For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

This package insert is continually updated: Please read carefully before using a new pack

RAMIPRIL & ATORVASTATIN TABLETS
Cardace® Protect

COMPOSITION

Cardace® Protect 2.5
Each uncoated tablet contains:
Ramipril IP 2.5 mg
Atorvastatin Calcium IP equivalent to Atorvastatin 10 mg

Cardace® Protect 5
Each uncoated tablet contains:
Ramipril IP 5 mg
Atorvastatin Calcium IP equivalent to Atorvastatin 10 mg

THERAPEUTIC INDICATIONS: Cardace® Protect is indicated for treatment of patients with both essential hypertension and hypercholesterolemia.

Ramipril has been found to reduce the risk of myocardial infarction (MI), stroke, or cardiovascular death in patients with an increased cardiovascular risk, such as manifest coronary heart disease (with or without a history of myocardial infarction), a history of stroke, a history of peripheral vascular disease, or diabetes mellitus that is accompanied by at least one other cardiovascular risk factor (microalbuminuria, hypertension, elevated total cholesterol levels, low high-density lipoprotein cholesterol levels, smoking).

Atorvastatin has been found to reduce the risk of MI, stroke, revascularization procedures and angina in patients without coronary heart disease (CHD) but with multiple risk factors. Atorvastatin also reduces the risk of MI and stroke in patients with type 2 diabetes without CHD but with multiple risk factors. Atorvastatin also reduces the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF and angina in patients with CHD.

DOSAGE AND ADMNISTRATION
The usual initial dose for Cardace® Protect is one tablet daily. If control is inadequate after a week or two, the dose may be increased to the higher strength. Dosage should be individualized.

CONTRAINDICATIONS:
Cardace® Protect must not be used:
- in patients with hypersensitivity to ramipril, to any other ACE inhibitor, atorvastatin or any of the excipients of Cardace® Protect.
- in patients with a history of angioedema.
- **concomitantly with sacubitril/valsartan therapy** (see Section Interactions)**. Do not initiate Cardace® Protect until sacubitril/valsartan is eliminated from the body. In case of switch from Cardace® Protect to sacubitril/valsartan, do not start sacubitril/valsartan until Cardace® Protect is eliminated from the body.**
- in patients with haemodynamically relevant renal artery stenosis, bilateral or unilateral in the single kidney.
- in patients with hypotensive or haemodynamically unstable states.
- With aliskiren-containing medicines in patients with diabetes or with moderate to severe renal impairment (creatinine clearance <60 ml/min).
- with angiotensin II receptor antagonists (AIIRAs) in patients with diabetic nephropathy.
- women who are pregnant or may become pregnant

- active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels
- nursing mothers

Concomitant use of ACE inhibitors and extracorporeal treatments leading to contact of blood with negatively charged surfaces must be avoided, since such use may lead to severe anaphylactoid reactions. Such extracorporeal treatments include dialysis or haemofiltration with certain high-flux (e.g. polyacrylonitril) membranes and low-density lipoprotein apheresis with dextran sulfate**.**

WARNINGS AND PRECAUTIONS

RAMIPRIL

Angioedema - Head, Neck or Extremities

Angioedema occurring during treatment with an ACE inhibitor necessitates immediate discontinuation of the drug**.**

Angioedema of the face, extremities, lips, tongue, glottis or larynx has been reported in patients treated with ACE inhibitors. Emergency treatment of life-threatening angioedema includes immediate administration of epinephrine (subcutaneous or slow intravenous injection) accompanied by monitoring of ECG and blood pressure. Hospitalization of the patient is advisable with observation for at least 12 to 24 hours and discharge only upon complete resolution of the symptoms.

Angioedema –Intestinal

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 facial angioedema also occurred. The intestinal angioedema symptoms resolved after stopping the ACE inhibitor.

Insufficient experience has been gained concerning the use of ramipril in children, in patients with severe impairment of renal function (creatinine clearance below 20 ml/min per 1.73 m² body surface area), and in dialysis patients.

An increased risk of angioedema is possible with concomitant use of other drugs which may cause angioedema (see Section Contraindications and Section Interactions)**.**

Treatment with Cardace® Protect requires regular medical supervision.

