraindicated in patients with diabetes and/or renal impairment, and is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia.	See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS).

Table 2 - Established or potential concomitant drug-drug interactions

Proper name	Ref	Effect	Clinical Comment
Estramustine		Risk of increased adverse effects such as angioneurotic oedema (angioedema).	Use with caution when ARCOSYL® PLUS LD / ARCOSYL® PLUS is co-administered with estramustine.
Extracorporeal treatments		Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (*e.g.* polyacrylonitril membranes) and low density lipoprotein apheresis with dextran sulphate due to increased risk of severe anaphylactoid reactions (see CONTRAINDICATIONS).	If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.
Gentamicin		Animal data have suggested the possibility of interaction between perindopril and gentamicin. However, this has not been investigated in human studies.	Co-administration of both drugs should proceed with caution.
Insulin		Although indapamide exerts minimal effect on glucose metabolism, insulin requirements may be affected in diabetics and hyperglycemia and glycosuria may occur in patients with latent diabetes.	
Lithium	C	Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. If a diuretic is also used, it may further increase the risk of lithium toxicity.	Perindopril / indapamide should be coadministered with caution and frequent monitoring of serum lithium levels is recommended.
mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus)		Patients taking concomitant mTOR inhibitors may be at increased risk for angioedema.	Caution should be used when initiating ARCOSYL® PLUS LD / ARCOSYL® PLUS in patients already taking mTOR inhibitors or *vice versa* (see WARNINGS AND PRECAUTIONS, Head and Neck Angioedema).
Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin ≥ 3g/day		The administration of a NSAID may reduce the antihypertensive effect of ACE inhibitors. NSAIDs also exert an additive effect on the increase in serum potassium and may result in a deterioration of renal function.	These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function such as those who are elderly or dehydrated.
Neutral endopeptidase inhibitor		ACE inhibitors are known to cause angioedema. This risk may be elevated when used concomitantly with a neutral endopeptidase inhibitor	Caution should be used when initiating ARCOSYL® PLUS LD / ARCOSYL® PLUS in patients already taking a neutral endopeptidase inhibitor or *vice versa* (see WARNINGS AND PRECAUTIONS, General, Head and Neck Angioedema).

Table 2 - Established or potential concomitant drug-drug interactions

Proper name	Ref	Effect	Clinical Comment
Tricyclic antidepressants/ Antipsychotic/ Anesthetics		Concomitant use of certain anesthetics, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure.	Use with caution when ARCOSYL® PLUS LD / ARCOSYL® PLUS is co-administered with these drugs
Gold	CT	Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and symptomatic hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including perindopril.	Use with caution when ARCOSYL® PLUS LD / ARCOSYL® PLUS is co-administered with gold.
Clofibrate	C	Synergetic effect of clofibrate with indapamide leading to hyponatremia, hypokalemia, hypoosmolarity, nausea and progressive loss of consciousness.	
- Class IA antiarrhythmic agents (quinidine, hydroquinidine, disopyramide); - Class III antiarrhythmic agents (amiodarone, dofetilide, ibutilide, bretylium, sotalol); - Some neuroleptics (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine), - Benzamides (amisulpride, sulpiride, sultopride, tiapride), - Butyrophenones (droperidol, haloperidol), - Other neuroleptics (pimozide); - Other substances such as bepridil, cisapride, diphemanil, IV erythromycin, halofantrine, mizolastine, moxifloxacin, pentamidine, sparfloxacin, IV vincamine, methadone, astemizole, terfenadine.	C	Torsades de pointe caused by excessive hypokalemia	Perindopril / indapamide should not be administered with medicinal products that induce torsade de pointes (see CONTRAINDICATIONS).
Sympathomimetics		Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.	Use with caution when ARCOSYL® PLUS LD / ARCOSYL® PLUS is co-administered with sympathomimetics.

Table 2 - Established or potential concomitant drug-drug interactions

Proper name	Ref	Effect	Clinical Comment
Skeletal muscle relaxants, including baclofen		Potentiation of antihypertensive effect.	Hydrate the patient, monitor blood pressure and renal function, and adapt the dose of the antihypertensive if necessary.
Corticosteroids		Reduction in antihypertensive effect (salt and water retention due to corticosteroids).	
Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids or procainamide		Concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia.	Monitor periodically white blood cell counts and instruct patients to report any sign of infection (e.g. sore throat, fever) (see WARNINGS AND PRECAUTIONS, Hematologic, Neutropenia / Agranulocytosis / Thrombocytopenia / Anaemia and Monitoring and Laboratory Tests, Hematological Monitoring).
Anesthetic and analgesic drugs		ACE inhibitors may enhance the hypotensive effects of certain anesthetic and analgesic drugs. In patients undergoing major surgery or during anesthesia with agents that produce hypotension, perindopril may block the angiotensin II formation that could otherwise occur secondary to compensatory renin release.	The treatment should be discontinued 1 day prior to the surgery. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion (see WARNINGS AND PRECAUTIONS, Peri-Operative Considerations).
Potassium-lowering drugs : amphotericin B (IV route), glucocorticoids and mineralocorticoids, ACTH (tetracosactide), stimulant laxatives		There is an increased risk of low potassium levels (additive effect).	Monitor-potassium levels, and correct if necessary; particular consideration is required in cases of treatment with cardiac glycosides. Non-stimulant laxatives should be used.
Antihyperglycemic drugs, including metformin		There is an increased risk of metformin-induced lactic acidosis caused by possible functional renal failure associated with diuretics and in particular with loop diuretics.	Do not use metformin when plasma creatinine levels are: > 15 mg/l (135 µmol/l) in men and > 12 mg/l (110 µmol/l) in women.
Iodinated contrast media		In cases of dehydration caused by diuretics, there is an increased risk of acute renal failure, particularly when large doses of iodinated contrast media are used.	Rehydration should be carried out before the iodinated compound is administered.
Calcium (salts)		There is a risk of hypercalcemia due to the reduced urinary elimination of calcium.	
Ciclosporin, tacrolimus		There is a risk of increased plasma creatinine levels with no change in circulating levels of ciclosporin, even in the absence of sodium and water depletion.	

Table 2 - Established or potential concomitant drug-drug interactions

Proper name	Ref	Effect	Clinical Comment
Citalopram		There is an increased risk of hyponatremia.	

Legend: C= Case Study; CT= Clinical Trial; T= Theoretical

Drug-Food Interactions

The presence of food in the gastrointestinal tract does not affect the rate or extent of perindopril absorption. However the extent of biotransformation of perindopril to perindoprilat is reduced resulting in a decrease of perindoprilat bioavailability by 35%. Therefore it is recommended that ARCOSYL® PLUS LD/ ARCOSYL® PLUS be taken before a meal.

Drug-Herb interactions

Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions

Interactions with laboratory products/ methods have not been established.

Drug-Lifestyle Interactions

Lifestyle interactions have not been established.

DOSAGE AND ADMINISTRATION

Dosing considerations

Dosage of ARCOSYL® PLUS LD/ ARCOSYL® PLUS (perindopril arginine/ indapamide) must be individualized and adjustment is required in the elderly, and in case of renal impairment.

ARCOSYL® PLUS is not for initial therapy and the dose should be determined by titration of the individual components.

Recommended Dose and Dosage Adjustment

Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation and salt restriction. The dosage of other antihypertensive agents being used with ARCOSYL® PLUS LD/ ARCOSYL® PLUS may need to be adjusted. The presence of food in the gastrointestinal tract reduces the bioavailability of perindoprilat.

- **Administration**

ARCOSYL® PLUS LD/ ARCOSYL® PLUS should be taken once daily, preferably in the morning before a meal (see DRUG INTERACTIONS-Drug-Food Interactions).

ARCOSYL® PLUS LD: 1 tablet per day as a single dose. In case of uncontrolled blood pressure the dose may be increased to 2 tablets of ARCOSYL® PLUS LD as a single dose or 1 tablet of ARCOSYL® PLUS (5mg/ 1.25mg).

ARCOSYL® PLUS: Once the patient has been successfully titrated with the individual components, 1 tablet per day of ARCOSYL® PLUS (5 mg/1.25 mg) or ARCOSYL® PLUS (10 mg/2.5 mg) may be substituted if the titrated doses and dosing schedule can be achieved by the fixed combination (see INDICATIONS AND CLINICAL USE and WARNINGS AND PRECAUTIONS).

- **The elderly**

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

- **Renal impairment**

The use of ARCOSYL® PLUS LD/ ARCOSYL® PLUS is contraindicated in patients with severe renal impairment (GFR < 30 ml/min/1.73m^2) (see CONTRAINDICATIONS).

ARCOSYL® PLUS (10 mg/ 2.5 mg) is contraindicated in patients with moderate renal impairment (GFR = 30-59 ml/min/1.73m^2) (see CONTRAINDICATIONS). Treatment with ARCOSYL® PLUS LD / ARCOSYL® PLUS (5 mg/ 1.25 mg) should start with the adequate dosage of the combination of the individual components. Caution should be exercised especially in the elderly patients as greater sensitivity in the elderly cannot be ruled out.

In patients with GFR ≥ 60 ml/min/1.73m^2, no dose modification is required. Usual medical follow-up will include frequent monitoring of creatinine and potassium levels.

Missed Dose

If a dose is missed, a double dose should not be taken; the patient should just carry on with the next dose at the normal time.

OVERDOSAGE

The most likely adverse event in case of ARCOSYL® PLUS LD/ ARCOSYL® PLUS overdose is hypotension with nausea, vomiting, cramps, dizziness, sleepiness, mental confusion, polyuria or oliguria which may progress to anuria. Electrolytes and water disturbances may occur.

The first measure is to rapidly eliminate ingested ARCOSYL® PLUS LD/ ARCOSYL® PLUS by gastric lavage and/or administration of activated charcoal. Fluid and electrolyte balance should then be restored.

If marked hypotension is produced, place the patient in a supine position with the head lower than the rest of the body. If necessary give an IV infusion of 0.9% sodium chloride, or use any other method of volume expansion.

Perindoprilat, the active form of perindopril, can be dialysed (see ACTIONS AND CLINICAL PHARMACOLOGY - Pharmacokinetics).

FOR MANAGEMENT OF A SUSPECTED DRUG OVERDOSE, CONTACT YOUR REGIONAL POISON CONTROL CENTRE.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

ARCOSYL® PLUS LD/ ARCOSYL® PLUS (perindopril arginine/ indapamide) are a combination of perindopril arginine, an angiotensin converting enzyme (ACE) inhibitor, and indapamide, a chlorosulphamoyl diuretic.

In ARCOSYL® PLUS LD (2.5 mg/ 0.625 mg), the ACE inhibitor component is half the usual dose used for monotherapy and the diuretic component is 4x lower than the highest dose recommended for monotherapy.

In ARCOSYL® PLUS (5 mg/ 1.25 mg), the ACE inhibitor component is the usual dose used for monotherapy and the diuretic component is half the highest dose recommended for monotherapy.

In ARCOSYL® PLUS (10 mg/ 2.5 mg), the ACE inhibitor and the diuretic components are at the highest doses recommended for monotherapy.

The pharmacological properties are derived from those of each of the components taken separately, in addition to those due to the additive synergistic action of the two products when combined.

