Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lipercosyl 40 mg/5 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 43.28 mg atorvastatin calcium trihydrate equivalent to 40 mg atorvastatin, 5 mg perindopril arginine equivalent to 3.395 mg perindopril.

Excipient with known effect: sucrose (72.6 mg for Lipercosyl 40/5 mg).

For the full list of excipients, see section6.1.

3 PHARMACEUTICAL FORM

Capsules, hard

Size 2 hard gelatin capsule, with black imprint "40 5" on blue body and black imprint  on blue cap, containing white to slightly white spherical pellets.

Size 2 hard gelatin capsules are approximately 18 mm in length.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Lipercosyl is indicated as substitution therapy as part of cardiovascular risk management (see section 5.1), in adult patients adequately controlled with atorvastatin and perindopril given concurrently at the same dose level but as separate products.

4.2 Posology and method of administration

Posology

Adults
The usual posology is one capsule once daily.

The fixed dose combination is not suitable for initial therapy.
If a change of posology is required, titration should be done with the individual components.
The patients should continue a standard cholesterol-lowering diet during treatment with Lipercosyl.

Co-administration with other medicines
In patients taking tipranavir, ritonavir, telaprevir or ciclosporine concomitantly with Lipercosyl, the dose of atorvastatin in Lipercosyl should not exceed 10 mg/day (see sections 4.4 and 4.5).
In patients taking hepatitis C antiviral agents containing boceprevir, elbasvir/grazoprevir or letermovir for cytomegalovirus infection prophylaxis concomitantly with Lipercosyl, the dose of atorvastatin in Lipercosyl should not exceed 20 mg/day (see sections 4.4 and 4.5). Use of Lipercosyl is not recommended in patients taking letermovir co-administered with ciclosporin (see sections 4.4 and 4.5).

Patients with renal impairment
Lipercosyl can be administered in patients with creatinine clearance ^{3} 60 mL/min, and is not suitable for patients with creatinine clearance < 60 mL/min. In these patients, an individual dose titration with the monocomponents is recommended (see section 4.4).

Elderly
Older people can be treated with Lipercosyl according to the renal function *(see sections4.4 and 5.2)*.

Patients with hepatic impairment
Lipercosyl should be used with caution in patients with hepatic impairment. Lipercosyl is contraindicated in patients with active liver disease (see sections 4.3, 4.4 and 5.2).

Paediatric population
The safety and efficacy of Lipercosyl in children and adolescents have not been established. No data are available. Therefore, use in children and adolescents is not recommended.

Method of administration
Oral use.
Lipercosyl should be taken as a single dose once daily in the morning before a meal.
The capsules must not be chewed or broken.

4.3 Contraindications

- Hypersensitivity to the active substances or to any other ACE (Angiotensin Converting Enzyme) inhibitor or statin or to any of the excipients of this medicinal product listed in section 6.1;
- Active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal;
- During pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures (see section 4.6);
- Concomitant use with the hepatitis C antivirals glecaprevir/pibrentasvir;
- History of angioedema associated with previous ACE inhibitor therapy;
- Hereditary or idiopathic angioedema;
- Concomitant use with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m^2) (see sections 4.5 and 5.1);
- Concomitant use with sacubitril/valsartan therapy. Lipercosyl must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.4 and 4.5);
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5);
- Significant bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney (see section 4.4).

4.4 Special warnings and precautions for use

Special warnings and precautions related to atorvastatin and perindopril are applicable to Lipercosyl.

Liver effects
Due to the atorvastatin component in Lipercosyl, liver function tests should be performed periodically. Patients who develop any signs or symptoms suggestive of hepatic dysfunction should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality (ies) resolve. Should an increase in transaminases of greater than 3 times the upper limit of normal (ULN) persist, reduction of atorvastatin dose using the individual components or withdrawal of atorvastatin is recommended (see section 4.8).

Rarely, ACE inhibitors such as perindopril 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 Lipercosyl who develop jaundice or marked elevations of hepatic enzymes should discontinue the product and receive appropriate medical follow-up (see section 4.8).

Taking into account the effect of atorvastatin and perindopril, Lipercosyl is contra-indicated in patients with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (see section 4.3). Lipercosyl should be used with caution in patients with hepatic impairment and in patients who consume substantial quantities of alcohol and/or have a history of liver disease. If a change of posology is required, titration should be done with the individual components.

Skeletal muscle effects
Atorvastatin, like other HMG-CoA reductase inhibitors, may in rare occasions affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis, a potentially life-threatening condition characterised by markedly elevated creatine kinase (CK) levels (> 10 times ULN), myoglobinaemia and myoglobinuria which may lead to renal failure.

In situations where pre-disposing factors for rhabdomyolysis have been identified before treatment initiation i.e.:

- Renal impairment
- Hypothyroidism

− Personal or familial history of hereditary muscular disorders
− Previous history of muscular toxicity with a statin or fibrate
− Previous history of liver disease and/or where substantial quantities of alcohol are consumed
− In elderly (age > 70 years), the need for CK measurement should be considered, taking account of the presence of other predisposing factors for rhabdomyolysis
− When an increase in plasma levels may occur, such as interactions (see section 4.5) and special populations including genetic subpopulations (see section 5.2)
the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended.
If CK levels are significantly elevated (> 5 times ULN) at baseline, treatment should not be started.

Creatine kinase measurement
Creatine kinase (CK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes value interpretation difficult. If CK levels are significantly elevated at baseline (> 5 times ULN), levels should be measured again within 5 to 7 days later to confirm the results.

Whilst on treatment

- Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing Lipercosyl.
- If such symptoms occur whilst a patient is receiving treatment with Lipercosyl, their CK levels should be measured. If these levels are found to be significantly elevated (> 5 times ULN), treatment should be stopped.
- If muscular symptoms are severe and cause daily discomfort, even if the CK levels are elevated to ≤ 5 x ULN, treatment discontinuation should be considered.
- If symptoms resolve and CK levels return to normal, then re-introduction of atorvastatin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.
- Lipercosyl must be discontinued immediately if clinically significant elevation of CK levels (> 10 x ULN) occur, or if rhabdomyolysis is diagnosed or suspected.

Concomitant treatment with other medicinal products

Due to atorvastatin component, risk of rhabdomyolysis is increased when Lipercosyl is administered concomitantly with certain medicinal products that may increase the plasma concentration of atorvastatin such as potent inhibitors of CYP3A4 or transport proteins (e.g. ciclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole, letermovir and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, tipranavir/ritonavir, etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivates, antivirals for the treatment of hepatitis C (HCV) (boceprevir, telaprevir, elbasvir/grazoprevir), erythromycin, niacin or ezetimibe. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products.

In cases where co-administration of these medicinal products with Lipercosyl is necessary, the benefit and the risk of concurrent treatment should be carefully considered. When patients are receiving medicinal products that increase the plasma concentration of atorvastatin, a lower maximum dose of atorvastatin is recommended, hence down-titration with the individual components should be considered. In addition, in the case of potent CYP3A4 inhibitors, a lower starting dose of atorvastatin should be considered and appropriate clinical monitoring of these patients is recommended (see section 4.5).

Atorvastatin must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination (see section 4.5). The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness.

Statin therapy may be re-introduced seven days after the last dose of fusidic acid.

In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for co-administration of Lipercosyl and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Immune-mediated necrotizing myopathy

There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterised by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, Lipercosyl therapy should be discontinued and switching to therapy with only perindopril should be considered.