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

Dual blockade of the renin-angiotensin-aldosterone system by combining Ramipril with an angiotensin-II receptor antagonist (AIIRA) or with aliskiren is not recommended since there are increased risk of hypotension, hyperkalemia and changes in renal function compared to monotherapy. The use of ramipril in combination with aliskiren is contraindicated in patients with diabetes mellitus or with renal impairment (creatinine clearance < 60 ml/min) (see Contraindications and Interactions).

Patients with hyper-stimulated renin angiotensin system

In the treatment of patients with a hyper-stimulated renin-angiotensin system, particular caution must be exercised (see also under “Dosage and Administration”). Such patients are at risk of an acute pronounced fall in blood pressure and deterioration of renal function due to ACE inhibition, especially when an ACE inhibitor or a concomitant diuretic is given for the first time or for the first time at an increased dose. Initial doses or initial dose increases must be accompanied by close blood pressure monitoring until such time as no further acute reduction in blood pressure is to be anticipated.

Significant activation of the renin angiotensin system is to be anticipated, for example:

- in patients with severe, and particularly with malignant hypertension. The initial phase of treatment requires special medical supervision.

- in patients with heart failure**,** particularly if severe or if treated with other substances having antihypertensive potential. If heart failure is severe, the initial phase of treatment requires special medical supervision.

- in patients with haemodynamically relevant left-ventricular inflow or outflow impediment (e.g., stenosis of the aortic or mitral valve). The initial phase of treatment requires special medical supervision.

- in patients with haemodynamically relevant renal artery stenosis. The initial phase of treatment requires special medical supervision. Discontinuation of diuretic therapy may be required. See also under 'Monitoring of renal function' below.

- in patients pre-treated with diuretics**.** Where discontinuing use or reducing the dose of the diuretic is not possible the initial phase of treatment requires special medical supervision.

- in patients in whom fluid or salt depletion exist or may develop (as a result of insufficient fluid or salt intake, or as a result of, e.g., diarrhoea, vomiting or excessive sweating in cases where salt and fluid replacement is inadequate).

Generally, it is recommended that dehydration, hypovolaemia or salt depletion be corrected before initiating treatment (in patients with heart failure, however, such corrective action must be carefully weighed against the risk of volume overload). When these conditions have become clinically relevant, treatment with Cardace® Protect must only be started or continued if appropriate steps are taken concurrently to prevent an excessive fall in blood pressure and deterioration of renal function

See also under 'Patients with liver diseases'.

- **Patients with liver diseases**

In patients with impaired liver function, response to the treatment with ramipril may be either increased or reduced. In addition, in patients in whom severe liver cirrhosis with oedema and/or ascites is present, the renin angiotensin system may be significantly activated; therefore, particular caution must be exercised in treating these patients (see also above and under "Dosage and Administration").

- **Patients at particular risk from a pronounced reduction in blood pressure**

In patients who would be at particular risk from an undesirably pronounced reduction in blood pressure (e.g. patients with haemodynamically relevant stenoses of the coronary arteries or of the blood vessels supplying the brain), the initial phase of treatment requires special medical supervision.

- **Elderly**

Some elderly patients may be particularly responsive to ACE inhibitors. Evaluation of renal function at the beginning of treatment is recommended. See under "Dosage and Administration".

- **Monitoring of renal function**

It is recommended that renal function be monitored, particularly in the initial weeks of treatment with an ACE inhibitor. Particularly careful monitoring is required in patients with

- heart failure
- renovascular disease, including patients with haemodynamically relevant unilateral renal artery stenosis. In the latter patient group, even a small increase in serum creatinine may be indicative of unilateral loss of renal function
- impairment of renal function
- kidney transplant**.**

- **Electrolyte monitoring**

It is recommended that serum potassium and serum sodium be monitored regularly. More frequent monitoring of serum potassium is necessary in patients with impaired renal function**.**

- **Haematological monitoring**

It is recommended that the white blood cell count be monitored to permit detection of a possible leucopenia. More frequent monitoring is advised in the initial phase of treatment and in patients with impaired renal function, those with concomitant collagen disease (e.g. lupus erythematosus or scleroderma) or those treated with other drugs that can cause changes in the blood picture. See "Adverse reactions".