ARCOSYL® PLUS LD/ ARCOSYL® PLUS exert a dose-dependent antihypertensive effect on diastolic and systolic arterial pressure whilst supine or standing in hypertensive patients regardless of age. This antihypertensive effect lasts for 24 hours. The reduction in blood pressure (BP) is obtained in < 1 month without tachyphylaxis; stopping treatment has no rebound effects. During clinical trials, the concomitant administration of perindopril and indapamide produced synergistic antihypertensive effects compared to each of the products administered alone.

Perindopril arginine

Perindopril is a nonsulphydryl ACE inhibitor used in the treatment of hypertension. Following oral administration, perindopril is rapidly hydrolysed to perindoprilat, its principal active metabolite.

ACE catalyses the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE

activity leads to decreased levels of angiotensin II, thereby resulting in decreased vasoconstriction and decreased aldosterone secretion. The latter change may result in a small increase in serum potassium (see WARNINGS AND PRECAUTIONS). Decreased levels of angiotensin II and the accompanying lack of negative feedback on renal renin secretion results in increases in plasma renin activity.

Perindopril administration may interfere with the degradation of the vasopressor peptide bradykinin. It is not known whether this effect contributes to the therapeutic activity of perindopril.

The mechanism through which perindopril lowers BP appears to result primarily from suppression of the RAAS.

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 diluting 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.

Pharmacodynamics

In most patients with mild to moderate essential hypertension, administration of 5-10 mg daily of perindopril results in a reduction of both supine and standing BP with little or no effect on heart rate. Antihypertensive activity commences within 1 hour with peak effects usually achieved by 4-6 hours after dosing. At recommended doses given once daily, antihypertensive effects persist over 24 hours. The BP reductions observed at trough plasma concentration were 75-100% of peak effects. When 1x and 2x daily dosing were compared, the 2x daily regimen was slightly superior, but by no more than about 0.5-1.0 mmHg. Abrupt withdrawal of perindopril has not been associated with a rapid increase in BP.

In studies carried out in patients with mild to moderate essential hypertension, the reduction in BP was accompanied by a reduction in peripheral resistance with no change in glomerular filtration rate. When perindopril is given together with thiazide-type diuretics, the antihypertensive effects are additive. In uncontrolled studies in patients with insulin-dependent diabetes, long term use of perindopril had no effect on urinary protein excretion.

Pharmacokinetics

The co-administration of perindopril and indapamide in healthy volunteers and hypertensive patients did not change their pharmacokinetic properties compared to their separate administration.

The bioavailabilities of perindopril erbumine and indapamide from a single dose administration of perindopril erbumine/ indapamide (4mg/ 1.25mg) fixed dose combination tablets or single dose concomitant administration of perindopril erbumine 4 mg tablets and indapamide 1.25 mg tablets were comparable under fasting conditions.

After repeated administration in elderly patients (69-97 years of age) and in patients with various degrees of renal failure, AUC of both indapamide and perindoprilat increased with renal failure, whereas C_{max} and AUC of indapamide only increased with age (1.5 x-2 x). The AUC ratio between indapamide and perindoprilat was not significantly affected by age and by creatinine clearance >30 mL/min.

Perindopril arginine

Absorption
After oral administration, perindopril is rapidly absorbed with peak plasma concentrations occurring at about 1 hour, with a bioavailability of 24%.

Following absorption, perindopril is converted into perindoprilat, its active metabolite, with a mean bioavailability of 25%. The peak plasma concentration of perindoprilat reached in about 4 hours after oral administration of perindopril.

The presence of food in the gastrointestinal tract does not affect the rate or extent of perindopril absorption after oral administration of perindopril. However the extent of biotransformation of perindopril to perindoprilat is reduced resulting in a decrease of perindoprilat bioavailability by 35%. Therefore it is recommended that ARCOSYL® PLUS LD/ ARCOSYL® PLUS be taken before a meal.

Distribution
Plasma protein binding of perindoprilat is low (10-35%), and concentration dependent due to the saturable binding of perindoprilat to the circulating ACE. The volume of distribution is approximately 0.5 L/kg for unbound perindoprilat.

Metabolism
Perindopril is extensively metabolised following oral administration, with only 4-12% of the dose recovered unchanged in the urine. Six metabolites have been identified. They include perindoprilat, the active form, and 5 others that do not possess appreciable therapeutic activity. These are comprised of perindopril glucuronide, perindoprilat glucuronide, a perindopril lactam, and 2 perindoprilat lactams. The 2 main circulating metabolites of perindopril are perindoprilat and perindoprilat glucuronide.

Two different pathways identified and quantified for the perindoprilat formation are the pre-systemic (first pass effect) and the systemic hydrolysis of perindopril. Perindopril is indeed sensitive to a pre-systemic first-past effect, accounting for 63% of the perindoprilat formation. The systemic hydrolysis of perindopril into perindoprilat accounts for the remaining 37%.

Excretion
The clearance of perindoprilat and other metabolites is primarily by the renal pathway. The systemic clearance of perindopril (367 mL/min) can be split into 39% leading to perindoprilat formation and 61% to renal excretion or other biotransformations. The terminal plasma half-life of perindopril is very short (1.2h), thus leading to no accumulation with a 1x daily oral dosing regimen. The terminal plasma half-life of unbound perindoprilat is about 17 hours resulting in a steady-state within 3 days.

Indapamide

Absorption
Indapamide is rapidly and completely absorbed after oral administration.

Distribution
Peak blood levels are obtained after 1-2 hours. Indapamide is distributed in the erythrocytes and is 79% bound to plasma proteins and to erythrocytes. It is taken up by the vascular wall in smooth vascular muscle according to its high lipid solubility.

Metabolism
Indapamide is metabolized to a marked degree, with approximately 5% of the total dose being recovered as unchanged drug in the urine within 48 hours after administration.

Excretion
Seventy per cent of a single oral dose of indapamide is eliminated by the kidneys and 23% is excreted in feces. The decrease in plasma concentrations of indapamide is biphasic with a terminal half-life between 14 and 25 hours.

Special Populations and Conditions

Pediatrics
The safety and effectiveness of ARCOSYL® PLUS LD/ ARCOSYL® PLUS in children have not been established. Therefore, its use in this age group, is not recommended.

Geriatrics (>65 years of age)
In a pharmacokinetic study with single dose administration, mean peak plasma concentrations of perindoprilat were significantly higher in elderly healthy volunteers (32.5 ng/mL) than in younger volunteers (13.5 ng/mL) due to both higher bioavailability and reduced renal clearance in the elderly group.

Single and multiple dose pharmacokinetics of perindopril were evaluated in a study of elderly hypertensive patients (72-91 years of age), C_{max} and AUC were found to be approximately 2x higher than in healthy younger subjects. The higher concentrations of perindoprilat observed in these patients were reflected by greater ACE inhibition (see WARNINGS AND PRECAUTIONS – Geriatrics, and DOSAGE AND ADMINISTRATION – The elderly).

Gender
The effectiveness of ARCOSYL® PLUS LD/ ARCOSYL® PLUS was not influenced by gender.

Race
The blood pressure lowering effects of ACE inhibitors are generally lower in black patients than in non-black patients.

Hepatic insufficiency
The bioavailability of perindoprilat was increased in patients with impaired hepatic function. Plasma concentrations in patients with hepatic impairment were about 50% higher than those observed in healthy subjects or hypertensive patients with normal liver function.

ARCOSYL® PLUS LD/ ARCOSYL® PLUS are contraindicated in patients with severe hepatic impairment.

Renal insufficiency
In patients with renal insufficiency, perindoprilat AUC increases with decreasing renal function. At GFR = 30-80 ml/min/1.73m^2, AUC is about 2x that at 100 ml/min/1.73m^2. When GFR drops <30 ml/min/1.73m^2, AUC increases more markedly.

In patients with severe renal impairment (GFR <30 ml/min/1.73m^2), ARCOSYL® PLUS LD and ARCOSYL® PLUS are contraindicated (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

ARCOSYL® PLUS (10 mg/ 2.5 mg) is contraindicated in patients with moderate renal impairment (GFR = 30-59 ml/min/1.73m^2), (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION). Treatment with ARCOSYL® PLUS LD/ ARCOSYL® PLUS (5 mg/ 1.25 mg) should start with the adequate dosage of the combination of the individual components. Caution should be exercised especially in the elderly patients as greater sensitivity in the elderly cannot be ruled out (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

In patients with ≥ 60 ml/min/1.73m^2, no dose modification is required (see DOSAGE AND ADMINISTRATION). Usual medical follow-up will include frequent monitoring of creatinine and potassium levels.

Perindopril, and its active metabolite perindoprilat, are dialysable. In a limited number of patients studied, perindopril hemodialysis clearance ranged from 41.7-76.7 ml/min (mean 52.0 ml/min). Perindoprilat hemodialysis clearance ranged from 37.4-91.0 ml/min (mean 67.2 ml/min). (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Heart Failure
Patients with heart failure have reduced perindoprilat clearance, which may result in a dose interval AUC that is increased up to 40%. Therefore, the initial dosage of perindopril should be reduced.

Genetic polymorphism
Pharmacokinetics differences due to genetic polymorphism have not been studied.

STORAGE AND STABILITY

Store at room temperature (15°C-30°C).

SPECIAL HANDLING INSTRUCTIONS

No special requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage form

ARCOSYL® PLUS LD (perindopril arginine/ indapamide) film-coated tablets:
Each white, rod-shaped film-coated tablet with an embossed line on both faces contains:
- 2.5 mg of perindopril arginine
- 0.625 mg of indapamide.

ARCOSYL® PLUS (perindopril arginine/ indapamide) film-coated tablets:
Each white, rod-shaped film-coated tablet contains:
- 5 mg of perindopril arginine
- 1.25 mg of indapamide.

ARCOSYL® PLUS (perindopril arginine/ indapamide) film-coated tablets:
Each white, round film-coated tablet contains:
- 10 mg of perindopril arginine
- 2.5 mg of indapamide.

Composition

In addition to the active ingredients, perindopril arginine and indapamide, each tablet contains the following non medicinal ingredients: Glycerol, Hypromellose, Lactose monohydrate, Macrogol 6000, Magnesium stearate, Maltodextrin, Silica colloidal anhydrous, Sodium starch glycolate**,** Titanium dioxide.

Packaging

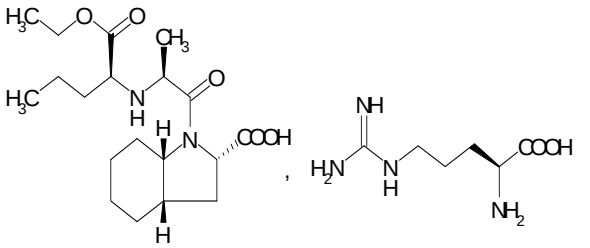
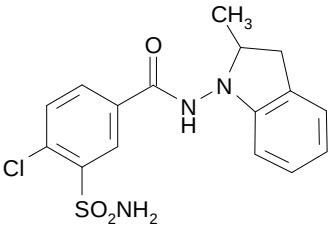
ARCOSYL® PLUS LD/ ARCOSYL® PLUS are available in polypropylene tube equipped with a low density polyethylene flow reducer and a low density polyethylene opaque stopper containing a desiccant gel.