Diabetes Mellitus

Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping Lipercosyl treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI > 30 kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines when treated with Lipercosyl.

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with medicines containing an ACE inhibitor, such as Lipercosyl (see section 4.5).

Hypotension

ACE inhibitors, such as perindopril, may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). In patients with symptomatic heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored (see sections 4.2 and 4.8). Similar considerations apply to patients who suffer from ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of sodium chloride 9 mg/mL (0.9 %) solution. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with perindopril. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose using the individual components or discontinuation of treatment with Lipercosyl may be necessary.

Aortic and mitral valve stenosis/ hypertrophic cardiomyopathy

As with other medicines containing ACE inhibitors such as perindopril, Lipercosyl 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.

Kidney transplantation

There is no experience regarding the administration of perindopril or Lipercosyl in patients with a recent kidney transplantation.

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 section 4.3). 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.

Renal impairment

Lipercosyl can be administered in patients with creatinine clearance ^{3} 60 mL/min, and is not suitable for patients with moderate renal impairment (creatinine clearance between 30 and 60 mL/min) or with severe renal impairment (creatinine clearance < 30 mL/min). In these patients, an individual dose titration with the monocomponents is recommended. Routine monitoring of potassium and creatinine are part of normal medical practice for patients with renal impairment (see section 4.8).

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when perindopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction using the individual components and/or discontinuation of the diuretic and/or Lipercosyl may be required.

The effect of the combination Lipercosyl has not been tested in patients with renal impairment. Lipercosyl doses should respect the dosing recommendations of the individual components taken separately.

Haemodialysis patients

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

Hypersensitivity/Angioedema

Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including perindopril (see section 4.8). This may occur at any time during therapy. In such cases, Lipercosyl should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

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

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

The combination of perindopril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see section 4.3). Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of perindopril therapy. If treatment with sacubitril/valsartan is stopped, perindopril therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5). Concomitant use of ACE inhibitors with NEP inhibitors (e.g. racecadotril), mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin) may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin) in a patient already taking an ACE inhibitor.

Anaphylactoid reactions during low- density lipoproteins (LDL) apheresis

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

Anaphylactic reactions during desensitisation

Patients receiving ACE inhibitor-containing medicines, such as Lipercosyl, during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In the same patients, these reactions have been avoided when the ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

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. Lipercosyl should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If Lipercosyl 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 (e.g. sore throat, fever).

Race

ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

Lipercosyl, which contains the ACE inhibitor perindopril, may be less effective in lowering blood pressure in black people than

in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Cough

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

Surgery/Anaesthesia

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

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril, ACE inhibitors can cause hyperkalaemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin, co-trimoxazole also known as trimethoprim/sulfamethoxazole) and especially aldosterone antagonists or angiotensin-receptor blockers. The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal arrhythmias. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored. If concomitant use of the above-mentioned agents with Lipercosyl is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

Combination with lithium

The combination of lithium and medicines containing perindopril, such as Lipercosyl, is not recommended (see section 4.5).

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

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Primary aldosteronism:

Patients with primary hyperaldosteronism generally will not respond to anti-hypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of this product is not recommended.

Excipients

Due to the presence of sucrose, patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take Lipercosyl.

Level of sodium
contains less than 1 mmol sodium (23 mg) per capsule, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

No drug interaction studies have been conducted with Lipercosyl and other drugs, although studies have been conducted with atorvastatin and perindopril separately. The results of these studies are provided below.

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

Drugs increasing the risk of angioedema
Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4). Sacubitril/valsartan must not be started until 36 hours after taking the last dose of perindopril therapy. Perindopril therapy must not be started until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.4). Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin) may lead to an increased risk for angioedema (see section 4.4).

Drugs inducing hyperkalaemia
Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with Lipercosyl. Some drugs or therapeutic classes may increase the occurrence of hyperkalaemia: aliskiren, potassium salts, potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), ACE inhibitors, angiotensin-II receptors antagonists, NSAIDs, heparins, immunosuppressant agents such as ciclosporine or tacrolimus, trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole), as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. The combination of these drugs increases the risk of hyperkalaemia. Therefore, the combination of Lipercosyl with the above-mentioned drugs is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Concomitant use contraindicated (see section 4.3)

Component	**Known interaction with the product**	**Interaction with other medicinal product**
Perindopril	Aliskiren	In diabetic or impaired renal patients, risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increase (see section 4.3).
	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 section 4.3). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.
Atorvastatin	Glecaprevir/pibrentasvir	The concomitant therapy with Lipercosyl is contra-indicated due to an

		increased risk of myopathy.

Concomitant use not recommended (see section 4.4)

Component	**Known interaction with the product**	**Interaction with other medicinal product**
Atorvastatin	Potent CYP3A4 inhibitors	Atorvastatin is metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin (see section 5.2). Concomitant administration of medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased with concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivates and ezetimibe (see section 4.4). Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin. Co-administration of potent CYP3A4 inhibitors (e.g. ciclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole, some antivirals used in the treatement of HCV (e.g. elbasvir/grazoprevir) and HIV protease inhibitors including, ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.) with Lipercosyl should be avoided if possible. In cases where co-administration of these medicinal products with Lipercosyl cannot be avoided, lowest doses of atorvastatin in Lipercosyl should be considered and appropriate clinical monitoring of the patient is recommended (see Table 1).
	Inhibitors of Breast Cancer Resistant Protein (BCRP)	Concomitant administration of products that are inhibitors of BCRP (e.g., elbasvir and grazoprevir) may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy; therefore a dose adjustment of atorvastatin should be considered depending on the prescribed dose. Co-administration of elbasvir and grazoprevir with atorvastatin increases plasma concentrations of atorvastatin 1.9 fold (see Table 1); therefore, the dose of atorvastatin in Lipercosyl should not exceed 20 mg daily in patients receiving concomitant medications with products containing elbasvir or grazoprevir (see sections 4.2 and 4.4).
	Grapefruit or grapefruit juice	Concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended (see Table 1).
Perindopril	Aliskiren	In patients other than diabetic or impaired renal patients, concomitant treatment with Lipercosyl and aliskiren is not recommended since risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increase.
	Concomitant therapy with ACE inhibitor and angiotensin-receptor blocker	It has been reported in the literature that in patients with established atherosclerotic disease, heart failure, or with diabetes with end organ damage, concomitant therapy with an ACE inhibitor, such as perindopril (contained in Lipercosyl) and an angiotensin-receptor blocker is associated with a higher frequency of hypotension, syncope, hyperkalaemia, and worsening renal function (including acute renal failure) as compared to use of a single renin-angiotensin-aldosterone system agent. Dual blockade (e.g, by combining an ACE-inhibitor with an angiotensin II receptor antagonist) should be limited to individually defined cases with close monitoring of renal function, potassium levels, and blood pressure.
	Estramustine	Risk of increased adverse effects such as angioneurotic oedema (angioedema).

	Lithium	Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Use of Lipercosyl with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).
	Potassium-sparing diuretics (e.g. triamterene, amiloride, eplerenone, spironolactone), potassium salts	These drugs are known to induce hyperkalaemia (potentially lethal), especially in conjunction with renal impairment (additive hyperkalaemic effects). The combination of Lipercosyl with these drugs is not recommended (see section 4.4). If concomitant use is nonetheless indicated, they should be used with caution and with frequent monitoring of serum potassium and creatinine.