ATORVASTATIN

Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin tablets and with other drugs in this class. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

Atorvastatin, like other statins, occasionally causes myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN. The concomitant use of higher doses of atorvastatin with certain drugs such as cyclosporine and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, and HIV protease inhibitors) increases the risk of myopathy/rhabdomyolysis.

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required. Consider risk of IMNM carefully prior to initiation of a different statin. If therapy is initiated with a different statin, monitor for signs and symptoms of IMNM.

Atorvastatin may cause myopathy (muscle pain, tenderness, or weakness with creatine kinase (CK) above ten times the upper limit of normal) and rhabdomyolysis (with or without acute renal failure secondary to myoglobinuria). Rare fatalities have occurred as a result of rhabdomyolysis with statin use, including Atorvastatin.

Risk Factors for Myopathy

Risk factors for myopathy include age 65 years or greater, uncontrolled hypothyroidism, renal impairment, concomitant use with certain other drugs, and higher Atorvastatin dosage

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing atorvastatin. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, clarithromycin, the hepatitis C protease inhibitor telaprevir, combinations of HIV protease inhibitors, combination of ritonavir plus saquinavir or lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamprenavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, clarithromycin, a combination of ritonavir plus saquinavir or lopinavir plus ritonavir, immunosuppressive drugs, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Lower starting and maintenance doses of atorvastatin should be considered when taken concomitantly with the aforementioned drugs (See Drug Interactions)..

Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. Prescribing recommendations for interacting agents are summarized in Table 1 (see also Dosage and Administration,Drug Interactions,)

Table 1. Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	**Prescribing Information**
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, Itraconazole, HIV protease inhibitors (Ritonavir plus saquinavir darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	Do not exceed 20mg atorvastatin daily
HIV protease inhibitor (nelfinavir) Hepatitis C protease inhibitor (boceprevir)	Do not exceed 40 mg atorvastatin daily

Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin co administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine (see Drug Interactions)

Cardace® Protect therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

- **Liver Dysfunction**

Statins, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. It is recommended that liver Enzyme obtained prior to initiating therapy with atorvastatin and repeated as clinically indicated. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including atorvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with atorvastatin, promptly interrupt therapy. If an alternate etiology is not found, do not restart atorvastatin.

Cardace® Protect should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of Cardace® Protect.

- **Endocrine Function**

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin.

Statins interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin tablets does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of statins on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if a statin is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

- **CNS Toxicity**

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose.

- **Use in Patients with Recent Stroke or TIA (Transient Ischemic Attack)**

In a post-hoc analysis of a clinical trial where atorvastatin tablets 80 mg vs. placebo was administered in subjects without CHD who had a stroke or TIA within the preceding 6 months, a higher incidence of hemorrhagic stroke was seen in the atorvastatin 80 mg group compared to placebo. The incidence of fatal hemorrhagic stroke was similar across treatment groups. The incidence of nonfatal hemorrhagic stroke was significantly higher in the atorvastatin group as compared to the placebo group. Some baseline characteristics, including hemorrhagic and lacunar stroke on study entry, were associated with a higher incidence of hemorrhagic stroke in the atorvastatin group.

PREGNANCY

Cardace® Protect must not be taken during pregnancy (see also under “Contraindications”). Therefore, pregnancy must be excluded before starting treatment. Pregnancy must be avoided in cases where treatment with ACE inhibitors is indispensable. If the patient intends to become pregnant, treatment with ACE inhibitors must be discontinued, i.e. replaced by another form of treatment. If the patient becomes pregnant during treatment, medication with Cardace® Protect must be replaced as soon as possible by a treatment regimen without ACE inhibitors. Otherwise there is a risk of harm to the fetus.

LACTATION

Because insufficient information is available Cardace® Protect is not recommended during lactation.

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS

Some adverse effects (e.g. some symptoms of a reduction in blood pressure such as lightheadedness, dizziness) may impair the patient's ability to concentrate and react and, therefore, constitute a risk in situations where these abilities are of particular importance (e.g. operating a vehicle or machinery).

INTERACTIONS

RAMIPRIL

Food

Absorption of ramipril is not significantly affected by food.

Drug interactions

Contra-indicated combinations

The concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see Section Contraindications).