The tablets are available in containers of 14, 20, 28, 30, 50 or 100 tablets.
Not all pack sizes may be marketed.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

	Perindopril arginine	**Indapamide**
Proper name:	Perindopril (INN) Perindopril arginine (INNM)	Indapamide
Chemical name:	L-arginine (2S, 3aS, 7aS) -1 - [(2S) - 2-[[(1S) - 1 - ethoxycarbonyl)butyl] amino] propanoyl] octahydro-1H-indole-2-carboxylate or as a synonym: (2S, 3aS, 7aS) -1 - [(S) - N - [(S) - 1 - ethoxycarbonyl)butyl] alanyl] octahydro - 1H-indole-2-carboxylic acid, arginine salt	Chloro-4-N-(methyl-2-indolinyl-1)-sulfamoyl-3 benzamide
Molecular formula:	$C_{19}H_{32}N_2O_5$, $C_6H_{14}N_4O_2$	$C_{16}H_{16}ClN_3O_3S$
Molecular weight:	368.47 (perindopril) / 542.7 (perindopril arginine)	365.8
Structural formula:		
Physicochemical properties:	Perindopril arginine is a white to almost white powder, freely soluble in water and slightly insoluble in organic solvents. The pH in aqueous solution (10 mg/mL) is 7.5. The pKa value for the NH^{2+}/NH pair is 5.66, and 3.50 for the COOH/COO^- pair.	Indapamide is a white, crystalline, lipophilic powder soluble in methanol, ethanol, acetic acid and ethyl acetate, very slightly soluble in ether, chloroform and benzene, and practically insoluble in water.

CLINICAL TRIALS

ARCOSYL® PLUS LD/ ARCOSYL® PLUS

Comparative Bioavailability Studies

The bioavailabilities of the 5 mg perindopril arginine salt/ 1.25 mg indapamide formulation (S 6590) and the 4 mg perindopril erbumine salt/ 1.25 mg indapamide formulation (S 5590) were compared following a single oral administration of one tablet of either S 6590 or S 5590 in 34 healthy male and female volunteers. The trial was performed as an open randomised two-way cross-over study with a 2-week wash-out between the two periods.

Table 3- Summary of patient demographics for comparative bioavailability study

Study #	Trial Design	Dosage, Route of Administration and Duration	Study subjects (n=number)	Mean Age	Mean Body Mass Index (BMI)	Gender
CL1-06590-001-FRA	open-labelled randomised two-period cross-over study	S 6590: Perindopril arginine salt 5mg /indapamide 1.25 mg administered as 1 tablet S 5590: Perindopril erbumine salt 4mg / indapamide 1.25 mg administered as 1 tablet. Two single doses with a 2-week wash-out period between each administration.	Caucasian healthy volunteers n=34	24.4 ± 3.5 years	21.5 ± 2.3 kg/m².	18 female 16 male

Table 4 - Summary table of the comparative bioavailability data

Perindopril
Single oral administration of 1 tablet of Perindopril arginine 5 mg / Indapamide 1.25 mg and 1 tablet of Perindopril erbumine 4 mg / Indapamide 1.25 mg
from measured data
Geometric Mean Arithmetic Mean (CV%)

Parameter (unit)	Test*	Reference&	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/ml)	37.6 38.9 (26.7%)	36.8 38.3 (29.6%)	102 %	98 % - 107 %
AUC_I (ng.h/ml)	38.3 39.5 (26.3%)	37.5 39.0 (28.9%)	102 %	98 % - 106 %
C_{max} (ng/ml)	30.7 32.6 (35.9%)	28.9 30.6 (33.5%)	106 %	97 % - 116 %
T_{max} (h) #	0.75 (0.50 – 2.0)	0.75 (0.50 – 1.5)		
$T_{1/2}$ (h) ##	0.67 (24.2%)	0.65 (15.6%)		

**: Perindopril arginine 5 mg / Indapamide 1.25 mg (S 6590)*
&: Perindopril erbumine 4 mg / Indapamide 1.25 mg tablets (S 5590)
#: expressed as median (range) *##: expressed as arithmetic mean (CV%)*

Table 5 - Summary table of the comparative bioavailability data

Indapamide Single oral administration of 1 tablet of Perindopril arginine 5 mg/ Indapamide 1.25 mg and 1 tablet of Perindopril erbumine 4 mg/ Indapamide 1.25 mg from measured data Geometric Mean Arithmetic Mean (CV%)				
Parameter (unit)	**Test***	**Reference&**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng.h/ml)	258.7 266.2 (23.9%)	256.9 265.8 (26.0%)	101 %	97% - 104%
AUC_I (ng.h/ml)	280.1 287.4 (22.4%)	277.6 286.4 (24.8%)	101 %	98% - 104%
C_{max} (ng/ml)	15.9 16.4 (23.8%)	15.7 16.3 (25.9%)	101 %	96%-107%
T_{max} (h) #	1.5 (0.75-6.0)	3.0 (1.0-6.0)		
$T_{1/2}$ (h) ##	14.1 (14.7%)	14.2 (16.2%)		

**: Perindopril arginine 5 mg / Indapamide 1.25 mg (S 6590)*
&: Perindopril erbumine 4 mg / Indapamide 1.25 mg tablets (S 5590)
#: expressed as median (range)
##: expressed as arithmetic mean (CV%)

ARCOSYL® PLUS LD

The clinical trials described in this subsection were performed using the perindopril erbumine/ indapamide fixed dose combination (COVERSYL® PLUS LD (2 mg/ 0.625 mg)).

Study demographics and trial design

The efficacy of perindopril erbumine 2 mg/ indapamide 0.625 mg in mild to moderate hypertension was based on 3 pivotal double blind short-term (3 months) studies either against placebo (CL3-05590-018 and CL3-05590-007/ 3 months, or an active comparator (atenolol) (CL3-05590-009).

Table 6 – Summary of patient demographics for pivotal clinical trials in mild to moderate hypertension

Study	Trial design	Dosage, Route of Administration and Duration	# Study subjects randomized	Mean age (Range)	Gender (%) M/F
Efficacy placebo-controlled trials					
CL3-05590-018	Multicenter, double-blind, randomized, placebo-controlled, six way study preceded by a 4-week single-blind placebo run-in period	Per 2 / Ind 0.625 Placebo Per 2 Ind 0.625 Per 4 Ind 1.5 SR Oral route 12 weeks	1748	55.7 (18-79)	48.9/51.1

Table 6 – Summary of patient demographics for pivotal clinical trials in mild to moderate hypertension

Study	Trial design	Dosage, Route of Administration and Duration	# Study subjects randomized	Mean age (Range)	Gender (%) M/F
CL3-05590-007 / 3 months	Multicenter, double-blind, randomized, placebo-controlled, two way study preceded by a 4-week single-blind placebo run-in period	Weeks 0-4: Placebo or Per 2 / Ind 0.625 (1 tablet) Weeks 4-12: Placebo or Per 2 / Ind 0.625 (2 tablets) Oral route 12 weeks	383	72.4 (64-85)	40.7/59.3
Efficacy controlled trial *versus* reference drugs					
CL3-05590-009	Multicenter, double-blind, randomized, controlled, parallel group, two way study preceded by a 4-week single-blind placebo run-in period	Per 2 / Ind 0.625 Atenolol 50 Oral route 12 weeks	446	55.8 (24-75)	47.5/52.5

Per: Perindopril ; Ind: Indapamide ; SR: Slow Release

Efficacy results

Table 7 — Efficacy results of pivotal placebo-controlled clinical studies in mild to moderate hypertension

Endpoints	Associated value for Per / Ind (mmHg)	Associated value for placebo (mmHg)	p-value
CL3-05590-018			
Change from baseline (at trough)	Per2/Ind0.625 (n=386)	Placebo (n=386)	
supine DBP	-10.8 ± 7.9	-5.6 ± 9.1	< 0.001
supine SBP	-15.2 ± 12.9	-6.7 ± 13.9	< 0.001
Responders*	63.0%	37.3%	< 0.001
Difference between Per2 / Ind0.625 and Placebo after 12 weeks of treatment			
supine DBP	-5.2 mmHg		< 0.001
supine SBP	-8.5 mmHg		< 0.001
CL3-05590-007			
Change from baseline (at trough)	Per/Ind (n=193)	Placebo (n=190)	
supine DBP	-13.2 ± 8.0	-7.3 ± 9.0	< 0.0001
supine SBP	-22.5 ± 13.9	-12.3 ± 15.2	< 0.0001
Responders**	81.3%	48.9%	< 0.0001
Difference between Per2/Ind0.625 and Placebo after 12 weeks of treatment			
supine DBP	-5.9 mmHg		< 0.0001
supine SBP	-10.2 mmHg		< 0.0001

In mmHg; Per: Perindopril ; Ind: Indapamide ; DBP: Diastolic Blood Pressure ; SBP: Systolic Blood Pressure;
** sSBP < 140 mmHg and sDBP < 90 mmHg and/or decrease in sSBP ≥ 20 mmHg and/or decrease in sDBP ≥ 10 mmHg;*
*** (decrease in sDBP ≥ 10 mmHg and/or sDBP ≤ 90 mmHg if systole-diastolic hypertension) and (decrease in sSBP ≥ 20 mmHg and/or sSBP ≤ 150 mmHg if isolated diastolic hypertension)*

Table 8 – Efficacy results of pivotal active-controlled clinical studies in mild to moderate hypertension

Endpoints	Associated value for Per 2 / Ind 0.625	Associated value for Atenolol 50 mg	p-value**
CL3-05590-009			
Change from baseline (at trough)	Per2 / Ind0.625 (n=222)	Atenolol 50 (n=224)	
supine DBP	-15.3 ± 7.7	-16.0 ± 8.2	< 0.001
supine SBP	-20.4 ± 12.3	-20.1 ± 14.0	< 0.001
Responders*	82%	87%	-
Difference between Per2/Ind0.625 and Atenolol after 12 weeks of treatment			
supine DBP	0.8 mmHg		-
supine SBP	-0.4 mmHg		-

In mmHg; Per: Perindopril ; Ind: Indapamide ; DBP: Diastolic Blood Pressure ; SBP: Systolic Blood Pressure;
** sDBP ≤ 90 mmHg and/or decrease in sDBP ≥ 10 mmHg ; ** p-value related to the equivalence between Per2/Ind0.625 and Atenolol 50 mg: two sided tests procedure*

ARCOSYL® PLUS (5 mg/ 1.25 mg)

The clinical trials described in this subsection were performed using the perindopril erbumine / indapamide fixed dose combination (COVERSYL® PLUS (4mg / 1.25mg)).

Study demographics and trial design

The efficacy of perindopril erbumine 4 mg/ indapamide 1.25 mg in mild to moderate hypertension was based on 4 pivotal double-blind short-term studies either against placebo (CL3-05590-007/ 3 months) or an active comparator (CL3-05590-003, CL3-05590-004 / 2 months and CL3-05590-008).

