

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 ADMINISTRATION

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, or any of the excipients of Cardace[®] Protect.
- Hypersensitivity to atorvastatin or any excipients in Atorvastatin calcium containing tablets.. Hypersensitivity reactions, including anaphylaxis, angioneurotic edema, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported (see Adverse Reactions)
- 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 hemodynamically relevant renal artery stenosis, bilateral or unilateral in the single kidney.
- In patients with hypotensive or hemodynamically 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.

- During pregnancy.
- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels.
-
- Acute liver failure or decompensated cirrhosis.

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 occur immediately after starting treatment with an ACE inhibitor however severe angioedema may also occur at any time during long-term treatment with an ACE inhibitor. In case of angioedema, Cardace® Protect must be discontinued immediately.

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. Healthcare professionals should review the response to treatment noting standard therapies for histamine-mediated angioedema may be ineffective for bradykinin-mediated angioedema. 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 section Contraindications and section Interactions).

The use of Cardace® Protect in combination with an AIIRA is contraindicated in patients with diabetic nephropathy (see section Contraindications and section 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 section 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 hemodynamically 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 hemodynamically 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 Cardace® Protect 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 section "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 hemodynamically 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 also 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 hemodynamically 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.

- **Hematological 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

Myopathy and Rhabdomyolysis

Atorvastatin may cause myopathy (muscle pain, tenderness, or weakness with elevated creatine kinase (CK)) and rhabdomyolysis. Acute kidney injury secondary to myoglobinuria and rare fatalities have occurred as a result of rhabdomyolysis in patients treated 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 (including other lipid-lowering therapies) and higher Atorvastatin dosage(see Drug Interactions).

Steps to Prevent or Reduce the Risk of Myopathy and Rhabdomyolysis

Atorvastatin exposure may be increased by drug interactions due to inhibition of cytochrome P450 enzyme 3A4 (CYP3A4) and/or transporters (e.g., breast cancer resistant protein [BCRP], organic anion-transporting polypeptide [OATP1B1/OATP1B3] and P-glycoprotein [P-gp]), resulting in an increased risk of myopathy and rhabdomyolysis. Concomitant use of cyclosporine, gemfibrozil, tipranavir plus ritonavir, or glecaprevir plus pibrentasvir with Atorvastatin is not recommended. Atorvastatin dosage modifications are recommended for patients taking certain anti-viral, azole antifungals, or macrolide antibiotic medications. Cases of myopathy/rhabdomyolysis have been reported with atorvastatin co-administered with lipid modifying doses (>1 gram/day) of niacin, fibrates, colchicine, and ledipasvir plus sofosbuvir. Consider if the benefit of use of these products outweighs the increased risk of myopathy and rhabdomyolysis.(see Drug Interactions).

Concomitant intake of large quantities, more than 1.2 liters daily, of grapefruit juice is not recommended in patients taking atorvastatin. (see Drug Interactions).

Discontinue atorvastatin if markedly elevated CK levels occur or if myopathy is either diagnosed or suspected. Muscle symptoms and CK elevations may resolve if Atorvastatin is discontinued. Temporarily discontinue Atorvastatin in patients experiencing an acute or serious condition at high risk of developing renal failure secondary to rhabdomyolysis (e.g., sepsis; shock; severe hypovolemia; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy).

Inform patients of the risk of myopathy and rhabdomyolysis when starting or increasing the Atorvastatin dosage. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Immune-Mediated Necrotizing Myopathy

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use, including reports of recurrence when the same or different statin was administered. IMNM is characterized by proximal muscle weakness and elevated serum creatine kinase that persist despite discontinuation of statin treatment; positive anti-HMG CoA reductase antibody; muscle biopsy showing necrotizing myopathy; and improvement with immunosuppressive agents. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required. Discontinue atorvastatin if IMNM is suspected.

Hepatic Dysfunction

Increases in serum transaminases have been reported with use of Atorvastatin [see Adverse Reactions]. In most cases, these changes appeared soon after initiation, were transient, were not accompanied by symptoms, and resolved or improved on continued therapy or after a brief interruption in therapy. Persistent increases to more than three times the ULN in serum transaminases have occurred in approximately 0.7% of patients receiving Atorvastatin in clinical trials. There have been rare post marketing reports of fatal and non-fatal hepatic failure in patients taking statins, including atorvastatin.