Concomitant use which requires special care

Component	**Known interaction with the product**	**Interaction with other medicinal product**
Atorvastatin	Moderate CYP3A4 inhibitors	Moderate CYP3A4 inhibitors (e.g. erythromycin, diltiazem, verapamil and fluconazole) may increase plasma concentrations of atorvastatin (see Table 1). An increased risk of myopathy has been observed with the use of erythromycin in combination with statins. Interaction studies evaluating the effects of amiodarone or verapamil on atorvastatin have not been conducted. Both amiodarone and verapamil are known to inhibit CYP3A4 activity and co-administration with atorvastatin may result in increased exposure to atorvastatin. Therefore, a lower maximum dose of the atorvastatin component in Lipercosyl should be considered and appropriate clinical monitoring of the patient is recommended when concomitantly used with moderate CYP3A4 inhibitors. Appropriate clinical monitoring is recommended after initiation or following dose adjustments of the inhibitor.
	CYP3A4 inducers	Concomitant administration of atorvastatin with inducers of cytochrome P450 3A (e.g. efavirenz, rifampicin, St. John's Wort) can lead to variable reductions in plasma concentrations of atorvastatin (see Table 1). Due to the dual interaction mechanism of rifampicin (cytochrome P450 3A induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous co-administration of Lipercosyl with rifampicin is recommended, as delayed administration of atorvastatin after administration of rifampicin has been associated with a significant reduction in atorvastatin plasma concentrations. The effect of rifampicin on atorvastatin concentrations in hepatocytes is, however, unknown and if concomitant administration cannot be avoided, patients should be carefully monitored for efficacy.
	Digoxin	When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steady-state digoxin concentrations increased slightly (see Table 2). Patients taking digoxin should be monitored appropriately.
	Ezetimibe	The use of ezetimibe alone is associated with muscle

		related events, including rhabdomyolysis. The risk of these events may therefore be increased with concomitant use of ezetimibe and Lipercosyl. Appropriate clinical monitoring of these patients is recommended.
	Fusidic acid	As with other statins, muscle related events, including rhabdomyolysis, have been reported in post-marketing experience with atorvastatin and fusidic acid given concurrently. The mechanism of this interaction is not known. The concomitant use of Lipercosyl and fusidic acid is not recommended, switching a patient to the individual component perindopril when discontinuation of Lipercosyl is required should be considered. Statin therapy could be restarted 7 days after the last dose of fusidic acid.
	Gemfibrozil / fibric acid derivatives	The use of fibrates alone is occasionally associated with muscle related events, including rhabdomyolysis (see Table 1). The risk of these events may be increased with the concomitant use of fibric acid derivatives and atorvastatin. If concomitant administration cannot be avoided, the lowest dose of atorvastatin in Lipercosyl to achieve the therapeutic objective should be used and the patients should be appropriately monitored (see section 4.4).
	Transport inhibitors	Inhibitors of transport proteins (e.g. ciclosporine, letermovir) can increase the systemic exposure of atorvastatin (see Table 1). The effect of inhibition of hepatic uptake transporters on atorvastatin concentrations in hepatocytes is unknown. If concomitant administration cannot be avoided, a dose reduction and clinical monitoring for efficacy is recommended (see Table 1). Use of Lipercosyl is not recommended in patients taking letermovir co-administered with ciclosporin (see section 4.4).
	Warfarin	In a clinical study in patients receiving chronic warfarin therapy, co-administration of atorvastatin 80 mg daily with warfarin caused a small decrease of about 1.7 seconds in prothrombin time during the first 4 days of dosing which returned to normal within 15 days of atorvastatin treatment. Although only very rare cases of clinically significant anticoagulant interactions have been reported, prothrombin time should be determined before starting Lipercosyl in patients taking coumarin anticoagulants and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of the atorvastatin component in Lipercosyl is changed or discontinued, the same procedure should be repeated. Atorvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.
Perindopril	Antidiabetic agents (insulins, oral hypoglycaemic agents)	Epidemiological studies have suggested that

		concomitant administration of ACE inhibitors and antidiabetic 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.
	Baclofen	Increased antihypertensive effect. Monitor blood pressure and adapt antihypertensive dosage if necessary.
	Non-potassium-sparing diuretics	Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating therapy with low and progressive doses of perindopril.
	Non-steroidal anti-inflammatory medicinal products (NSAIDs) (including acetylsalicylic acid ≥ 3 g/day)	When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination of Lipercosyl with NSAIDs should be administered with caution, especially in elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Concomitant use to be taken into consideration:

Component	**Known interaction with the product**	**Interaction with other medicinal product**
Atorvastatin	Colchicine	Although interaction studies with atorvastatin and colchicine have not been conducted, cases of myopathy have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.
	Colestipol	Plasma concentrations of atorvastatin and its active metabolites were lower (by approx. 25 %) when colestipol was co-administered with atorvastatin. However, lipid effects were greater when atorvastatin and colestipol were co-administered than when either medicinal product was given alone.
	Oral contraceptives	Co-administration of atorvastatin with an oral contraceptive produced increases in plasma concentrations of norethindrone and ethinyl oestradiol (see Table 2).
Perindopril	Sympathomimetics	Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.
	Tricyclic antidepressants/	Concomitant use of certain anaesthetic medicinal products, tricyclic

	Antipsychotics/Anaesthetics	antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).
	Gold	Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including perindopril.
	Antihypertensive agents and vasodilators	Concomitant use of these agents may increase the hypotensive effects of Lipercosyl. Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

Table 1. Effect of co-administered medicinal product on the pharmacokinetics of atorvastatin

Co-administered medicinal product and dosing regimen	**Atorvastatin**		
	Dose	**Change in AUC[&]**	**Clinical recommendation[#]**
Tipranavir 500 mg BID/Ritonavir 200 mg BID, 8 days (days 14 to 21)	40 mg on day 1, 10 mg on day 20	↑ 9.4 fold	In cases where co-administration with atorvastatin is necessary, do not exceed 10 mg atorvastatin daily. Clinical monitoring of these patients is recommended.
Telaprevir 750 mg, q8h, 10 days	20 mg, SD	↑ 7.9 fold	
Ciclosporine 5.2 mg/kg/day, stable dose	10 mg, OD, for 28 days	↑ 8.7 fold	
Lopinavir 400 mg BID/ Ritonavir 100 mg BID, 14 days	20 mg, OD, for 4 days	↑ 5.9 fold	In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 20 mg, clinical monitoring of these patients is recommended.
Clarithromycin 500 mg BID, 9 days	80 mg, OD, for 8 days	↑ 4.4 fold	
Saquinavir 400 mg BID/ Ritonavir (300 mg BID from days 5-7, increased to 400 mg BID on day 8), days 4-18, 30 min after atorvastatin dosing	40 mg, OD, for 4 days	↑ 3.9 fold	In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 40 mg, clinical monitoring of these patients is recommended.
Darunavir 300 mg BID/ Ritonavir 100 mg BID, 9 days	10 mg, OD, for 4 days	↑ 3.3 fold	
Itraconazole 200 mg OD, 4 days	40 mg, SD	↑ 3.3 fold	
Fosamprenavir 700 mg BID/ Ritonavir 100 mg BID, 14 days	10 mg, OD, for 4 days	↑ 2.5 fold	
Fosamprenavir 1400 mg BID, 14 days	10 mg, OD, for 4 days	↑ 2.3 fold	
Nelfinavir 1250 mg BID, 14 days	10 mg, OD, for 28 days	↑ 1.7 fold[^]	No specific recommendation.
Letermovir 480 mg OD, 10 days	20 mg SD	↑ 3.29 fold	The dose of atorvastatin should not exceed a daily dose of 20 mg during co-administration with products containing letermovir.
Grapefruit Juice, 240 mL OD*	40 mg, SD	↑ 37 %	Concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended.
Diltiazem 240 mg OD, 28 days	40 mg, SD	↑ 51 %[^]	After initiation or following dose adjustments of diltiazem, appropriate clinical monitoring of these patients is recommended.
Erythromycin 500 mg QID, 7 days	10 mg, SD	↑ 33 %[^]	Lower maximum dose and clinical monitoring of these patients is recommended.
Amlodipine 10 mg, single dose	80 mg, SD	↑ 18 %	No specific recommendation.