Table 9 – Summary of patient demographics for pivotal clinical trials in mild to moderate hypertension

Study	Trial design	Dosage, Route of Administration and Duration	# Study subjects randomized	Mean age (Range)	Gender (%) M/F
Efficacy placebo-controlled trials					
CL3-05590-007 / 3 months	Multicenter, randomized, placebo-controlled, two way study preceded by a 4-week single-blind placebo run-in period	Weeks 0-4: Placebo or Per 2 / Ind 0.625 (1 tablet) Weeks 4-12: Placebo or Per 2 / Ind 0.625 (2 tablets) Oral route 12 weeks	383	72.4 (64-85)	40.7/59.3
Efficacy controlled trials versus reference drugs					
CL3-05590-003	Multicenter, double-blind, randomized, controlled, parallel group, three way study preceded by a 4-week single-blind placebo run-in period	Per 4 / Ind 1.25 Per 4 Ind 1.25 Oral route 12 weeks	1633	53.7 (19-78)	50.3/49.7

Table 9 – Summary of patient demographics for pivotal clinical trials in mild to moderate hypertension

Study	Trial design	Dosage, Route of Administration and Duration	# Study subjects randomized	Mean age (Range)	Gender (%) M/F
CL3-05590-004 / 2 months	Multicenter, double-blind, randomized, controlled, three way study preceded by a 4-week single-blind placebo run-in period	Per 4 / Ind 1.25 Captopril 50 / HCT 25 Enalapril 20 / HCT 12.5 Oral route 8 weeks	527	54.5 (21-75)	53.5/46.5
CL3-05590-008	Multicenter, double-blind, randomized, controlled, parallel group, three way study preceded by a 3-week single-blind placebo run-in period (wk –7 to wk –4) and a 4-week single-blind treatment with Per 4mg (wk –4 to wk 0)	Per 4 / Ind 1.25 Per 4 Per 8 Oral route 4 weeks	515	54.3 (19-77)	52.4/47.6

Per: Perindopril ; Ind: Indapamide ; HCT: Hydrochlorothiazide ; SR: Slow Release ; wk: week ; m: months

Efficacy results

Table 10– Efficacy results of pivotal placebo-controlled clinical studies in mild to moderate hypertension

Endpoints	Associated value for Per / Ind	Associated value for placebo	p-value
CL3-05590-007			
Change from baseline (at trough)	Per/Ind (n=193)	Placebo (n=190)	
supine DBP	-13.2 ± 8.0	-7.3 ± 9.0	< 0.0001
supine SBP	-22.5 ± 13.9	-12.3 ± 15.2	< 0.0001
Responders*	81.3%	48.9%	< 0.0001
Difference between Per/Ind and Placebo after 12 weeks of treatment			
supine DBP		-5.9 mmHg	< 0.0001
supine SBP		-10.2 mmHg	< 0.0001

Per: Perindopril ; Ind: Indapamide ; DBP: Diastolic Blood Pressure ; SBP: Systolic Blood Pressure;
** (decrease in sDBP ≥ 10 mmHg and/or sDBP ≤ 90 mmHg if systole-diastolic hypertension) and (decrease in sSBP ≥ 20 mmHg and/or sSBP ≤ 150 mmHg if isolated diastolic hypertension)*

Table 11– Efficacy results of pivotal controlled clinical studies in mild to moderate hypertension

Endpoints	Associated value for Per / Ind	Associated value for active control		p-value Per / Ind versus:	
CL3-05590-003					
Change from baseline (at trough)	**Per 4 / Ind 1.25**	**Per 4**	**Ind 1.25**	**Per 4**	**Ind 1.25**
supine DBP (whole population)	-13.4 ± 8.6 (n=542)	-11.2 ± 9.0 (n=551)	-11.5 ± 9.0 (n=540)	< 0.001	< 0.001
supine DBP (elderly (> 65 years)	-14.7 ± 8.5 (n=92)	-10.7 ± 8.4 (n=96)	-11.9 ± 9.0 (n=85)	< 0.001	0.020
supine SBP	-19.8 ± 14.7 (n=542)	-14.1 ± 14.4 (n=551)	-15.8 ± 14.4 (n=540)	< 0.001	< 0.001
Responders*	74.5% (n=542)	65.2% (n=551)	64.8% (n=540)	< 0.001	< 0.001
Difference between Per4/Ind1.25 and Active Controls after 12 weeks of treatment					
		Per 4	**Ind 1.25**	**Per 4**	**Ind 1.25**
supine DBP (whole population)		-2.2 mmHg	-2.0 mmHg	< 0.001	< 0.001
supine DBP (elderly (> 65 years)		-4.0 mmHg	-2.7 mmHg	< 0.001	0.020
supine SBP		-5.6 mmHg	-4.0 mmHg	< 0.001	< 0.001
CL3-05590-004					
Change from baseline (at trough)	**Per 4 / Ind 1.25** (n=175)	**Cap / HCT** (n=175)	**Ena / HCT** (n=177)	**Cap / HCT**	**Ena / HCT**
supine DBP	-13.1 ± 7.8	-13.4 ± 8.0	-14.2 ± 9.4	< 0.001**	0.001**
supine SBP	-18.7 ± 12.5	-19.4 ± 13.3	-21.1 ± 15.4	< 0.001**	< 0.001**
Responders*	73.0%	75.0%	80.0%	-	-
Difference between Per4/ Ind1.25 and Active Controls after 8 weeks of treatment					
		Cap / HCT	**Ena / HCT**	**Cap / HCT**	**Ena / HCT**
supine DBP		0.3 mmHg	1.1 mmHg	< 0.001**	0.001**
supine SBP		0.7 mmHg	2.4 mmHg	< 0.001**	< 0.001**
CL3-05590-008					
Change from baseline	**Per 4 / Ind 1.25** (n=173)	**Per 4** (n=172)	**Per 8** (n=170)	**Per 4**	**Per 8**
supine DBP	-8.5 ± 8.2	-6.4 ± 7.5	-7.4 ± 7.8	0.008†	< 0.001††
supine SBP	-10.1 ± 12.0	-7.8 ± 11.0	-9.8 ± 12.3	0.035	< 0.001
Responders*	62.4%	55.2%	60.6%	0.106†††	-
Difference between Per4 / Ind1.25 and Active Controls after 4 weeks of treatment					
		Per 4	**Per 8**	**Per 4**	**Per 8**
supine DBP		-2.1 mmHg	-1.1 mmHg	0.008†	< 0.001††
supine SBP		-2.2 mmHg	-0.3 mmHg	0.035	< 0.001

*Per: Perindopril ; Ind: Indapamide ; Cap: Captopril ; Ena: Enalapril ; HCT: Hydrochlorothiazide ; DBP: Diastolic Blood Pressure ; SBP: Systolic Blood Pressure; * Δ sDBP ≥ 10 mmHg and/or sDBP ≤ 90 mmHg ;*

*** Research of equivalence in terms of the 90% confidence interval for the change on the difference between Per4/Ind1.25 and the active control;*

† *Research of superiority of Per4/Ind1.25 over Per 4: 95% confidence interval, one-sided Student t test ;*

†† *Research of equivalence between Per4/Ind1.25 and Per8: 90% confidence interval, two-sided tests procedure;*

††† *Research of superiority of Per4/Ind1.25 over Per4: one-sided Fischer exact test.*

ARCOSYL® PLUS (10 mg/ 2.5 mg)

The clinical trials described in this subsection were performed using the perindopril erbumine/ indapamide fixed dose combination (COVERSYL® PLUS HD (8 mg / 2.5 mg)).

Study demographics and trial design

The efficacy of perindopril erbumine 8 mg/ indapamide 2.5 mg in mild to moderate hypertension was based on 2 pivotal double-blind, active control, long-term studies (CL3-05590-011 and CL3-05590-005).

Table 12– Summary of patient demographics for pivotal clinical trials in mild to moderate hypertension

Study	Trial design	Dosage, Route of Administration and Duration	# Study subjects (randomized)	Mean age (Range)	Gender (%) (M/F)
CL3-05590-011	Phase III, randomised, double blind, multicenter, 2 parallel groups, controlled versus enalapril trial in hypertensive type 2 diabetic patients with albuminuria	Per2/Ind0.625 Per4/Ind1.25 (non-forced up titration) Per8/Ind2.5 (non-forced up titration) Oral 52 weeks	N=481 Per/Ind: n = 244 Ena: n =237 Maximal dosage Per8/Ind2.5: n = 72	Total: 59.1 (30-78) Per/Ind: 58.3 (30-78) Maximal dosage Per8/Ind2.5: 57.7 (30-72)	Total: 61.1/38.9 Per/Ind: 57.0/43.0 Maximal dosage Per8/Ind2.5: 66.7/33.3
CL3-05590-005	Phase III, randomised, double blind, multicenter, 2 parallel groups, controlled versus enalapril trial in hypertensive patients with LVH	Per2/Ind0.625 Per4/Ind1.25 (non-forced up titration) Per8/Ind2.5 (non-forced up titration) Oral 52 weeks	N=679 Per/Ind: n = 341 Ena: n=338 Maximal dosage Per8/Ind2.5: n = 65	Total: 55.5 (18-93) Per/Ind: 54.8 (18-93) Maximal dosage Per8/Ind2.5: 53.5 (37-70)	Total: 47.1/52.9 Per/Ind: 46.9/53.1 Maximal dosage Per8/Ind2.5: 55.4/44.6

Per: Perindopril erbumine; Ind: Indapamide; Ena: enalapril; LVH : Left Ventricular Hypertrophy

Efficacy results

Table 13– Efficacy results of pivotal clinical studies in mild to moderate hypertension

Endpoints	Associated value for Per 8 / Ind 2.5	p-value
CL3-05590-011 - Maximal Per8/Ind2.5 dose, n=69		
Change $WEnd_{Per8/Ind2.5}$ – W0		
DBP (mmHg)	-5.4 ± 9.1	p < 0.0001
SBP (mmHg)	-8.4 ± 16.9	p < 0.0001
Change $WEnd_{Per8/Ind2.5}$ – $WEnd_{Per4/Ind1.25}$		
DBP (mmHg)	-2.6 ± 8.1	p = 0.0088
SBP (mmHg)	-2.5 ± 13.8	p = 0.1427
BP normalised (last value under Per8 / Ind2.5)	17.4% (12/69)	NA
Responders (last value under Per8 / Ind2.5)	44.9% (31/69)	NA
CL3-05590-005 - Maximal Per8 / Ind2.5 dose, n=63		
Change $WEnd_{Per8/Ind2.5}$ – W0		
DBP (mmHg)	-9.7 ± 9.6	p < 0.0001
SBP (mmHg)	-27.7 ± 18.3	p < 0.0001
Change $WEnd_{Per8/Ind2.5}$ – $WEnd_{Per4/Ind1.25}$		
DBP (mmHg)	-8.1 ± 8.4	p < 0.0001
SBP (mmHg)	-16.3 ± 16.5	p < 0.0001
BP normalised (last value under Per8 / Ind2.5)	22.2% (14/63)	NA
Responders (last value under Per8 / Ind2.5)	68.3% (43/63)	NA

Per: Perindopril ; Ind: Indapamide ; DBP: Diastolic Blood Pressure ;SBP: Systolic Blood Pressure; NA: Not Available; W0: baseline

DETAILED PHARMACOLOGY

Perindopril arginine

In Vitro Studies

Perindopril was an inhibitor of angiotensin converting enzyme (ACE) in both plasma and tissue. Perindoprilat, the diacid form of perindopril, exhibited greater inhibition of ACE activity than perindopril (IC_{50}=2x10^{-9}M and 800x10^{-9}M, respectively). Perindoprilat and ramiprilat (the active diacid of ramipril) had a similar inhibitory potency against rat plasma converting enzyme (IC_{50} = 2-3x10^{-9}M). Both diacids were more active than enalaprilat or captopril (IC_{50} = 1-6x10^{-8}M).