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 sulfate: Risk of severe anaphylactoid reactions; see also under "Contraindications".

The combination of Ramiprilwith aliskiren-containing medicines is contraindicated in patients with diabetes mellitus or with moderate to severe renal impairment (creatinine clearance < 60 ml/min) and is not recommended in other patients (see Contraindications and Precautions).

Angiotensin-II Receptor Antagonists (AIIRAs): The use of Ramipril in combination with an AIIRA is contraindicated in patients with diabetic nephropathy and is not recommended in other patients (see section Contraindications and section Precautions).

Not recommended associations:
Potassium salts, potassium-retaining diuretics or other medicinal products that may increase kalaemia: Rise in serum potassium concentration, sometimes severe, is to be anticipated. Concomitant treatment with potassium retaining diuretics (e.g. spironolactone), potassium salts or other medicinal products that may increase kalaemia requires close monitoring of serum potassium.

Precautions for use:
Antihypertensive agents (e.g. diuretics) and other substances with antihypertensive potential (e.g. nitrates, tricyclic antidepressants, anaesthetics): Potentiation of the antihypertensive effect is to be anticipated (concerning diuretics see also under “Precautions”, “Adverse reactions” and "Dosage and administration"). Regular monitoring of serum sodium is recommended in patients undergoing concurrent diuretic therapy.

Vasopressor Sympathomimetics: These may reduce the antihypertensive effect of ramipril. Particularly close blood pressure monitoring is recommended.

Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood picture: Increased likelihood of haematological reactions (see also under “Precautions”).

Lithium Salts: Excretion of lithium may be reduced by ACE inhibitors. Such reduction may lead to increased serum lithium levels and increased lithium toxicity. Lithium levels must, therefore, be monitored.

Antidiabetic Agents (e.g. insulin and sulfonylurea derivatives): ACE inhibitors may reduce insulin resistance. In isolated cases, such reduction may lead to hypoglycaemic reactions in patients concomitantly treated with anti-diabetics. Particularly close blood glucose monitoring is, therefore, recommended in the initial phase of co-administration.

Vildagliptin: An increased incidence of angioedema was found in patients taking ACE Inhibitors and vildagliptin.

mTOR Inhibitors (e.g. temsirolimus): An increased incidence of angioedema was observed in patients taking ACE Inhibitors and mTOR Inhibitors (mammalian target of rapamycin inhibitors).

Neprilysin (NEP) inhibitors: An increased risk of angioedema has been reported with concomitant use of ACE inhibitors and NEP inhibitors (such as racecadotril and) (see Section Warnings)

Take into account:
Nonsteroidal anti-inflammatory drugs (e.g. Indomethacin) and acetylsalicylic acid: Attenuation of the antihypertensive effect of ramipril is to be anticipated. Furthermore, concomitant treatment of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium.

HEPARIN: Rise in serum potassium concentration possible.

ALCOHOL: Increased vasodilatation. Ramipril may potentiate the effect of alcohol.

SALT: Increased dietary salt intake may attenuate the antihypertensive effect of ramipril.

DESENSITIZATION THERAPY: The likelihood and severity of anaphylactic and anaphylactoid reactions to insect venoma is increased under ACE inhibition. It is assumed that this effect may also occur in connection with other allergens.

ATORVASTATIN
The risk of myopathy during treatment with statins is increased with concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin, cyclosporine, or strong CYP 3A4 inhibitors (e.g., clarithromycin, HIV protease inhibitors, and itraconazole).

Strong Inhibitors of CYP 3A4: Atorvastatin tablets is metabolized by cytochrome P450 3A4. Concomitant administration of atorvastatin tablets with strong inhibitors of CYP 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depend on the variability of effect on CYP 3A4.

Clarithromycin: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin tablets 80 mg with clarithromycin (500 mg twice daily) compared to that of atorvastatin alone. Therefore, in patients taking clarithromycin, caution should be used when the atorvastatin dose exceeds 20mg.