Cimetidine 300 mg QID, 2 weeks	10 mg, OD, for 4 weeks	↓ less than 1 %^	No specific recommendation.
Colestipol 10 g BID, 24 weeks	40 mg OD for 8 weeks	0.74**	No specific recommendation
Antacid suspension of magnesium and aluminium hydroxides, 30 mL QID, 2 weeks	10 mg, OD, for 4 weeks	↓ 35 %^	No specific recommendation.
Efavirenz 600 mg OD, 14 days	10 mg for 3 days	↓ 41 %	No specific recommendation.
Rifampicin 600 mg OD, 7 days (co-administered)	40 mg SD	↑ 30 %	If co-administration cannot be avoided, simultaneous co-administration of atorvastatin with rifampicin is recommended, with clinical monitoring.
Rifampicin 600 mg OD, 5 days (doses separated)	40 mg SD	↓ 80 %	
Gemfibrozil 600 mg BID, 7 days	40 mg SD	↑ 35 %	Lower starting dose and clinical monitoring of these patients is recommended.
Fenofibrate 160 mg OD, 7 days	40 mg SD	↑ 3 %	Lower starting dose and clinical monitoring of these patients is recommended.
Boceprevir 800 mg TID, 7 days	40 mg SD	↑ 2.3 fold	Lower starting dose and clinical monitoring of these patients is recommended. The dose of atorvastatin should not exceed a daily dose of 20 mg during co-administration with boceprevir.
Glecaprevir 400 mg OD/ Pibrentasvir 120 mg OD, 7 days	10 mg OD for 7 days	↑ 8.3 fold	Co-administration with products containing glecaprevir or pibrentasvir is contraindicated (see section 4.3).
Elbasvir 50 mg OD/ Grazoprevir 200 mg OD, 13 days	10 mg SD	↑1.95 fold	The dose of atorvastatin should not exceed a daily dose of 20 mg during coadministration with products containing elbasvir or grazoprevir.
• OD= once daily, SD = single dose, BID = twice daily, QID = Four times daily, TID = three times daily			
• Increase is indicated as "↑", decrease as "↓"			
• [&] Data given as x-fold change represent a simple ratio between co-administration and atorvastatin alone (i.e., 1-fold = no change). Data given as % change represent %			

difference relative to atorvastatin alone (i.e., 0 % = no change).			
# See sections 4.4 and 4.5 for clinical significance.			
* Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of medicinal products metabolized by CYP3A4. Intake of one 240 mL glass of grapefruit juice also resulted in a decreased AUC of 20.4 % for the active orthohydroxy metabolite. Large quantities of grapefruit juice (over 1.2 l daily for 5 days) increased AUC of atorvastatin 2.5 fold and AUC of active (atorvastatin and metabolites). ** Ratio based on a single sample taken 8-16 h post dose			
^ Total atorvastatin equivalent activity			

Table 2. Effect of atorvastatin on the pharmacokinetics of co-administered medicinal products

Atorvastatin dosing regimen	**Co-administered medicinal product**		
	Medicinal product/Dose (mg)	**Change in AUC[&]**	**Clinical recommendation**
80 mg, OD, for 10 days	Digoxin, 0.25 mg, OD, 20 days	↑ 15 %	Patients taking digoxin should be monitored appropriately.
40 mg, OD, for 22 days	Oral contraceptive OD, 2 months • Norethindrone, 1 mg • Ethinyl estradiol, 35 microgram	↑ 28 % ↑ 19 %	No specific recommendation.
80 mg, OD, for 15 days	*Phenazone, 600 mg, SD	↑ 3 %	No specific recommendation.
10 mg, SD	Tipranavir 500 mg, BID/ritonavir 200 mg BID, 7 days	No change	No specific recommendation.
10 mg, OD, for 4 days	Fosamprenavir 1400 mg, BID, 14 days	↓ 27 %	No specific recommendation.

10 mg, OD, for 4 days	Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	No change	No specific recommendation.
• OD= once daily, SD = single dose, BID = twice daily			
• Increase is indicated as "↑", decrease as "↓"			
• [&] Data given as % change represent % difference relative to atorvastatin alone (i.e., 0 % = no change)			
• * Co-administration of multiple doses of atorvastatin and phenazone showed little or no detectable effect in the clearance of phenazone.			

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of child-bearing potential should use appropriate contraceptive measures during treatment with Lipercosyl (see section 4.3).

Pregnancy
Based on existing data with the individual components as described below, Lipercosyl is contraindicated during pregnancy (see section 4.3).

Atorvastatin
Safety in pregnant women has not been established. No controlled clinical trials with atorvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. Animal studies have shown toxicity to reproduction (see section 5.3).

Maternal treatment with atorvastatin may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia.

For these reasons, atorvastatin should not be used in women who are pregnant, trying to become pregnant or suspected to be pregnant.

Perindopril
Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

For these reasons the use of ACE inhibitors is not recommended during the first trimester of pregnancy. The use of ACE inhibitors is contraindicated during the 2nd and 3rd trimester of pregnancy.

Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see also sections 4.3 and 4.4).

Breast-feeding

Based on existing data with the individual components as described below, Lipercosylis contra-indicated during breast-feeding (see section 4.3).

Atorvastatin
It is not known whether atorvastatin or its metabolites are excreted in human milk. In rats, plasma concentrations of atorvastatin and its active metabolites are similar to those in milk (see section 5.3). Because of the potential for serious adverse reactions, women taking atorvastatin should not breast-feed their infants. Atorvastatin is contraindicated during breastfeeding (see section 4.3).

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

Fertility
There are no clinical data on fertility with the use of Lipercosyl

Atorvastatin
In animal studies atorvastatin had no effect on male or female fertility (see section 5.3).

Perindopril
There was no effect on reproductive performance or fertility.

4.7 Effects on ability to drive and use machines

No studies have been performed on the effect of Lipercosyl on the ability to drive and use machines.

- Atorvastatin has negligible influence on the ability to drive and use machines.
- Perindopril has no direct influence on the ability to drive and use machines but individual reactions related to low blood pressure may occur in some patients, particularly at the start of treatment or in combination with another antihypertensive medication.

As a result the ability to drive or operate machinery may be impaired in patients taking Lipercosyl.

4.8 Undesirable effects

Summary of the profile:
The most commonly reported adverse reactions with atorvastatin and perindopril given separately include: nasopharyngitis, hypersensitivity, hyperglycaemia, dizziness, headache, dysgeusia, paraesthesia, visual impairment, tinnitus, vertigo, hypotension, pharyngolaryngeal pain, epistaxis, cough, dyspnoea, nausea, vomiting, abdominal pain upper and lower, dyspepsia, diarrhoea, constipation, flatulence, rash, pruritus, joint swelling, pain in extremity, arthralgia, muscle spasms, myalgia, back pain, asthenia, liver function test abnormal, blood creatine kinase increased.