In Vivo Studies

Following oral dosing of perindopril to normotensive (at a dose equivalent to 0.04- 1.23 mg/kg of perindopril arginine) or to hypertensive (at a dose equivalent to 0.37- 3.68 mg/kg of perindopril arginine) rats, plasma ACE inhibition was assessed *in vivo* by the decrease in pressor response to intravenous (IV) angiotensin I.

Orally administered to conscious dogs, perindopril produced a dose-dependent reduction (34% at a dose equivalent to 0.12 mg/kg of perindopril arginine, 60% at a dose equivalent to 0.37 mg/kg

of perindopril arginine, and 92% at a dose equivalent to 1.23 mg/kg of perindopril arginine) of angiotensin I (150 ng/kg IV perindopril at a dose equivalent to 184.34 ng/kg IV of perindopril arginine) pressor response, but had no effect on angiotensin II (100 ng/kg IV perindopril, at a dose equivalent to 122.89 ng/kg IV of perindopril arginine) response.

In normotensive rats, plasma ACE was maximally inhibited (≥ 90%) by perindopril (at a dose equivalent to 1.23, 5 or 10 mg/kg per os of perindopril arginine) 1 hour following administration, then returned to control levels 24 hours later. After 4 weeks of oral treatment (at a dose equivalent to 12.29 mg/kg of perindopril arginine) in stroke-prone spontaneously hypertensive rats, ACE inhibition was mostly demonstrated in kidney (96%), aorta (64%), heart (52%), lung (36%) and brain (26%). Perindopril orally administered at a dose equivalent to 1.23 mg/kg of perindopril arginine to sodium replete spontaneous hypertensive rats was more potent than enalapril (1 mg/kg) both in terms of intensity (91% of inhibition versus 64%, 4 hours after dosing) and duration of action (68% of inhibition versus 12%, 12 hours after dosing).

In human subjects, perindopril at single oral doses equivalent to 5-10 mg/day of perindopril arginine produced 80% inhibition of plasma ACE activity between 2 and 8 hours post-dose, with 40-60% inhibition persisting at 24 hours post-dose. Multiple oral doses of perindopril over 7 days (perindopril at a dose equivalent to 5-10 mg/day of perindopril arginine) confirmed the inhibitory effect on plasma ACE and showed that it produces corresponding decreases in angiotensin II with significant increases in plasma renin activity.

Indapamide

Anti-hypertensive Action

In normal animals, indapamide had no antihypertensive effect. In hypertensive animals, single oral doses of indapamide at doses of 1-10 mg/kg elicited antihypertensive activity as follows: In desoxycorticosterone acetate (DOCA)/ saline hypertensive rats with unilateral nephrectomy, a single dose of 10 mg/kg indapamide produced a maximal fall in systolic blood pressure (SBP) of 25 mmHg after 24 hours and the antihypertensive action lasted for 72 hours. Similar results were observed without nephrectomy. Higher doses up to 100 mg/kg produced only small increases in activity but BP reduction continued for > 4 days.

Following repeated oral administration of indapamide (1 mg/kg) or trichlormethiazide (3 mg/kg) to DOCA/ saline nephrectomized rats for 14 days, mean SBP fell more with indapamide (33 mmHg) than with trichlormethiazide (23 mmHg). One week after indapamide treatment, BP had only partially returned towards pre-treatment value.

In the renal hypertensive dog, indapamide 5 mg/kg per os produces a maximal reduction (37 mmHg) in SBP after 48 hours and an antihypertensive effect was still evident after 4 days.

Repeated administration of 0.5 mg/kg/day per os for 11 weeks prevented the onset of hypertension of DOCA/ saline hypertensive rats with unilateral nephrectomy, the effect was still apparent 5 weeks after interrupting treatment.

Hypertensive response induced by norepinephrine, tyramine or sympathetic stimulation were markedly reduced by indapamide (10 mg/kg per os) in amyelinated or DOCA/ saline hypertensive rats.

Indapamide (10^{-5} and 10^{-4}M) diminished vascular hyper-reactivity to epinephrine, norepinephrine and angiotensin in isolated organ preparations. Indapamide (10^{-6} g/mL) inhibited vascular smooth muscle cell contractility.

In renal hypertensive dogs, BP was reduced at a dose of 1 mg/kg IV and cardiac output showed an increase after 2 hours, and a slight decrease over 24 hours.

Action on the Kidney
Diuretic activity has been studied in rats and dogs. Parameters were modified differently depending on the dose: the natriuretic and chloruretic activity was observed after doses of 0.1-0.3 mg/kg per os or IV; while increased urinary output was seen at 1 mg/kg per os or IV; and significant increases in urinary potassium excretion were reported after doses of 3-10 mg/kg per os.

Indapamide did not alter glomerular filtration rate or renal haemodynamics in dogs, suggesting that it acts directly on renal tubules. Studies of positive and negative free water clearance suggested that diuresis may have resulted from inhibition of water, sodium, and chloride reabsorption in the proximal portion of the distal tubule of the nephron.

Perindopril / Indapamide

Anti-hypertensive Effects of Perindopril/ Indapamide
The antihypertensive effects of the combination of perindopril (76%) and indapamide (24%) was studied in normotensive rats (Wistar) and in rats with stable or developing hypertension, *i.e.* genetic (SHR) and mineralocorticoid (Dahl salt sensitive (DS)). The combination was administered orally at different doses between 0.3-6 mg/kg/day and for 1 day to 12 weeks. The studies showed that:

- at 1 mg/kg/day for 3 months, the combination induced a significant antihypertensive effect, with a mean decrease in SBP of 21% (24 hours after last administration);
- these effects were dose-related with averaged decreases of 17%, 28% and 47% after 6 weeks of treatment at doses of 0.3, 1 or 3 mg/kg/day, respectively;
- in DS rats, a 6 mg/kg/day dose normalized BP (-31%) while the corresponding doses of perindopril and indapamide administered separately had no or limited effect on BP.

TOXICOLOGY

Perindopril

The toxicological evaluation of perindopril is based on the overall well known safety profile of the erbumine salt of perindopril and was completed by some specific studies with the arginine salt: acute and repeated general toxicity studies, genotoxic studies and the qualification of process-related impurities.

The data collected during the toxicological evaluation demonstrate that the arginine salt of perindopril displays a similar toxicologic profile to that of perindopril erbumine.

Results for pivotal studies are provided hereafter, first for perindopril erbumine and then for the arginine salt.

Acute toxicity studies

Perindopril erbumine

The following LD_{50} are expressed in terms of perindopril erbumine salt. 1 mg of perindopril erbumine corresponds to 0.83 mg of free acid of perindopril and is equivalent to a dose of 1.23 mg perindopril arginine.

Single dose toxicity studies were carried out in the mouse and rat by oral and intravenous (IV) routes. The acute toxicity was low: the LD_{50} by the oral route was > 2500 mg/kg in the mouse and > 3000 mg/kg in the rat. Following IV administration, the LD_{50} was 323 mg/kg and 423 mg/kg in male and female rats, and 704 mg/kg and 679 mg/kg in male and female mice, respectively.

No mortality occurred during the oral studies carried out in the mouse and rat. Signs of toxicity observed in animals treated IV were convulsive symptoms and severe dyspnea in mice, increased activity in rats, and death by respiratory arrest occurring within minutes of the injection.

Perindopril arginine

The acute toxicity of perindopril arginine salt was investigated in Wistar rats and Swiss OF1 mice.

Table 14 – Acute Toxicity Studies with Perindopril Arginine

Species	Number of animal	Route of adminis-ration	Doses (mg perindopril free acid/kg)	Treatment duration	Major investigations	Conclusion
Swiss OF1 mice	6 per gender per group	Oral gavage	0 and 2000	Acute	-Mortality Clinical signs Bodyweights Gross observations Necropsy	No death occurred throughout the study No changes in appearance and behaviour were noted for dosed animals or for controls Mean bodyweights and mean bodyweight gains of dosed animals were similar to those of their respective controls No target organ identified macroscopically. The only gross anomaly was one whitish area (5 mm) on the left liver lobe of one male given 2000 mg free acid/kg. This change was considered to belong to the spontaneous background of laboratory mice of this strain and age.
Wistar rat	6 per gender per group	Oral gavage	0 and 2000	Acute	Mortality Clinical signs Bodyweights Gross observations Necropsy	No death occurred throughout the study Excess salivation was the only change in appearance and behaviour noted after dosing with arginine salt. It was observed for all rats within 30 min after dosing. Mean bodyweights and mean bodyweight gains of dosed animals were similar to those of their respective controls No gross change was noted in any of the control of the arginine salt dosed animals of the study. No target organs identified macroscopically.

Under the conditions of these studies, no mortality occurred up to the maximum recommended dose of 2000 mg perindopril free acid/kg, for males and females. No target organs were identified macroscopically.

Only post-dose excess salivation was noted for all arginine salt-dosed rats. No arginine salt-related changes in mean bodyweights and in mean bodyweight gains were noted.

Chronic Toxicity Studies

Perindopril erbumine

The following doses or concentrations are expressed in terms of perindopril erbumine salt. 1 mg of perindopril erbumine corresponds to 0.83 mg of free acid of perindopril and is equivalent to a dose of 1.23 mg perindopril arginine.

The chronic oral toxicity of perindopril was determined in the rat, dog and monkey during 3-18 months. The highest doses used were 30, 25 and 16 mg/kg/day in the rat, dog and monkey, respectively. The kidney was the organ most sensitive to perindopril. At high doses, perindopril induced osmotic nephrosis-type lesions and tubular dilatations. The reversibility of the renal lesions was demonstrated.

Perindopril arginine

The oral toxicity was studied in four-week study in Wistar Rats and Beagle Dogs.

Studies are tabulated hereafter.

Table 15 – Chronic Toxicity Studies

Species (+age at the beginning of treatment)	Number of animal	Route of adminis-tration	Doses (mg perindopril free acid/kg)	Treatment duration	Major investigations	Conclusion
Wistar rat (6 weeks)	10 per gender per main group + 6 /gender for toxicokinetic evaluation (D1 and D28)	Oral gavage	0 Arginine salt: 0.8 8 33 Erbumine salt: 8 33	Daily administration during 4 weeks	Mortality, Clinical signs Bodyweight and feed intake Water intake Ophthalmology Hematology Clinical chemistry Urinalysis Anatomic pathology (body weight at necropsy and organ weights) Gross observations Histomorphology Toxicokinetics	The overall picture of perindopril was broadly similar whatever the salt administered. Most of the salient findings, including increases of water intake and urine volumes, decreases in serum electrolyte concentrations Na^+ & Cl^-, lower heart weight, erosions/ulcerations in the glandular stomach mucosa, following the oral administration of perindopril arginine and erbumine salts were of similar or lower severity than those observed in the previous 6-week rat toxicology study conducted at the same dose levels with perindopril erbumine. They were considered as class-effects of ACE inhibitors, in agreement with the literature. In conclusion, under the conditions of the study, the arginine salt and erbumine salt had a similar safety profile.
Beagle dog (6 weeks)	3 per gender per group + 6 /gender for toxicokinetic evaluation (D1 and D28)	Oral gavage	0 Arginine salt: 0.83 4.17 20.87 Erbumine salt: 4.17 20.87	Daily administration during 4 weeks	Mortality, Clinical signs Bodyweight Feed intake Vital signs (rectal temperature, electrocardiography, quantitative and qualitative evaluations) Examination of faeces Ophthalmology Clinical pathology (haematology, clinical chemistry, urinalysis) Anatomic pathology (organ weights, gross observations, histomorphology) Toxicokinetics	Under the conditions of the study, there was no difference in the safety and toxicokinetic profile of perindopril arginine and erbumine salts.