Patients who consume substantial quantities of alcohol and/or have a history of liver disease may be at increased risk for hepatic injury.

Consider liver enzyme testing before Atorvastatin initiation and when clinically indicated thereafter. Atorvastatin is contraindicated in patients with acute liver failure or decompensated cirrhosis [see Contraindications]. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue Atorvastatin.

Increases in HbA1c and Fasting Serum Glucose Levels

Increases in HbA1c and fasting serum glucose levels have been reported with statins, including atorvastatin. Optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices.

Increased Risk of Hemorrhagic Stroke in Patients on Atorvastatin 80mg with recent Hemorrhagic Stroke

In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial where 2365 adult patients, without CHD who had a stroke or TIA within the preceding 6 months, were treated with Atorvastatin calcium 80 mg, a higher incidence of hemorrhagic stroke was seen in the atorvastatin 80 mg group compared to placebo (55, 2.3% Atorvastatin calcium vs. 33, 1.4% placebo; HR: 1.68, 95% CI:1.09, 2.59; p=0.0168).. The incidence of fatal hemorrhagic stroke was similar across treatment groups (17 vs. 18 for the atorvastatin and placebo groups, respectively). The incidence of nonfatal hemorrhagic stroke was significantly higher in the atorvastatin calcium group (38, 1.6%) as compared to the placebo group (16, 0.7%). Some baseline characteristics, including hemorrhagic and lacunar stroke on study entry group, were associated with a higher incidence of hemorrhagic stroke in the atorvastatin calcium group [see Adverse Reactions]. Consider the risk/benefit of use of atorvastatin 80 mg in patients with recent hemorrhagic stroke.

PREGNANCY

RAMIPRIL

Cardace® Protect must not be taken during pregnancy (see also under section “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.

ATORVASTATIN

Discontinue atorvastatin when pregnancy is recognized. Alternatively, consider the ongoing therapeutic needs of the individual patient. Atorvastatin decreases synthesis of cholesterol and possibly other biologically active substances derived from cholesterol; therefore, atorvastatin may cause fetal harm when administered to pregnant patients based on the mechanism of action. In addition, treatment of hyperlipidemia is not generally necessary during pregnancy. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hyperlipidemia for most patients.

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 Ramipril with 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 Interactions).

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 Interactions).

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 "Interactions", section "Adverse reactions" and section "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 section “Interactions”).

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 venom 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 (see Warnings and Precautions)

Drug Interactions that may Increase the Risk of Myopathy and Rhabdomyolysis with Atorvastatin

Atorvastatin is a substrate of CYP3A4 and transporters (e.g., OATP1B1/1B3, P-gp, or BCRP). Atorvastatin plasma levels can be significantly increased with concomitant administration of inhibitors of CYP3A4 and transporters. Table 1 includes a list of drugs that may increase exposure to Atorvastatin and may increase the risk of myopathy and rhabdomyolysis when used concomitantly and instructions for preventing or managing them.

Table 1: Drug Interactions that may Increase the Risk of Myopathy and Rhabdomyolysis with Atorvastatin
Cyclosporine or Gemfibrozil

Concomitant use of cyclosporine or gemfibrozil with Atorvastatin is not recommended.
Anti-Viral Medications
- Concomitant use of tipranavir plus ritonavir or glecaprevir plus pibrentasvir with Atorvastatin is not recommended. - In patients taking lopinavir plus ritonavir, or simeprevir, consider the risk/benefit of concomitant use with atorvastatin. - In patients taking saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, elbasvir plus grazoprevir or letermovir, do not exceed atorvastatin 20 mg. - In patients taking nelfinavir, do not exceed atorvastatin 40 mg - Consider the risk/benefit of concomitant use of ledipasvir plus sofosbuvir with Atorvastatin. - Monitor all patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Select Azole Antifungals or Macrolide Antibiotics
In patients taking clarithromycin or itraconazole, do not exceed Atorvastatin 20 mg. Consider the risk/benefit of concomitant use of other azole antifungals or macrolide antibiotics with Atorvastatin. Monitor all patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Niacin
Consider if the benefit of using lipid modifying dosages of niacin concomitantly with Atorvastatin outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Fibrates (other than Gemfibrozil)
Consider if the benefit of using fibrates concomitantly with Atorvastatin outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Colchicine
Consider the risk/benefit of concomitant use of colchicine with Atorvastatin. If concomitant use is decided, monitor patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Grapefruit Juice
Avoid intake of large quantities of grapefruit juice, more than 1.2 liters daily, when taking Atorvastatin.