Tabulated list of adverse reactions:
The following undesirable effects have been observed during treatment with atorvastatin and perindopril, or given separately and ranked under the MedDRA classification by body system and under heading of frequency using the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data)).

MedDRA System Organ Class	**Undesirable effects**	**Frequency**	
		Atorvastatin	**Perindopril**
Infections and infestation	Nasopharyngitis	Common	-
	Rhinitis	-	Very rare
Blood and lymphatic system disorders	Thrombocytopenia	Rare	Very rare

	Leukopenia/ Neutropenia (see section 4.4)	-	Very rare
	Eosinophilia	-	Uncommon*
	Agranulocytosis /Pancytopenia (see section 4.4)		Very rare
	Haemolytic anaemia in patients with a congenital deficiency of G-6PDH (see section 4.4)	-	Very rare
Immune system disorders	Hypersensitivity	Common	-
	Anaphylaxis	Very rare	-
Endocrine disorders	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	-	Rare
Metabolism and nutrition disorders	Hyperglycaemia	Common	-
	Hypoglycaemia (see sections 4.4 and 4.5)	Uncommon	Uncommon*
	Hyponatraemia	-	Uncommon*
	Hyperkalaemia reversible on discontinuation (see section 4.4)	-	Uncommon*
	Anorexia	Uncommon	-
Psychiatric disorders	Insomnia	Uncommon	-
	Depression	-	Uncommon*
	Mood altered	-	Uncommon
	Sleep disorder		Uncommon
	Nightmare	Uncommon	-
	Confusional state	-	Very rare
Nervous system disorders	Somnolence	-	Uncommon*
	Dizziness	Uncommon	Common
	Headache	Common	Common
	Dysgeusia	Uncommon	Common
	Syncope	-	Uncommon*
	Hypoaesthesia	Uncommon	-
	Paraesthesia	Uncommon	Common
	Peripheral neuropathy	Rare	-
	Stroke possible secondary to excessive hypotension in high-risk patients (see section 4.4)	-	Very rare
	Amnesia	Uncommon	-
Eye disorders	Visual impairment	Rare	Common
	Vision blurred	Uncommon	-
Ear and labyrinth disorders	Tinnitus	Uncommon	Common
	Vertigo	-	Common
	Hearing loss	Very Rare	-
Cardiac disorders	Myocardial infarction, possibly secondary to excessive hypotension in high-risk patients (see section 4.4)	-	Very rare
	Angina pectoris	-	Very rare
	Arrhythmia	-	Very rare
	Tachycardia	-	Uncommon*
	Palpitations	-	Uncommon*
Vascular disorders	Hypotension (and effects related to hypotension)	-	Common
	Vasculitis	-	Uncommon*
	Flushing	-	Rare*
	Raynaud's phenomenon	-	Not known
Respiratory, thoracic and mediastinal	Pharyngolaryngeal pain	Common	-

disorders			
	Epistaxis	Common	-
	Cough	-	Common
	Dyspnoea	-	Common
	Bronchospasm	-	Uncommon
	Eosinophilic pneumonia	-	Very rare
Gastro-intestinal disorders	Nausea	Common	Common
	Vomiting	Uncommon	Common
	Abdominal pain upper and lower	Uncommon	Common
	Dyspepsia	Common	Common
	Diarrhoea	Common	Common
	Constipation	Common	Common
	Dry mouth	-	Uncommon
	Pancreatitis	Uncommon	Very rare
	Eructation	Uncommon	-
	Flatulence	Common	-
Hepato-biliary disorders	Hepatitis either cytolytic or cholestatic (see section 4.4)	Uncommon	Very rare
	Cholestasis	Rare	-
	Hepatic failure	Very rare	-
Skin and subcutaneous tissue disorders	Rash	Uncommon	Common
	Pruritus	Uncommon	Common
	Urticaria (see section 4.4)	Uncommon	Uncommon
	Hyperhidrosis	-	Uncommon
	Psoriasis aggravation	-	Rare*
	Alopecia	Uncommon	-
	Angioedema (see section 4.4)	Rare	Uncommon
	Pemphigoid	-	Uncommon*
	Stevens-Johnson syndrome	Rare	-
	Photosensitivity reaction	-	Uncommon*
	Toxic epidermal necrolysis	Rare	-
	Erythema multiforme	Rare	Very rare
Musculoskeletal and connective tissue disorders	Joint swelling	Common	-
	Pain in extremity	Common	-
	Arthralgia	Common	Uncommon*
	Muscle spasms	Common	Common
	Myalgia	Common	Uncommon*
	Back pain	Common	-
	Neck pain	Uncommon	-
	Muscle fatigue	Uncommon	-
	Myopathy	Rare	-
	Myositis	Rare	-
	Rhabdomyolysis	Rare	-
	Muscle rupture	Rare	-
	Tendinopathy sometimes complicated by rupture	Rare	-
	Lupus-like syndrome	Very rare	-
	Immune-mediated necrotizing myopathy (see section 4.4)	Not known	-
Renal and urinary disorders	Renal failure	-	Uncommon
	Acute renal failure	-	Rare
	Anuria/Oliguria	-	Rare*

Reproductive system and breast disorders	Erectile dysfunction	-	Uncommon
	Gynaecomastia	Very rare	-
General disorders and administration site conditions	Asthenia	Uncommon	Common
	Fatigue	Uncommon	-
	Chest pain	Uncommon	Uncommon*
	Malaise	Uncommon	Uncommon*
	Oedema peripheral	Uncommon	Uncommon*
	Pyrexia	Uncommon	Uncommon*
Investigations	Blood urea increased	-	Uncommon*
	Blood creatinine increased	-	Uncommon*
	Hepatic enzymes increased	-	Rare
	Blood bilirubin increased	-	Rare
	Haemoglobin decreased and haematocrit decreased (see section 4.4)	-	Very rare
	Weight increased	Uncommon	-
	White blood cells urine positive	Uncommon	-
	Liver function test abnormal	Common	-
	Blood creatine phosphokinase increased	Common	-
Injury, poisoning and procedural complications	Fall	-	Uncommon*

** Frequency calculated from clinical trials for adverse events detected from spontaneous report*

As with other HMG-CoA reductase inhibitors elevated serum transaminases have been reported in patients receiving atorvastatin. These changes were usually mild, transient, and did not require interruption of treatment. Clinically important (> 3 times upper normal limit) elevations in serum transaminases occurred in 0.8 % patients on atorvastatin. These elevations were dose related and were reversible in all patients section 4.4).

Elevated serum creatine kinase (CK) levels greater than 3 times upper limit of normal occurred in 2.5 % of patients on atorvastatin, similar to other HMG-CoA reductase inhibitors in clinical trials. Levels above 10 times the normal upper range occurred in 0.4 % atorvastatin -treated patients (see section 4.4).

The following adverse events have been reported with some statins:
• Sexual dysfunction.
• Depression.
• Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4).
• Diabetes Mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI > 30 kg/m^2, raised triglycerides, history of hypertension).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
HPRA Pharmacovigilance,
Website: www.hpra.ie

4.9 Overdose

There is no information on overdose with Lipercosyl in humans.