The arginine salt of perindopril was well tolerated after repeated administration in rats and dogs and did not elicit unexpected toxicity in comparison with the known effects of the erbumine salt. The no observed adverse effect level (NOAEL) was set at 0.8 mg perindopril free acid/kg/day in rats, with minor serum electrolytes changes and decreased heart weight in females. These changes were related to the pharmacology of perindopril. Gastric lesions were seen at higher dosages. No overt toxicity was observed in dogs, and the NOAEL was set at 20.87 mg perindopril free acid/kg/day for beagle dog.

Carcinogenicity Studies

Carcinogenicity studies have not been conducted with perindopril arginine.

In two studies, $B_6C_3F_1$ mice and Fischer 344 rats were given an oral treatment of perindopril equivalent to a dose of 0.92, 2.5 and 9.21 mg/kg/day of perindopril arginine for 104 weeks. No evidence of carcinogenicity of perindopril was observed.

Genotoxicity Studies

Perindopril erbumine did not induce genetic mutation (AMES test and mouse lymphoma test), chromosomal mutation (*in vivo* and *in vitro* clastogenicity tests and micronuleus test) in prokaryotes and eukaryotes, or primary changes of yeast DNA (gene conversion test).

The genotoxic potential of perindopril arginine was investigated in a series of *in vitro* and *in vivo* tests tabulated below.

In vitro

Table 16 – Genotoxicity Studies with Perindopril Arginine- *in vitro*

Test	Concentration (mcg perindopril free acid/plate)	Conclusion
Detection of reverse mutation in histidine-requiring *Salmonella typhimurium* and tryptophan-requiring *Escherichia coli* (Ames test)		
Salmonella typhimurium (TA100, TA1535, TA1537 and TA98) and *Escherichia coli (WP2 (pKM101) and WP2 uvrA (pKM101)*	0 50 150 500 1500 5000 in the presence and absence of S9 mix	No significant, reproducible or concentration-related increase in the number of revertant colonies was seen at any tested concentrations of perindopril arginine, with and without metabolic activation by preincubation of direct plating assay with any strain. Under the conditions of the study, perindopril arginine salt was considered to be devoid of mutagenic potential.
Mutation of the thymidine kinase (tk) locus of mouse lymphoma assay on L5178Y cells (MLA)		
Mouse lymphoma cells L5178Y	0 112.5 225 450 900 1800 3685 in the presence and absence of S9	When tested up to 10mM, Perindopril arginine salt did not induce mutation at the tk locus of L5178Y mouse lymphoma cells in two independent experiments, in the absence and presence of S9. It was concluded that, under the conditions employed in this study, perindopril arginine salt is not mutagenic in this test system in the absence and presence of S9.
Induction of chromosome aberrations in cultured human peripheral blood lymphocytes		
Primary human lymphocytes from the pooled blood of three healthy male volunteers	1887 2358 3685 in the presence and absence of S9	It was concluded that perindopril arginine induced chromosome aberrations in cultured human peripheral blood lymphocytes. The effect was restricted to prolonged exposure in the absence of S9. Mitotic accumulation and the effects of the test article on chromosome morphology meant that following prolonged (20 hour) exposure, shortening of the chromosomes, mitotic accumulation and chromosomes aberrations were observed. In these instances, it was not possible to accurately assess toxicity at concentrations selected for chromosome aberration analysis, making interpretation of the biological significance of the data difficult to assess. It was considered that a meaningful selection of concentrations to be analysed for chromosome aberrations could not be made for this phase of the study.

In vivo

Table 17 – Genotoxicity Studies with Perindopril Arginine- *in vivo*

Species (+ age at the beginning of treatment)	Number of animal	Route of administration	Concentration (mg perindopril free acid/kg)	Major investigations	Conclusion
Micronucleus cytogenic assay in mice bone marrow after oral administration					
Mouse/ Swiss (OF1) (8 weeks)	4 groups of 6 to 12 per gender	Oral gavage	0 500 1000 2000	General toxicity Plasma levels Acceptability of the study Evaluation of genotoxicity	No statistically significant or dose-related increase in the number of micronucleated polychromatic erythrocytes versus negative controls was seen in the animals dosed with perindopril arginine salt. Under the conditions of this study, perindopril arginine salt was devoid of clastogenic potential.

No mutagenic or clastogenic potential was found in the Ames test, in the mouse lymphoma assay, in the chromosomal aberration test or in the bone marrow micronucleus assay up to 2000 mg perindopril free acid/kg. Chromosomal aberrations were found after prolonged (20h) treatment of human lymphocytes with 1294 µg perindopril free acid/mL but the test was considered as inappropriate since the accurate assessment of toxicity was not possible. The absence of clastogenic effect in vitro after more prolonged exposure (24h) to higher concentrations (up to 3685 µg perindopril free acid/mL) in the mouse lymphoma assay, combined with the absence of clastogenic potential in vivo after one administration up to 2000 mg perindopril free acid/kg, supported the overall non genotoxicity potential of perindopril arginine salt.

Fertility Studies

Studies were performed by administrating perindopril erbumine by oral route. The following doses or concentrations are expressed in terms of perindopril erbumine salt. 1 mg of perindopril erbumine corresponds to 0.83 mg of free acid of perindopril and is equivalent to a dose of 1.23 mg perindopril arginine.

Two studies were carried out in Wistar rats using oral doses of 1-10 mg/kg/day. In both cases, the body weight gain of the animals was reduced. Fertility of the males was reduced at doses of 2 and 4 mg/kg/day in 1 study, although there was no effect on fertility of the females or on embryonic and fetal development. The mortality of the G1 pups was increased at 4 mg/kg/day, and their growth and physical development were delayed. These changes did not affect the reproductive capacity of the G1 generation.

Teratogenicity Studies

Studies were performed by administrating perindopril erbumine by oral route. The following doses or concentrations are expressed in terms of perindopril erbumine salt. 1 mg of perindopril erbumine corresponds to 0.83 mg of free acid of perindopril and is equivalent to a dose of 1.23 mg perindopril arginine.

In the mouse treated orally with doses ≤ 20 mg/kg/day, perindopril was not embryotoxic or teratogenic.

In the rat treated orally with doses ≤ 16 mg/kg/day, the in-utero development of the fetus was unchanged though there was a higher incidence of hydronephrosis, which appeared to be dose-dependent and a delayed ossification of the fetuses in the high dose group only. There was no sign of teratogenicity.

In the rabbit treated orally with doses ≤ 5 mg/kg/day (as drinking water with 0.9% sodium chloride), there was no maternal toxicity and no embryotoxicity or teratogenicity on the fetuses, except for a slight increase in post-implantation losses with the high dose.

In the monkey treated orally with doses ≤ 16 mg/kg/day, maternal toxicity at high dose resulted in a reduction in water consumption during the treatment period. Nevertheless, no adverse effects on the fetuses were noted.

Peri- and Post-Natal Studies

Studies were performed by administrating perindopril erbumine by oral route. The following doses or concentrations are expressed in terms of perindopril erbumine salt. 1 mg of perindopril erbumine corresponds to 0.83 mg of free acid of perindopril and is equivalent to a dose of 1.23 mg perindopril arginine.

A first study was carried out in pregnant Wistar rats receiving orally 0, 1, 2 and 3 mg/kg/day of perindopril. At high dose, there was a minor but significant reduction in food consumption.

A second study was carried out with doses of 0, 1, 4 and 16 mg/kg. From 4 mg/kg/day, maternal toxicity was observed at the end of gestation and caused a reduction in food consumption and weight gain. Dystocia caused the death of 4 females during parturition at the high dose. There were also significantly fewer neonates born at all 3 doses, although the average weight of the G1 pups was unchanged. During the lactation period, doses of 4 and 16 mg/kg/day showed a dose-related reduction in the weight gain of the G0 dams and of the G1 pups, and an increase in post-natal mortality. At the highest dose, there was delayed physical and behavioural development in the G1 pups, reduced fertility in the G1 dams, polyuria in the G1 animals, and renal lesions in the G1 parents. No secondary effects were observed in the G2 generation.

A complementary study was carried out under the same conditions, on pregnant rats treated with a single dose of 16 mg/kg/day and fed rat-diet with a sodium enriched diet (1.9 g/kg). The correction of the dietary sodium intake reduced the general toxicity of perindopril for the dams and their progeny.

Indapamide

Acute Toxicity Studies

Single dose toxicity studies were carried in the mouse, rat and guinea pig by the oral and IV routes. Orally, toxicity was very low (LD_{50} > 3000 mg/kg) IV, the LD_{50} ranged between 272 mg/kg in guinea pigs to 635 mg/kg in mice. Signs of toxicity were piloerection, bradypnea, hypotonia, diminished motor activity, hypersensitivity, mydriasis, and vasodilation at parenteral doses > 400 mg/kg. Indapamide administered with hydralazine, methyldopa or propranolol did not modify the oral LD_{50} of the other antihypertensive agents.

Chronic Toxicity Studies

In rats treated once daily for 4 weeks at 50, 100 and 200 mg/kg, there was a reduction in body weight gain and in food intake at 100 and 200 mg/kg. Renal dystrophic mineralization was detected in all females (5/5) at 200 mg/kg, considered to be due to increased urinary output.

In rats treated once daily for 52 weeks at 0, 1, 10 or 100 mg/kg, growth rates of treated males declined significantly during the first 6 weeks but terminal weights were comparable with controls. Two females at each dose showing renal dystrophic mineralization died.

In dogs treated once daily for 6 months at 0, 2, 20, 200 mg/kg, the relevant findings were reduction in food intake, reduction in body weight gain in males at the high dose, decreased glucose tolerance and marked saliuretic effect.

In dogs treated once daily for 56 weeks with 0, 1, 10, and 100 mg/kg (the highest dose was reduced to 50 mg/kg on day 86), the findings were excessive diuresis in all dosed animals and reduction in body weight gain. In the high dose group, there were reductions in food consumption, ECG changes (alteration of ventricular repolarization) related to reduced levels of potassium, replacement of cardiac muscle by adipose tissue in 4/8 animals and apparent enlargement of adrenal cortex in 3/4 dogs.