- **Combination of Protease Inhibitors:** Atorvastatin AUC was significantly increased with several combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor telaprevir, compared to that of atorvastatin alone . Therefore, in patients taking HIV protease inhibitor, Tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of atorvastatin should be avoided. In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing atorvastatin and the lowest dose necessary should be used. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the dose of atorvastatin should not exceed 20 mg and should be used with caution (see *Warnings and Precautions,* and *Dosage and Administration)* In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, the dose of atorvastatin should not exceed 40 mg and close clinical monitoring is recommended.
    - **Itraconazole:** Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 40 mg and itraconazole 200 mg. Therefore, in patients taking itraconazole, caution should be used when the atorvastatin dose exceeds 20 mg.

      Grapefruit Juice: Contains one or more components that inhibit CYP 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 liters per day).

    - **Cyclosporine:** Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g., cyclosporine) can increase the bioavailability of atorvastatin. Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day compared to that of atorvastatin tablets alone.The coadministration of atorvastatin with cyclosporine should be avoided (see "Warnings and Precautions").

    - **Gemfibrozil:** Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are coadministered with gemfibrozil, concomitant administration of atorvastatin with gemfibrozil should be avoided (see "Warnings and Precautions")

    - **Other Fibrates**: Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of other fibrates, atorvastatin should be administered with caution when used concomitantly with other fibrates (see "Warnings and Precautions")

    - **Niacin:** The risk of skeletal muscle effects may be enhanced when atorvastatin is used in combination with niacin; a reduction in atorvastatin dosage should be considered in this setting (see "Warnings and Precautions")

    - **Rifampin or other Inducers of Cytochrome P450 3A4:** Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (e.g., efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

- **Digoxin:** When multiple doses of Atorvastatin Tablets and digoxin were coadministered, steady state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.

- **Oral Contraceptives:** Co-administration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

- **Warfarin:** Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

- **Colchicine**: Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin co administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.

ADVERSE REACTIONS

Ramipril

As ramipril is an antihypertensive, many of its adverse reactions are effects secondary to its blood-pressure lowering action which results in adrenergic counter-regulation or organ hypoperfusion. Numerous other effects (e.g. effects on electrolyte balance, certain anaphylactoid reactions or inflammatory reactions of the mucous membranes) are due to the ACE inhibition or to other pharmacologic actions of this drug class.

The following CIOMS frequency rating is used, when applicable:
Very common ≥ 10 %; Common ≥ 1 and <10 % ; Uncommon ≥ 0.1 and < 1 %;
Rare ≥ 0.01 and < 0.1 %; Very rare < 0.01 %, Unknown (cannot be estimated from available data).

	Common	Uncommon	Rare	Very rare	Not known
Cardiac Disorders		Myocardial ischaemia including angina pectoris or myocardial infarction, tachycardia, arrhythmia, palpitations, oedema peripheral			
Blood and lymphatic system disorders		Eosinophilia	White blood cell count decreased (including neutropenia or agranulocytosis), red blood cell count decreased, haemoglobin decreased, platelet count decreased		Bone marrow failure, pancytopenia, haemolytic anaemia
Nervous system Disorders	Headache, dizziness (lightheadedness)	Vertigo, paraesthesia, ageusia (loss of	Tremor, balance disorder		Cerebral ischaemia including

		taste), dysgeusia (taste disturbances)			ischaemic stroke and transient ischaemic attack, psychomotor skills impaired (impaired reactions), burning sensation, parosmia (smell disturbances)
Eye disorders		Visual disturbance including blurred vision	Conjunctivitis		
Ear and labyrinth disorders			Hearing impaired, tinnitus		
Respiratory, thoracic and mediastinal disorders	Non-productive tickling cough, bronchitis, sinusitis, dyspnoea	Bronchospasm including asthma aggravated, nasal congestion			
Gastrointestinal Disorders	Gastrointestinal inflammation (inflammatory reactions of the gastrointestinal tract), digestive disturbances, abdominal discomfort, dyspepsia, diarrhoea, nausea, vomiting	Fatal pancreatitis (cases of fatal outcome have been very exceptionally reported with ACE inhibitors), pancreatic enzymes increased, small bowel angioedema, abdominal pain upper including gastritis, constipation, dry mouth	Glossitis		Aphtous stomatitis (inflammatory reactions of the oral cavity)
Renal and urinary disorders		Renal impairment including renal failure acute, urine output increased, worsening of a pre-existing proteinuria,			