Atorvastatin:

Symptoms and Management

Specific treatment is not available for atorvastatin overdose. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Liver function tests should be performed and serum CK levels should be monitored. Due to extensive atorvastatin binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

Perindopril:

Symptoms:
Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

Management:
The recommended treatment of overdosage is intravenous infusion of sodium chloride 9 mg/mL (0.9 %) solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis (see section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Lipid modifying agents,HMG CoA reductase inhibitors, other combinations**, ATC code:**C10BX15

Mechanism of action and pharmacodynamics effects

Atorvastatin
Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Triglycerides and cholesterol in the liver are incorporated into very low-density lipoproteins (VLDL) and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolized primarily through the receptor with high affinity to LDL (LDL receptor).

Atorvastatin lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG-CoA reductase and subsequently cholesterol biosynthesis in the liver and increases the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL.

Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles. Atorvastatin is effective in reducing LDL-C in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering medicinal products.

Perindopril
Perindopril is an inhibitor of the enzyme that converts angiotensin I into angiotensin II (Angiotensin Converting Enzyme ACE). The converting enzyme, or kinase, is an exopeptidase that allows conversion of angiotensin I into the vasoconstrictor angiotensin II as well as causing the degradation of the vasodilator bradykinin into an inactive heptapeptide. Inhibition of ACE results in a reduction of angiotensin II in the plasma, which leads to increased plasma renin activity (by inhibition of the negative feedback of renin release) and reduced secretion of aldosterone. Since ACE inactivates bradykinin, inhibition of ACE also results in an increased activity of circulating and local kallikrein-kinin systems (and thus also activation of the prostaglandin system). It is possible that this mechanism contributes to the blood pressure-lowering action of ACE inhibitors and is partially responsible for certain of their side effects (e.g. cough).

Perindopril acts through its active metabolite, perindoprilat. The other metabolites show no inhibition of ACE activity *in vitro*.

Heart failure:
Perindopril reduces cardiac work by a decrease in pre-load and after-load.

Clinical efficacy and safety:
Lipercosyl has not been studied on morbidity andmortality.

Atorvastatin
Atorvastatin has been shown to reduce concentrations of total-C (30 % - 46 %), LDL-C (41 % - 61 %), apolipoprotein B (34 % - 50 %), and triglycerides (14 % - 33 %) while producing variable increases in HDL-C and apolipoprotein A1 in a dose response study. These results are consistent in patients with heterozygous familial hypercholesterolaemia, nonfamilial forms of hypercholesterolaemia, and mixed hyperlipidaemia, including patients with non-insulin-dependent diabetes mellitus.

Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce risk for cardiovascular events and cardiovascular mortality.

Homozygous familial hypercholesterolaemia
In a multicenter 8 week open-label compassionate-use study with an optional extension phase of variable length, 335 patients were enrolled, 89 of which were identified as homozygous familial hypercholesterolaemia patients. From these 89 patients, the mean percent reduction in LDL-C was approximately 20 %. Atorvastatin was administered at doses up to 80 mg/day.

Atherosclerosis
In the Reversing Atherosclerosis with Aggressive Lipid- Lowering Study (REVERSAL), the effect of intensive lipid lowering with atorvastatin 80 mg and standard degree of lipid lowering with pravastatin 40 mg on coronary atherosclerosis was assessed by intravascular ultrasound (IVUS), during angiography, in patients with coronary heart disease (CHD). In this randomised double-blind, multicenter, controlled clinical trial, IVUS was performed at baseline and at 18 months in 502 patients. In the atorvastatin group (n=253), there was no progression of atherosclerosis.

The median percent change, from baseline, in total atheroma volume (the primary study criteria) was -0.4 % (p=0.98) in the atorvastatin group and +2.7 % (p=0.001) in the pravastatin group (n=249). When compared to pravastatin the effects of atorvastatin were statistically significant (p=0.02). The effect of intensive lipid lowering on cardiovascular endpoints (e. g. need for revascularisation, non-fatal myocardial infarction, and coronary death) was not investigated in this study.

In the atorvastatin group, LDL-C was reduced to a mean of 2.04 mmol/L ± 0.8 mmol/L (78.9 mg/dL ± 30 mg/dL) from baseline 3.89 mmol/l ± 0.7 mmol/L (150 mg/dl ± 28 mg/dL) and in the pravastatin group, LDL-C was reduced to a mean of 2.85 mmol/L ± 0.7 mmol/L (110 mg/dL ± 26 mg/dL) from baseline 3.89 mmol/L ± 0.7 mmol/L (150 mg/dl ± 26 mg/dL) (p<0.0001). Atorvastatin also significantly reduced mean TC by 34.1 % (pravastatin: --18.4 %, p<0.0001), mean TG levels by 20 % (pravastatin: --6.8 %, p<0.0009), and mean apolipoprotein B by 39.1 % (pravastatin: --22.0 %, p<0.0001). Atorvastatin increased mean HDL-C by 2.9 % (pravastatin: +5.6 %, p=NS). There was a 36.4 % mean reduction in CRP in the atorvastatin group compared to a 5.2 % reduction in the pravastatin group (p<0.0001).

Study results were obtained with the 80 mg dose strength. Therefore, they cannot be extrapolated to the lower dose strengths. The safety and tolerability profiles of the two treatment groups were comparable.
The effect of intensive lipid lowering on major cardiovascular endpoints was not investigated in this study. Therefore, the clinical significance of these imaging results with regard to the primary and secondary prevention of cardiovascular events is unknown.

Acute coronary syndrome
In the MIRACL study, atorvastatin 80 mg has been evaluated in 3,086 patients (atorvastatin n=1,538; placebo n=1,548) with an acute coronary syndrome (non Q-wave MI or unstable angina). Treatment was initiated during the acute phase after hospital admission and lasted for a period of 16 weeks. Treatment with atorvastatin 80 mg/day increased the time to occurrence of the combined primary endpoint, defined as death from any cause, nonfatal MI, resuscitated cardiac arrest, or angina pectoris with evidence of myocardial ischemia requiring hospitalization, indicating a risk reduction by 16 % (p=0.048). This was mainly due to a 26 % reduction in re-hospitalisation for angina pectoris with evidence of myocardial ischemia (p=0.018). The other secondary endpoints did not reach statistical significance on their own (overall: Placebo: 22.2 %, Atorvastatin: 22.4 %).

The safety profile of atorvastatin in the MIRACL study was consistent with what is described in section 4.8.

Prevention of cardiovascular disease
The effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in a randomized, double-blind, placebo-controlled study, the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA). Patients were hypertensive, 40-79 years of age, with no previous myocardial infarction or treatment for angina, and with TC levels ≤ 6.5 mmol/L (251 mg/dL). All patients had at least 3 of the pre-defined cardiovascular risk factors: male gender, age ≥ 55 years, smoking, diabetes, history of CHD in a first-degree relative, TC:HDL-C >6, peripheral vascular disease, left ventricular

hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria. Not all included patients were estimated to have a high risk for a first cardiovascular event.

Patients were treated with anti-hypertensive therapy (either amlodipine or atenolol-based regimen) and either atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137).