Drug Interactions that may Decrease Exposure to Atorvastatin

Table 2 presents drug interactions that may decrease exposure to Atorvastatin and instructions for preventing or managing them.

Table 2: Drug Interactions that may Decrease Exposure to Atorvastatin.
Rifampin

Intervention:	Administer Atorvastatin and rifampin simultaneously.
---------------	--

Atorvastatin Effects on Other Drugs

Table 3 presents Atorvastatin's effect on other drugs and instructions for preventing or managing them.

Table 3: Atorvastatin Effects on Other Drugs	
Oral Contraceptives	
Intervention:	Consider this when selecting an oral contraceptive for patients taking Atorvastatin.
Digoxin	
Intervention:	Monitor patients taking digoxin appropriately.

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 $\geq 10\%$; 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).

Table 4:

	Common	Uncommon	Rare	Very rare	Not known
Cardiac Disorders		Myocardial ischemia 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, hemolytic anemia
Nervous system Disorders	Headache, dizziness (lightheadedness)	Vertigo, paresthesia, ageusia (loss of taste),	Tremor, balance disorder		Cerebral ischemia including ischemic

		dysgeusia (taste disturbances)			stroke and transient ischemic 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, dyspnea	Bronchospasm including asthma aggravated, nasal congestion			
Gastrointestinal Disorders	Gastrointestinal inflammation (inflammatory reactions of the gastrointestinal tract), digestive disturbances, abdominal discomfort, dyspepsia, diarrhea, 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			Gynecomastia
Psychiatric Disorders		Depressed mood, anxiety, nervousness, restlessness, sleep disorder including somnolence (drowsiness)	Confusional state		Disturbance in Attention

ATORVASTATIN

The following important adverse reactions are described below and elsewhere in the labelling:

- Myopathy and Rhabdomyolysis [See Warnings and Precautions]
- Immune-Mediated Necrotizing Myopathy [See Warnings and Precautions].
- Hepatic Dysfunction [See Warnings and Precautions].
- Increases in HbA1c and Fasting Serum Glucose Levels [See Warnings and Precautions]

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the Atorvastatin placebo-controlled clinical trial database of 16,066 patients (8755 Atorvastatin vs. 7311 placebo; age range 10-93 years, 39% women, 91% White, 3% Black, 2% Asian, 4% other) with a median treatment duration of 53 weeks, the most common adverse reactions in patients treated with atorvastatin that led to treatment discontinuation and occurred at a rate greater than placebo were: myalgia (0.7%), diarrhea (0.5%), nausea (0.4%), alanine aminotransferase increase (0.4%), and hepatic enzyme increase (0.4%).

Table 5 summarizes adverse reactions reported in $\geq 2\%$ and at a rate greater than placebo in patients treated with atorvastatin (n=8755), from seventeen placebo-controlled trials.

Table 5: Adverse Reactions Occurring in $\geq 2\%$ in Patients Atorvastatin-Treated with any Dose and Greater than Placebo						
Adverse Reaction	% Placebo N=7311	% 10 mg N=3908	% 20 mg N=188	% 40 mg N=604	% 80 mg N=4055	% Any dose N=8755
Nasopharyngitis	8.2	12.9	5.3	7.0	4.2	8.3
Arthralgia	6.5	8.9	11.7	10.6	4.3	6.9
Diarrhea	6.3	7.3	6.4	14.1	5.2	6.8
Pain in extremity	5.9	8.5	3.7	9.3	3.1	6.0
Urinary tract infection	5.6	6.9	6.4	8.0	4.1	5.7
Dyspepsia	4.3	5.9	3.2	6.0	3.3	4.7
Nausea	3.5	3.7	3.7	7.1	3.8	4.0
Musculoskeletal pain	3.6	5.2	3.2	5.1	2.3	3.8
Muscle spasms	3.0	4.6	4.8	5.1	2.4	3.6
Myalgia	3.1	3.6	5.9	8.4	2.7	3.5
Insomnia	2.9	2.8	1.1	5.3	2.8	3.0
Pharyngolaryngeal pain	2.1	3.9	1.6	2.8	0.7	2.3

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.