Carcinogenicity Studies

Indapamide was administered to Charles River CDI rats and mice at dietary levels of 0, 10, 30 and 100 mg/kg/day for 104 and 91 weeks, respectively. Both strains are susceptible to known carcinogens. Drug-related changes in the kidney (tubular nephrosis and mineralization of parenchyma) were seen in rats. Increased liver cytoplasmic vacuolization was seen in mice. Under the conditions of testing, indapamide was not tumorigenic.

Teratology Studies

In the mouse and rat, no apparent teratological effects were noted with indapamide.

In the domestic rabbit receiving 0, 1, 5, 10 and 50 mg/kg per os once daily, increased resorption rate was seen at 50 mg/kg.

In the New Zealand white rabbit receiving 0, 5, 30 and 180 mg/kg/day per os once daily, there was a reduction in food consumption and weight gain at 180 mg/kg during the first 4 days of dosing. Total loss of litters occurred in 2 animals at high dose. In the other animals, abortion rate and litter size were unchanged.

Fertility and Reproduction Study

Three generation tests were carried out on Wistar rats (SPF Strain). Indapamide was administered at 0, 0.5, 2.5 and 25 mg/kg per os once daily for 70 days. No effects were reported on reproductive functions. Behaviour and reproductive performance of off-spring were unaffected, but the death rate of neonates (F2 generations) was adversely affected: 35% at low dose and 47% at the high dose vs. 16% in controls (the lack of milk formation in the mothers may have been the cause). No adverse effects on the F3 generation pups were observed.

Perindopril / Indapamide

The toxicology studies carried out on the combination of perindopril erbumine (76%) and indapamide (24%) are summarized below.

Acute Toxicity Studies

Table 18 –Acute Toxicity Studies

Species	Sex	Route	LD_{50} (mg/kg)
Mouse	Male	Oral	> 3000
Mouse	Female	Oral	> 3000
Mouse	Male	Intravenous	> 336
Mouse	Female	Intravenous	> 336
Rat	Male	Oral	> 3000
Rat	Female	Oral	> 3000
Rat	Male	Intravenous	> 336
Rat	Female	Intravenous	> 336
Dog	Male	Oral	590*
Dog	Female	Oral	590*

** Maximum Tolerated Dose*

Signs of toxicity: No mortality occurred during the oral and IV studies in mice, and no signs of toxicity were observed.

Following oral administration to rats, signs of gastric toxicity and 1 female death (1/6) occurred. After IV administration to rats, most animals had a decreased spontaneous motor activity, half-closed eyes, curled-up position, tachypnoea, ventral posture, piloerection, with signs of gastric toxicity at autopsy in 2 males; 1 male (1/6) receiving 336 mg/kg died.

In the dog treated orally with increasing doses, induced neuromuscular effects, hypothermia, tachycardia and hypotension were observed (animals were sacrificed).

Chronic Toxicity Studies

Table 19 – Chronic Toxicity Studies

Species	Duration	No. of animals / group	Route	Dose (mg/kg/day)	Results
Rat	13-Week	10M + 10F	Oral	0 0.88 2.63 7.90	The most marked abnormalities were related to the action of perindopril and were dose-dependent: increased water intake, reduced blood pressure, increased blood levels of urea, creatinine, potassium, cholesterol, increased diuresis (also attributable to indapamide), increased weight of kidneys. Histological findings of renal impairment (from tubular abnormalities to fibrosis) were observed from intermediate dose upwards and were identifiable as osmotic nephrosis, as in the case of perindopril. Proposed NOAEL: 0.88 mg/kg/day.
Rat	26-Week + 8-Week recovery period	30M + 30F (0 and 4.5 doses) 20M + 20F (0.5 and 1.5 doses)	Oral	0 0.5 1.5 4.5	A pattern of dose related changes was seen at dose levels between 0.5-4.5 mg/kg/day. All these changes concern the kidney and were consistent with the pharmacological activity of the compounds. At high dose: increased excretion of calcium, chloride, urea and creatinine, from 13th week onwards, not reversible, indicating impairment in renal function. At high dose (both sexes) and intermediate dose (males): increased weight of kidney, irreversible at high dose. Histological findings: hypertrophy of juxtaglomerular apparatus and afferent arterioles with tubular lesions suggestive of osmotic nephrosis, at high dose (both sexes) and intermediate dose (males). Weight of heart decreased reversibly in females (high and intermediate doses), with no histological changes. Proposed NOAEL: 0.5 mg/kg/day.
Dog	13-Week	4M+ 4F	Oral	0 1.31 5.25 21.0/10.5	At high dose, animals were sacrificed for ethical reasons after 24 days of treatment (despite a 50% reduction of the dose at day 17): death was related to GI lesions, accompanied by dehydration and severe hypotension. Intermediate dose was the maximum tolerated non-lethal dose, with clinical signs (anorexia, weight loss), hypotension, renal effects and digestive lesions (confirmed at histopathology). Proposed NOAEL: 1.31 mg/kg/day, with signs related to the pharmacological properties of test compounds.
Dog	13-Week + 8-Week recovery period	6M + 6F (0 and 3.93 doses) 4M+4F (1.31 and 2.26 doses)	Oral	0 1.31 2.26 3.93	No mortality was detected. Changes observed were related to the pharmacological action of the products and were markedly dose-dependent. At the high dose: initial degree of toxicity on the gastric mucosa (1 male) and modification of RBC related parameters (males). No histopathological abnormality was observed at the end of the reversibility period. Proposed NOAEL: between 2.26-3.93 mg/kg/day.
Dog	26-Week + 8-Week recovery period	6M + 6F (0 and 3.93 doses) 4M + 4F (1.31 and 2.26 doses)	Oral	0 1.31 2.26 3.93	The only abnormalities observed were related to the pharmacological action of test substances: reduction in plasma electrolytes, reduction in weight of heart, increase in weight of kidney (females on high dose). No GI lesions and no histological lesions were reported. Proposed NOAEL: 3.93 mg/kg/day.

Teratology Studies

Table 20 – Teratology Studies

Species	Duration	No. of animals / group	Route	Dose (mg/kg/day)	Results
Rat	Days 6 through 17 of gestation	25	Oral	0 1.31 5.25 21.0	No teratogenic effect was observed; a NOAEL of 21 mg/kg/day can therefore be suggested for this effect in this study. As in studies on indapamide and perindopril alone, body weight gain and food intake were reduced in a dose-dependent manner while water intake increased. These maternal effects did not affect the parameters relating to implantation and embryo development of the litters, but resulted in a decrease in the mean weight of fetuses and a delayed bone formation (at and above the low dose).
Rabbit	Days 6 through 18 of gestation	20 (control group) 25 (treated groups)	Oral	0 1.3 3.3 8.2	Dose-dependent decreases in body weight gain, increases in fluid intake and episodes of diarrhoea were detected in the mothers at all doses. Post-implantation losses increased and fetal body weight was slightly reduced. The incidence of various malformations observed in the fetuses from the treated mothers was not statistically significantly different from control litters and was comparable to that of historical results for the strain and species used in this study. Proposed NOAEL: < 1.3 mg/kg/day for maternal effects and > 8.2 mg/kg/day for embryo-fetal toxicity and teratogenic potential.

Mutagenicity Studies

As perindopril and indapamide tested separately were not shown to have any mutagenic potential in a battery of mutagenic and chromosomal aberration studies, no new investigation was carried out on their combination.

Carcinogenicity Studies

The carcinogenic potential of perindopril and indapamide was evaluated during long-term studies in 2 animal species (mouse and rat). Since these studies were found to be negative, no new studies were performed on the combination.

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PART III: CONSUMER INFORMATION

[Pr]ARCOSYL® PLUS LD 2.5 mg/ 0.625 mg
[Pr]ARCOSYL® PLUS 5 mg/ 1.25 mg & 10 mg/ 2.5 mg

Perindopril arginine / indapamide film-coated tablets

Read this carefully before you start taking ARCOSYL® PLUS LD/ ARCOSYL® PLUS and each time you get a refill. This leaflet is a summary and will not tell you everything about ARCOSYL® PLUS LD/ ARCOSYL® PLUS. Talk to your doctor, nurse, or pharmacist about your medical condition and treatment and ask if there is any new information about ARCOSYL® PLUS LD/ ARCOSYL® PLUS

ABOUT THIS MEDICATION

What the medication is used for:
ARCOSYL® PLUS LD/ ARCOSYL® PLUS are combinations of two active ingredients, perindopril and indapamide used to treat mild to moderate **High Blood Pressure.**

What it does:
Perindopril is an angiotensin converting enzyme (ACE) inhibitor. You can recognize ACE inhibitors because their medicinal ingredient ends in **'-PRIL'.**
Indapamide is a diuretic often called a "water pill". It increases urination. This lowers blood pressure. Indapamide affects the kidney's ability to reabsorb electrolytes.

Each of the active ingredients reduces blood pressure and they work together to control your blood pressure.

High blood pressure increases the workload of the heart and arteries. If this condition continues for a long time, damage to the blood vessels of the brain, heart, and kidneys can occur, and may eventually result in a stroke, heart or kidney failure. High blood pressure also increases the risk of heart attacks. Reducing your blood pressure decreases your risk of developing these illnesses.

This medicine does not cure high blood pressure. It helps to control it. Therefore, it is important to continue taking ARCOSYL® PLUS LD/ ARCOSYL® PLUS regularly even if you feel fine. Do not stop taking your medicine without the advice of your doctor.

When it should not be used:
Do not take ARCOSYL® PLUS LD/ ARCOSYL® PLUS if you:
- Are allergic to perindopril arginine or any other ACE inhibitor, or to indapamide or any other sulphonamides or to any other non-medicinal ingredients of ARCOSYL® PLUS LD/ ARCOSYL® PLUS
- Previously experienced an allergic reaction (angioedema) with swelling of the hands, feet, or ankles, face, lips, tongue, throat, or sudden difficulty breathing or swallowing, to any ACE inhibitor or without a known cause. Be sure to tell your doctor, nurse, or pharmacist that this has happened to you,
- Have been diagnosed with hereditary angioedema: an increased risk of getting an allergic reaction that is passed down through families. This can be triggered by different factors, such as surgery, flu, or dental procedures,
- Are taking a drug containing the combination of sacubitril/ valsartan, due to the increased risk of serious allergic reaction which causes swelling of the face or throat (angioedema) when taken with ARCOSYL® PLUS LD/ ARCOSYL® PLUS,
- Are already taking a blood pressure-lowering medicine that contains aliskiren (such as RASILEZ) and you have diabetes or kidney disease,
- Have trouble urinating,
- Have severe liver disease or suffer from a condition called hepatic encephalopathy (degenerative disease of the brain),
- Have a kidney disease,
- Have low or high blood potassium,
- Are suspected of having untreated decompensated heart failure (severe water retention, difficulty in breathing),
- Are pregnant or intend to become pregnant. Taking of ARCOSYL® PLUS LD/ ARCOSYL® PLUS during pregnancy can cause injury and even death to your baby,
- Are breast feeding. ARCOSYL® PLUS LD/ ARCOSYL® PLUS passes into breast milk,
- Are lactose intolerant or have one of the following rare hereditary diseases:
  - Galactose intolerance
  - Lapp lactase deficiency
  - Glucose-galactose malabsorption

  Because lactose is a non-medicinal ingredient in ARCOSYL® PLUS LD/ ARCOSYL® PLUS.
- Are taking drugs to treat heart rhythm disturbances (antiarrythmics) that might cause severe cardiac arrhythmias
- Are on dialysis or any other type of blood filtration. Depending on the machine that is used, ARCOSYL® PLUS LD/ ARCOSYL® PLUS may not be suitable for you.
- Have kidney problems where the blood supply to your kidneys is significantly reduced (renal artery stenosis).