The absolute and relative risk reduction effect of atorvastatin was as follows:

Event	Relative Risk Reduction (%)	No. of Events (atorvastatin vs placebo)	Absolute Risk Reduction[1] (%)	p-value
Fatal CHD plus non-fatal MI	36 %	100 vs. 154	1.1 %	0.0005
Total cardiovascular events and revascularization procedures	20 %	389 vs. 483	1.9 %	0.0008
Total coronary events	29 %	178 vs 247	1.4 %	0.0006

[1]Based on difference in crude events rates occurring over a median follow-up of 3.3 years.
CHD = coronary heart disease; MI = myocardial infarction.

Total mortality and cardiovascular mortality were not significantly reduced (185 vs. 212 events, p = 0.17 and 74 vs. 82 events, p = 0.51). In the subgroup analyses by gender (81 % males, 19 % females), a beneficial effect of atorvastatin was seen in males but could not be established in females possibly due to the low event rate in the female subgroup. Overall and cardiovascular mortality were numerically higher in the female patients (38 vs. 30 and 17 vs. 12), but this was not statistically significant. There was significant treatment interaction by antihypertensive baseline therapy. The primary endpoint (fatal CHD plus non-fatal MI) was significantly reduced by atorvastatin in patients treated with amlodipine (HR 0.47 (0.32-0.69), p=0.00008), but not in those treated with atenolol (HR 0.83 (0.59-1.17), p=0.287).

In a post-hoc analysis, a subgroup of patients randomised to the amlodipine-based regimen were treated with perindopril and either atorvastatin (n=1,950) or placebo (n=1,926).
The risk of total CHD [non-fatal MI (including silent) + fatal CHD] was reduced of 42 % (95 % CI [0.396;0.837]). There were also a significant reduction of 46 % for the risk of cardiovascular mortality (95 % CI [0.344, 0.854]), a reduction of 40 % for the composite cardiovascular mortality + MI + stroke (95 % CI [0.461;0.779]), a reduction of 36 % for the composite total CHD + fatal and non-fatal stroke (95 % CI [0.490;0.846]), a reduction of 32 % for the total coronary events (95 % CI [0.516;0.883]) and a reduction of 29 % for all cause of mortality (95 %CI [0.555;0.915]).

The effect of atorvastatin on fatal and non-fatal cardiovascular disease was also assessed in a randomized, double-blind, multicenter, placebo-controlled trial, the Collaborative Atorvastatin Diabetes Study (CARDS) in patients with type 2 diabetes, 40-75 years of age, without prior history of cardiovascular disease, and with LDL-C ≤ 4.14 mmol/L (160 mg/dL) and TG ≤ 6.78 mmol/L (600 mg/dL). All patients had at least 1 of the following risk factors: hypertension, current smoking, retinopathy, microalbuminuria or macroalbuminuria. Patients were treated with either atorvastatin 10 mg daily (n=1,428) or placebo (n=1,410) for a median follow-up of 3.9 years.
The absolute and relative risk reduction effect of atorvastatin was as follows:

Event	Relative Risk Reduction (%)	No. of Events (atorvastatin vs placebo)	Absolute Risk Reduction[1] (%)	p-value
Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularization, stroke)	37 %	83 vs. 127	3.2 %	0.0010
MI (fatal and non-fatal AMI, silent MI)	42 %	38 vs 64	1.9 %	0.0070
Strokes (fatal and non-fatal)	48 %	21 vs. 39	1.3 %	0.0163

[1]Based on difference in crude events rates occurring over a median follow-up of 3.9 years.
AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CHD = coronary heart disease;
MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

There was no evidence of a difference in the treatment effect by patient's gender, age, or baseline LDL-C level. A favourable trend was observed regarding the mortality rate (82 deaths in the placebo group vs. 61 deaths in the atorvastatin group, p=0.0592).

Recurrent stroke
In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, the effect of atorvastatin 80 mg daily or placebo on stroke was evaluated in 4,731 patients who had a stroke or transient ischemic attack (TIA) within the preceding 6 months and no history of coronary heart disease (CHD). Patients were 60 % male, 21-92 years of age (average age 63 years), and had an average baseline LDL of 133 mg/dL (3.4 mmol/L). The mean LDL-C was 73 mg/dL (1.9 mmol/L) during treatment with atorvastatin and 129 mg/dL (3.3 mmol/L) during treatment with placebo. Median follow-up was 4.9 years.

Atorvastatin 80 mg reduced the risk of the primary endpoint of fatal or non-fatal stroke by 15 % (HR 0.85; 95 % CI, [0.72;-1.00]; p = 0.05 or 0.84; 95 % CI, [0.71-0.99]; p=0.03 after adjustment for baseline factors) compared to placebo. All cause mortality was 9.1 % (216/2,365) for atorvastatin versus 8.9 % (211/2,366) for placebo.

In a post-hoc analysis, atorvastatin 80 mg reduced the incidence of ischemic stroke (218/2,365, 9.2 % vs. 274/2,366, 11.6 %, p=0.01) and increased the incidence of hemorrhagic stroke (55/2,365, 2.3 % vs. 33/2,366, 1.4 %, p=0.02) compared to placebo.

- The risk of hemorrhagic stroke was increased in patients who entered the study with prior hemorrhagic stroke (7/45 for atorvastatin versus 2/48 for placebo; HR 4.06; 95 % CI [, 0.84;-19.57]), and the risk of ischemic stroke was similar between groups (3/45 for atorvastatin versus 2/48 for placebo; HR 1.64; 95 % CI, [0.27;-9.82]).
- The risk of hemorrhagic stroke was increased in patients who entered the study with prior lacunar infarction (20/708 for atorvastatin versus 4/701 for placebo; HR 4.99; 95 % CI [1.71;-14.61]), but the risk of ischemic stroke was also on the other hand decreased in these patients (79/708 for atorvastatin versus 102/701 for placebo; HR 0.76; 95 % CI, [0.57;-1.02]). It is possible that the net risk of stroke is increased in patients with prior lacunar infarction who receive atorvastatin 80 mg/day.

All cause mortality was 15.6 % (7/45) for atorvastatin versus 10.4 % (5/48) for placebo in the subgroup of patients with prior hemorrhagic stroke. All cause mortality was 10.9 % (77/708) for atorvastatin versus 9.1 % (64/701) for placebo in the subgroup of patients with prior lacunar infarction.

Perindopril

Hypertension
Perindopril is active in all grades of hypertension: mild, moderate, severe; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed.
Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate.
Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged.
The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 87-100 % of peak effects.
The decrease in blood pressure occurs rapidly. In responding patients, normalisation is achieved within a month and persists without the occurrence of tachyphylaxis.
Discontinuation of treatment does not lead to a rebound effect.
Perindopril reduces left ventricular hypertrophy.
In man, perindopril has been confirmed to demonstrate vasodilatory properties. It improves large artery elasticity and decreases the media:lumen ratio of small arteries.
An adjunctive therapy with a thiazide diuretic produces an additive-type of synergy. The combination of an ACE inhibitor and a thiazide also decreases the risk of hypokalaemia induced by the diuretic treatment.

Heart failure
Perindopril reduces cardiac work by a decrease in pre-load and after-load.
Studies in patients with heart failure have demonstrated:
- decreased left and right ventricular filling pressures,
- reduced total peripheral vascular resistance,
- increased cardiac output and improved cardiac index.

In comparative studies, the first administration of 2.5 mg of perindopril arginine to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo

Patients with stable coronary artery disease
The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years.

Twelve thousand two hundred and eighteen (12,218) patients aged over 18 were randomised to 8 mg perindopril tert-butylamine (equivalent to 10 mg perindopril arginine) (n=6,110) or placebo (n=6,108).