Elevations in Liver Enzyme Tests

Persistent elevations in serum transaminases, defined as more than 3 times the ULN and occurring on 2 or more occasions, occurred in 0.7% of patients who received Atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.

One patient in clinical trials developed jaundice. Increases in liver enzyme tests in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent liver enzyme elevations continued treatment with a reduced dose of atorvastatin

Treating to New Targets Study (TNT)

In TNT, 10,001 patients (age range 29-78 years, 19% women; 94% White, 3% Black, 1% Asian, 2% other) with clinically evident CHD were treated with atorvastatin 10 mg daily (n=5006) or atorvastatin 80 mg daily (n=4995). In the high-dose atorvastatin group, there were more patients with serious adverse reactions (1.8%) and discontinuations due to adverse reactions (9.9%) as compared to the low-dose group (1.4%; 8.1%,

respectively) during a median follow-up of 4.9 years. Persistent transaminase elevations ($\geq 3 \times \text{ULN}$ twice within 4-10 days) occurred in 1.3% of individuals with atorvastatin 80 mg and in 0.2% of individuals with atorvastatin 10 mg. Elevations of CK ($\geq 10 \times \text{ULN}$) were higher in the high-dose atorvastatin group (0.3%) compared to the low-dose atorvastatin group (0.1%).

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)

In SPARCL, 4731 patients (age range 21 to 92 years, 40% women; 93% White, 3% Black, 1% Asian, 3% other) without clinically evident CHD but with a stroke or transient ischemic attack (TIA) within the previous 6 months were treated with Atorvastatin 80 mg (n=2365) or placebo (n=2366) for a median follow-up of 4.9 years. There was a higher incidence of persistent hepatic transaminase elevations ($\geq 3 \times \text{ULN}$ twice within 4-10 days) in the atorvastatin group (0.9%) compared to placebo (0.1%). Elevations of CK ($>10 \times \text{ULN}$) were rare, but were higher in the atorvastatin group (0.1%) compared to placebo (0.0%). Diabetes was reported as an adverse reaction in 6.1% of subjects in the atorvastatin group and 3.8% of subjects in the placebo group.

In a post-hoc analysis, Atorvastatin 80 mg reduced the incidence of ischemic stroke (9.2% vs. 11.6%) and increased the incidence of hemorrhagic stroke (2.3% vs. 1.4%) compared to placebo. The incidence of fatal hemorrhagic stroke was similar between groups (17 atorvastatin vs. 18 placebo). The incidence of non-fatal hemorrhagic strokes was significantly greater in the atorvastatin group (38 non-fatal hemorrhagic strokes) as compared to the placebo group (16 non-fatal hemorrhagic strokes). Patients who entered the trial with a hemorrhagic stroke appeared to be at increased risk for hemorrhagic stroke (16% atorvastatin vs. 4% placebo).

Adverse Reactions from Clinical Studies of atorvastatin in Pediatric Patients with HeFH

In a 26-week controlled study in pediatric patients with HeFH (ages 10 years to 17 years) (n=140, 31% female; 92% White, 1.6% Blacks, 1.6% Asians, 4.8% other), the safety and tolerability profile of atorvastatin 10 to 20 mg daily, as an adjunct to diet to reduce total cholesterol, LDL-C, and apo B levels, was generally similar to that of placebo.

Postmarketing Experience

The following adverse reactions have been identified during post-approval 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.

Gastrointestinal disorders: pancreatitis

General disorders: fatigue

Hepatobiliary Disorders: fatal and non-fatal hepatic failure

Immune system disorders: anaphylaxis

Injury: tendon rupture

Musculoskeletal and connective tissue disorders: rhabdomyolysis, myositis.

There have been rare reports of immune-mediated necrotizing myopathy associated with statin use

Nervous system disorders: dizziness, peripheral neuropathy.

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

Psychiatric disorders: depression

Respiratory disorders: interstitial lung disease

Skin and subcutaneous tissue disorders: angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis)

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 also under section “Contraindications”).

ATORVASTATIN

No specific antidotes for atorvastatin are known. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

MANUFACTURED BY:

Sanofi India Limited, L-121, Verna Industrial Estate, Verna, Goa- 403722, India

Updated: April 2026

Source: CCDS version 19 dated 15th January 2026 + [Atorvastatin: Package Insert / Prescribing Information](#) updated on 31st March, 2026 (Accessed on 6th April 2026).