What the medicinal ingredients are:
Perindopril arginine and indapamide.

What the non-medicinal ingredients are:
Glycerol, Hypromellose, Lactose monohydrate, Macrogol, Magnesium stearate, Maltodextrin, Silica colloidal anhydrous, Sodium starch glycolate, Titanium dioxide.

What dosage forms it comes in:
ARCOSYL® PLUS LD: film-coated tablets of 2.5 mg perindopril arginine/ 0.625 mg indapamide.
ARCOSYL® PLUS (5 mg/ 1.25 mg): film-coated tablets of 5 mg perindopril arginine/ 1.25 mg indapamide,
ARCOSYL® PLUS (10 mg/ 2.5 mg): film-coated tablets of 10 mg perindopril arginine/ 2.5 mg indapamide.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions- Pregnancy
ARCOSYL® PLUS LD/ ARCOSYL® PLUS should not be used during pregnancy. If you discover that you are pregnant while taking ARCOSYL® PLUS LD or ARCOSYL® PLUS, stop the medication and contact your doctor, nurse, or pharmacist as soon as possible.

BEFORE you use ARCOSYL® PLUS LD/ ARCOSYL® PLUS talk to your doctor or pharmacist if you:
- Are allergic to any drug used to lower blood pressure,
- Have recently received or are planning to get allergy shots for bee or wasp stings,
- Have aortic stenosis (narrowing of the main blood vessel leading from the heart) or hypertrophic cardiomyopathy (cardiac muscle disease) or

renal artery stenosis (narrowing of the artery supplying the kidney with blood),
- Have / had a heart attack or a stroke,
- Have diabetes, liver or kidney disease,
- Are taking a medicine that contains aliskiren, such as RASILEZ, used to lower high blood pressure. The combination with ARCOSYL® PLUS LD/ ARCOSYL® PLUS is not recommended,
- Are taking an angiotensin receptor blocker (ARB). You can recognize an ARB because its medicinal ingredient ends in "-SARTAN",
- Are on haemodialysis,
- Have a history of angioedema (swelling around your face, throat or tongue),
- Suffer from a collagen disease (skin disease) such as systemic lupus erythematosus or scleroderma,
- Have atherosclerosis (hardening of the arteries),
- Suffer from hyperparathyroidism (dysfunctioning of the parathyroid gland),
- Suffer from gout,
- Are on a salt restricted diet or use salt substitutes which contain potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of "water pill"),
- Take lithium or potassium-sparing diuretics (spironolactone, triamterene) as their use with ARCOSYL® PLUS LD/ ARCOSYL® PLUS should be avoided,
- Are dehydrated or have recently suffered from excessive vomiting or diarrhoea or sweating,
- Are receiving gold (sodium aurothiomalate) injections,
- Are on LDL Apheresis (a treatment to lower the LDL cholesterol in the blood),
- Have any congenital or a family history of heart rhythm problems,
- Are less than 18 years old,
- Are malnourished,
- Are over 65 years old,
- Have any other heart problems,
- Are to undergo anesthesia and/or surgery
- Have abnormally increased levels of a hormone called aldosterone in your blood (primary aldosteronism).

You may become sensitive to the sun while taking ARCOSYL® PLUS LD/ ARCOSYL® PLUS. Exposure to sunlight should be minimized until you know how you respond.

Athletes should be aware that ARCOSYL® PLUS LD/ ARCOSYL® PLUS contains a medicinal ingredient (indapamide) which may give a positive reaction in doping tests.

If you are going to have surgery and will be given an anaesthetic, be sure to tell your doctor or dentist that you are taking ARCOSYL® PLUS LD/ ARCOSYL® PLUS.

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to ARCOSYL® PLUS LD/ ARCOSYL® PLUS. Dizziness, lightheadedness, or fainting can especially occur after the first dose and when the dose is increased.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with ARCOSYL® PLUS LD/ ARCOSYL® PLUS:
- Lithium (used to treat bipolar disorder),
- Agents affecting sympathetic activity,
- Agents causing renin release,
- Blood pressure-lowering drugs, including diuretics ("water pills"), aliskiren-containing products (e.g. RASILEZ), or angiotensin receptor blockers (ARBs),
- Agents increasing serum potassium, such as a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of "water pill"),
- Dextran sulphate, special intravenous fluid used to counteract life-threatening low blood pressure.
- Digoxin (a heart medication),
- Medicines to treat diabetes such as insulin, gliptins or metformin,
- Non-steroidal anti-inflammatory drugs (NSAIDS), such as ibuprofen, naproxen, or Celecoxib or high doses of acetylsalicylic acid (more than 3 g/day),
- Drugs used to treat anxiety and schizophrenia (e.g. clozapine, risperidone, pimozide),
- Drugs used to treat depression, in particular serotonin reuptake inhibitors (SSRIs eg. paroxetine, sertraline, citalopram) and tricyclic antidepressants (imipramine),
- Gold for the treatment of rheumatoid arthritis,
- Drugs to treat heart rhythm disturbances (e.g. digoxine, quinidine, hydroquinidine, disopyramide, amiodarone, sotalol, ibutilide, dofetilide, procainamide),
- Allopurinol (for the treatment of gout),
- Oral corticosteroids for treatment of asthma,
- Ciclosporin, tacrolimus or other medications to depress the immune system after organ transplantation,
- Medicines for the treatment of cancer,
- Baclofen, a skeletal muscle relaxant,
- Calcium tablets or other calcium supplements,
- Anaesthetics,
- Iodinated contrast media,
- Stimulant laxatives such as bisacodyl and senna,
- Antifungal medications such as amphotericin B (IV),
- ACTH (e.g. tetracosactide) for treatment of arthritis or inflammatory bowel disease,
- Alcohol, barbiturates (sleeping pills), or narcotics (strong pain medications). They may cause low blood pressure and dizziness when you go from lying or sitting to standing up,
- Antimicrobial medications such as pentamidine,
- Antibiotics such as moxifloxacin, erythromycin IV, gentamycin,
- Trimethoprim (for the treatment of infections),
- Estramustine (used in cancer therapy),
- Neutral endopeptidase (NEP) inhibitors. The combination with ARCOSYL® PLUS LD or ARCOSYL® PLUS is not recommended.
- Sirolimus, everolimus, temsirolimus and other drugs belonging to the class of mTOR inhibitors (used to avoid rejection of transplanted organs).

PROPER USE OF THIS MEDICATION

Take ARCOSYL® PLUS LD/ ARCOSYL® PLUS exactly as prescribed. It is recommended to take your dose at about the same time every day. Swallow the tablet whole with water.

Usual Adult Dose

The recommended dose of ARCOSYL® PLUS LD/ ARCOSYL® PLUS is 1 tablet once daily taken in the morning before a meal. Your doctor may decide to modify the dosage regimen in particular if you suffer from kidney disease renal impairment.

Overdose:

If you think you have taken too much ARCOSYL® PLUS LD / ARCOSYL® PLUS, contact your doctor, nurse, pharmacist, hospital emergency department or regional poison control center immediately, even if there are no symptoms.

Missed Dose:

If you have forgotten to take your dose during the day, carry on with the next one at the usual time. Do not double the dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- Dizziness, drowsiness, fatigue, weakness, headache, vertigo, malaise, fall
- Rash, itching
- Gastro-intestinal disorders, stomach or abdominal pain, loss of appetite, nausea, vomiting, constipation, diarrhea
- Taste disturbance
- Dry mouth, dry cough
- Mood swings, sleep disturbances
- Sweating
- Muscle cramps and/or pain, joint pain, pins and needles sensation

If any of these affects you severely, tell your doctor, nurse or pharmacist.

If you faint, discontinue the drug and contact your doctor.

ARCOSYL® PLUS LD/ ARCOSYL® PLUS can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Uncommon	Possible worsening of pre-existing lupus : a disease affecting the skin, joints and kidney			✓
	Low Blood Pressure: dizziness, fainting, light-headedness. May occur when you go from lying or sitting to standing up	✓		
	Angioedema and Severe Allergic Reaction: Swelling of the face, eyes or tongue, difficulty swallowing, wheezing, difficulty breathing, abdominal cramps, chest discomfort or tightness, hives and generalized itching, rash, fever, unconsciousnes*			✓
	Liver Disorder: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		✓	
	Kidney disorder: change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue		✓	
	Fast or irregular heartbeat		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / Effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Uncommon	Bronchospasm (difficulty in breathing)			✓
	Chest pain		✓	
	Edema: swelling of the legs, feet and ankles	✓		
	Pemphigoid/ Pemphigus: formation of blister clusters over the skin			✓
Rare	**Increased levels of Calcium in the blood:** loss of appetite, nausea, vomiting, constipation, stomach pain		✓	
	Psoriasis Aggravation		✓	
Very rare	**Anemia:** fatigue, loss of energy, weakness, shortness of breath		✓	
	Decreased White Blood Cells: infections, fatigue, fever, aches, pains and flu-like symptoms		✓	
	Decreased Platelets: bruising, bleeding, fatigue, weakness		✓	
	Inflammation of the Pancreas: abdominal pain that lasts and gets worse when you lie down, nausea, vomiting		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / Effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Very rare	**Severe Skin Reactions (Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Hyper-sensitivity Syndrome):** any combination of itchy skin rash, redness, blistering and peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands, joint pain, yellowing of the skin or eyes, dark urine.			✓
Unknown	**SIADH (syndrome of inappropriate antidiuretic hormone secretion):** concentrated urine (dark in colour), feel or are sick, have muscle cramps, confusion and fits (seizures) which may be due to inappropriate secretion of ADH (anti-diuretic hormone).		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / Effect		**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate medical help**
		Only if severe	**In all cases**	
Unknown	**Torsade de Pointes:** life-threatening irregular heartbeat			✓
	Increased Blood Sugar: frequent urination, thirst, hunger	✓		
	Increased Levels of Potassium in the Blood: irregular heartbeat, muscle weakness and generally feeling unwell		✓	
	Increased Levels of Uric Acid in the Blood: swelling and redness in the joints		✓	
	Eye Disorders: -Myopia: sudden near sightedness or blurred vision			✓
	Rhabdomyoly-sis: muscle pain that you cannot explain, muscle tenderness or weakness, dark brown urine		✓	
	Electrolyte Imbalance: weakness, drowsiness, muscle pain or cramps, irregular heartbeat		✓	

*This is known to occur more frequently in black patients.

This is not a complete list of side effects. For any unexpected effects while taking ARCOSYL® PLUS LD/ ARCOSYL® PLUS, contact your doctor, nurse or pharmacist.

HOW TO STORE IT

Keep out of reach or sight of children.

Store at room temperature (15°C - 30°C).

Do not use after the expiry date stated on the carton or bottle.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- **Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or**
- **Calling toll-free at 1-866-234-2345.**

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at www.servier.ca or by contacting the sponsor, Servier Canada Inc. at: 1-800-363-6093.

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