The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure. Overall, 90 % of the patients had a previous myocardial infarction and/or a previous coronary revascularisation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers.

The main efficacy criterion was the composite of cardiovascular mortality, non-fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with 8 mg perindopril tert-butylamine (equivalent to 10 mg perindopril arginine) once daily resulted in a significant absolute reduction in the primary endpoint of 1.9 % (relative risk reduction of 20 %, 95 %CI [9.4; 28.6] – p<0.001).

In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2.2 % corresponding to a RRR of 22.4 % (95 % CI [12.0; 31.6] – p<0.001) in the primary endpoint was observed by comparison to placebo.

At randomization, 89.41 % of patients with a lipid lowering therapy (LLT) received statins (89.02 % in the Perindopril group and 89.80 % in the placebo group).

In a subgroup of patients treated with LLT from EUROPA study defined in a post-hoc analysis, the addition of perindopril on top of LLT (n=3534) showed a significant absolute risk reduction of 1.7 % (RRR of 21.8 %, 95 % CI [0.634 ; 0.964] compared to placebo on top of LLT (n=3499) in the composite endpoint of cardiovascular mortality, non-fatal acute myocardial infarction and cardiac arrest with successful resuscitation.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) clinical trial data
Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of a combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Paediatric population
No data are available with Lipercosyl in children.
The European Medicines Agency has granted a product-specific waiver for Lipercosyl in all subsets of the paediatric population forthe treatment of cardiovascular diseases(see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

In a drug-drug interaction study in healthy subjects, co-administration of atorvastatin 40 mg, perindopril arginine 10 mg and amlodipine 10 mg resulted in a 23 % increase in atorvastatin AUC, which is not clinically meaningful. The maximum

concentration of perindopril was increased by about 19 %, but the pharmacokinetics of perindoprilat, the active metabolite, was unaffected. The rate and extent of absorption of amlodipine when co-administered with atorvastatin and perindopril were not significantly different from the rate and extent of absorption of amlodipine when taken alone.

In a drug-drug interaction study in healthy subjects, co-administration of atorvastatin 40 mg, perindopril arginine 10 mg and acetylsalicylic acid 100 mg resulted in a 32 % increase in the maximum concentration of perindopril, but the pharmacokinetics of perindoprilat, the active metabolite were unaffected. No pharmacokinetic interaction was identified for atorvastatin, acetylsalicylic acid and their respective metabolites.

Atorvastatin

Absorption
Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (Cmax) occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. After oral administration, atorvastatin film-coated tablets are 95 % to 99 % bioavailable compared to the oral solution. The absolute bioavailability of atorvastatin is approximately 12 % and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30 %. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.

Distribution
Mean volume of distribution of atorvastatin is approximately 381 L. Atorvastatin is ≥ 98 % bound to plasma proteins.

Biotransformation
Atorvastatin is metabolized by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolized via glucuronidation. *In vitro*, inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70 % of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Elimination
Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, atorvastatin does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is approximately 20 to 30 hours due to the contribution of active metabolites.

Atorvastatin is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporters multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin.

Special populations

Elderly
Plasma concentrations of atorvastatin and its active metabolites are higher in healthy elderly subjects than in young adults while the lipid effects were comparable to those seen in younger patient populations.

Gender
Concentrations of atorvastatin and its active metabolites in women differ from those in men (Women: approx. 20 % higher for Cmax and approx. 10 % lower for AUC). These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.

Renal impairment
Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin and its active metabolites.

Hepatic impairment
Plasma concentrations of atorvastatin and its active metabolites are markedly increased (approx. 16-fold in Cmax and approx. 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh B).

SLOC1B1 polymorphism

Hepatic uptake of all HMG-CoA reductase inhibitors including atorvastatin, involves the OATP1B1 transporter. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of atorvastatin, which may lead to an increased risk of rhabdomyolysis (see section 4.4). Polymorphism in the gene encoding OATP1B1 (SLCO1B1 c.521CC) is associated with a 2.4-fold higher atorvastatin exposure (AUC) than in individuals without this genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients. Possible consequences for the efficacy are unknown.

Perindopril

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

Biotransformation
Perindopril is a prodrug. Twenty seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.
As ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril arginine should be administered orally in a single daily dose in the morning before a meal.

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

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

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

Special populations
Elderly
Elimination of perindoprilat is decreased in older people, and also in patients with heart or renal failure.

Renal impairment
Dosage adjustment in renal insufficiency is desirable depending on the degree of impairment (creatinine clearance).
Dialysis clearance of perindoprilat is equal to 70 mL/min.

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

5.3 Preclinical safety data

No preclinical studies have been performed with Lipercosyl.

Atorvastatin

Reproductive toxicology and effect on fertility
There is evidence from animal experimental studies that HMG-CoA reductase inhibitors may affect the development of embryos or fetuses. In rats, rabbits and dogs atorvastatin had no effect on fertility and was not teratogenic. However, at maternally toxic doses, fetal toxicity was observed in rats and rabbits. The development of the rat offspring was delayed and post-natal survival reduced during exposure of the dams to high doses of atorvastatin. In rats, there is evidence of placental transfer. In rats, plasma concentrations of atorvastatin are similar to those in milk. It is not known whether atorvastatin or its metabolites are excreted in human milk.

Carcinogenesis, mutagenesis
Atorvastatin was negative for mutagenic and clastogenic potential in a battery of 4 in vitro tests and 1 in vivo assay. Atorvastatin was not found to be carcinogenic in rats, but high doses in mice (resulting in 6-11 fold the AUC0-24h reached in

humans at the highest recommended dose) showed hepatocellular adenomas in males and hepatocellular carcinomas in females.

Perindopril

Chronic toxicity
In the chronic oral toxicity studies (rats and monkeys), the target organ is the kidney, with reversible damage.

Reproductive toxicology and effect on fertility
Reproduction toxicology studies (rats, mice, rabbits and monkeys) showed no sign of embryotoxicity or teratogenicity. However, angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects on late fetal development, resulting in fetal death and congenital effects in rodents and rabbits: renal lesions and an increase in peri- and postnatal mortality have been observed. Fertility was not impaired either in male or in female rats.

Carcinogenesis, mutagenesis
No mutagenicity has been observed in *in vitro* or *in vivo* studies. No carcinogenicity has been observed in long term studies in rats and mice.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Talc (E553b)
Atorvastatin pellets

- Calcium carbonate (E170)

- Hydroxypropyl cellulose (E463)

- Polysorbate 80 (E433)

- Croscarmellose sodium (E468)

- Sugar spheres (sucrose and maize starch)

Perindopril arginine pellets

- Hydroxypropyl cellulose (E463)

- Sugar spheres (sucrose and maize starch)

Capsule shell
- Titanium dioxide (E171)
- Brilliant blue FCF – FD&C Blue 1 (E133)
- Gelatin

Ink content:

- shellac (E904)

- propylene glycol (E1520)

- strong ammonia solution (E527)

- black iron oxide (E172)
- potassium hydroxide (E525).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original container in order to protect from moisture.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

30 hard capsules in a PP container closed with a LDPE stopper

90 (3x30) hard capsules in 3 PP containers closed with a LDPE stopper

100 hard capsules in a HDPE bottle closed with a PP stopper

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier
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92284 Suresnes Cedex
France

8 MARKETING AUTHORISATION NUMBER

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10 DATE OF REVISION OF THE TEXT