		blood urea increased, blood creatinine increased			
Skin and subcutaneous tissue disorders	Rash in particular maculo-papular	Angioedema with fatal outcome (maybe/become Life-threatening, rarely severe course can cause fatal obstruction); pruritus, hyperhidrosis (sweating)	Exfoliative dermatitis, urticaria, onycholysis	Photosensitivity reaction	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pemphigus, psoriasis aggravated, dermatitis psoriasiform, pemphigoid or lichenoid exanthema or enanthema, alopecia
Musculoskeletal and connective tissue disorders	Muscle spasms (muscle cramps), myalgia	Arthralgia			
Endocrine disorders					Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	Blood potassium increased	Anorexia, decreased appetite			Blood sodium Decreased
Vascular Disorders	Hypotension, orthostatic blood pressure decreased (disturbed orthostatic regulation), syncope	Flushing	Vascular stenosis, hypoperfusion (exacerbation of perfusion disturbances, vasculitis		Raynaud's Phenomenon
General disorders and administration site conditions	Chest pain, fatigue	Pyrexia (fever)	Asthenia (weakness)		
Immune system Disorders					Anaphylactic or anaphylactoid reactions (severe anaphylactic and

					anaphylactoid reactions to insect venoma is increased under ACE inhibition), antinuclear antibody increased
Hepatobiliary Disorders		Hepatic enzymes and/or bilirubin conjugated increased	Jaundice cholestatic, hepatocellular damage		Acute hepatic failure, cholestatic or cytolytic hepatitis (fatal outcome has been very exceptional)
Reproductive system and breast disorders		Transient erectile impotence, libido decreased			Gynaecomastia
Psychiatric Disorders		Depressed mood, anxiety, nervousness, restlessness, sleep disorder including somnolence (drowsiness)	Confusional state		Disturbance in Attention

Atorvastatin

The following serious adverse reactions Rhabdomyolysis and myopathy , Liver enzyme abnormalities are mentioned under Warnings and Precautions

The most commonly reported adverse reactions (incidence ≥ 2%) in patients treated with atorvastatin in placebo controlled trials regardless of causality were : nasopharyngitis, arthralgia, diarrhea, pain in extremity, urinary tract infection.

Other adverse reactions reported in placebo-controlled studies include :

Body as a whole: malaise, pyrexia; *Digestive system:* abdominal discomfort, eructation, flatulence, hepatitis, cholestasis; *Musculoskeletal system:* musculoskeletal pain, muscle fatigue, neck pain, joint swelling; *Metabolic and nutritional system:* transaminases increase, liver function test abnormal, blood alkaline phosphatase increase, creatine phosphokinase increase, hyperglycemia; *Nervous system:* nightmare; *Respiratory system:* epistaxis; *Skin and appendages:* urticaria; *Special senses:* vision blurred, tinnitus; *Urogenital system:* white blood cells urine positive.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Atorvastatin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions associated with atorvastatin therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic

epidermal necrolysis), rhabdomyolysis, myositis, fatigue, tendon rupture, fatal and non-fatal hepatic failure, dizziness, depression, peripheral neuropathy, and pancreatitis and interstitial lung disease.

There have been rare reports of immune-mediated necrotizing myopathy associated with statin use [see *Warnings and Precautions*].

There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

OVERDOSE

RAMIPRIL

Signs and Symptoms:

Overdosage may cause excessive peripheral vasodilatation (with marked hypotension, shock), bradycardia, electrolyte disturbances, and renal failure.

Management:

Primary detoxification by, for example, gastric lavage, administration of adsorbents, sodium sulfate; (if possible during the first 30 minutes). In the event of hypotension administration of α_1-adrenergic agonists (e.g. norepinephrine, dopamine) or angiotensin II (angiotensinamide), which is usually available only in scattered research laboratories, must be considered in addition to volume and salt substitution**.**

No experience is available concerning the efficacy of forced diuresis, alteration in urine pH, haemofiltration, or dialysis in speeding up the elimination of ramipril or ramiprilat. If dialysis or haemofiltration is nevertheless considered, see under “Contraindications”.

ATORVASTATIN

There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

MANUFACTURED BY:

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Source: CCDS version 18 dated 09th November 2017 + Lipitor pack insert dated 12/2018 (accessed on 16th March 2021)