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INSTRUCTION
for medical use

ATSAT®

Composition:
active substance: atorvastatin;
1 tablet contains atorvastatin calcium equivalent to 10 mg, 20 mg, 40 mg or 80 mg of atorvastatin;
excipients: lactose monohydrate, microcrystalline cellulose, calcium carbonate, povidone K30, sodium croscarmellose, silica colloidal anhydrous, magnesium stearate, Opadry 03F84827 pink*;
*Opadry 03F84827 pink: hypromellose, titanium dioxide (E 171), polyethylene glycol, talc, iron oxide red (E 172).

Pharmaceutical form. Coated tablets.
Main physico-chemical properties:
10 mg, 20 mg coated tablets: round biconvex pink coated tablets, marked with "10" or "20" on one side;
40 mg, 80 mg coated tablets: round biconvex pink coated tablets, smooth on both sides.

Pharmacotherapeutic group.
Serum cholesterol and triglyceride reducing agents.
HMG-CoA reductase inhibitors. ATC Code C10A A05.

Pharmacological properties.
Pharmacodynamics.
Atsat® contains the active substance atorvastatin. Atorvastatin is a selective competitive inhibitor of HMG-CoA-reductase, an enzyme that determines the rate of conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A into mevalonate, a precursor of sterols, including cholesterol.
In experimental animal models atorvastatin lowered plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL; atorvastatin also reduces LDL production and the number of these particles.
Atorvastatin as well as some of its metabolites are pharmacologically active in humans. The liver is the primary site of action of atorvastatin and the principal site of cholesterol synthesis and LDL clearance. Drug dosage rather than systemic drug concentration correlates better with LDL cholesterol reduction. Individualization of drug dosage should be based on the therapeutic response (see section “Dosage and administration”).
Pharmacokinetics.
Absorption.
Atorvastatin is rapidly absorbed after oral administration and reaches maximum plasma concentrations within 1–2 hours. The level of absorption increases in proportion to the dose of atorvastatin. The absolute

bioavailability of atorvastatin (parent drug) is approximately 14 % and the systemic availability of inhibitory activity relative to HMG-CoA reductase is about 30 %. The low systemic bioavailability is due to presystemic clearance in the gastrointestinal mucosa and/or presystemic biotransformation in the liver. Although food intake reduces the rate and extent of drug absorption by approximately 25 % and 9 % respectively, as confirmed by C_{max} and AUC (area under the "concentration-time" curve), LDL cholesterol reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (by approximately 30 % according to C_{max} and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of drug administration (see section “Dosage and administration”).

Distribution.

The mean volume of distribution of atorvastatin is approximately 381 liters. Over 98 % of the drug is bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Atorvastatin is thought to be able to penetrate into breast milk (see sections “Contraindications” and “Administration details”).

Metabolism.

Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. In *in vitro* studies, the 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. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4 (CYP 3A4), consistent with increased plasma concentrations of atorvastatin in humans following co-administration with erythromycin, a known inhibitor of this isozyme (see “Interaction with other medicinal products and other types of interaction”).

Excretion.

Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism, however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2 % of the dose is recovered in urine following oral administration.

Special patient populations

Elderly patients.

Plasma concentrations of atorvastatin are higher (approximately 40 % for C_{max} and 30 % for AUC) in healthy elderly subjects (over 65 years of age) than in young adults. Clinical data suggest a greater degree of LDL reduction at any dose of the drug in elderly patients compared to younger adults (see section “Administration details”).

Children.

The apparent clearance upon oral administration of atorvastatin in children was similar to the clearance in adults when scaled allometrically by body weight, since body weight was the only significant covariate in the population pharmacokinetic model of atorvastatin with data that included children with heterozygous familial hypercholesterolemia (aged 10 to 17 years old, n = 29) in an open 8-week study.

Gender.

Plasma concentrations of atorvastatin in women differ from those in men (approximately 20 % higher for C_{max} and 10 % lower for AUC). However, there is no clinically significant difference in LDL-C reduction with atorvastatin between men and women.

Renal dysfunction.

Renal disease has no influence on the plasma concentrations of atorvastatin or LDL-C reduction, thus, dose adjustment in patients with renal dysfunction is not necessary (see section “Dosage and administration”, “Administration details”).

Hemodialysis.

While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance the clearance of atorvastatin since the drug is extensively bound to plasma proteins.

Hepatic insufficiency.

Plasma concentrations of atorvastatin are markedly increased in patients with chronic alcoholic liver disease. C_{max} and AUC are each 4-fold greater in patients with Child-Pugh class A disease. C_{max} and AUC

are approximately 16-fold and 11-fold increased, respectively, in patients with Child-Pugh class B liver disease (see section “Contraindications”).

Interaction studies.

Atorvastatin is a substrate of hepatic transporters, OATP1B1 and OATP1B3 transporters. Metabolites of atorvastatin are OATP1B1 substrates. Atorvastatin is also identified as a substrate of the breast cancer resistance protein (BCRP) efflux transporter, which may limit the intestinal absorption and biliary clearance of atorvastatin.

Table 1

Effect of co-administered medicinal products on the pharmacokinetics of atorvastatin

Co-administered medicinal products and dosing regimen	Atorvastatin		
	Dose (mg)	*Ratio of AUC*[&]	*Ratio of* C_{max}[&]
[#]Ciclosporin 5,2 mg/kg/day, stable dose	10 mg once daily for 28 days	8,69	10,66
[#]Tipranavair 500 mg twice daily / ritonavir 200 mg twice daily, 7 days	10 mg single dose	9,36	8,58
[#]Glecaprevir 400 mg once daily / pibrentasvir 120 mg once daily, 7 days	10 mg once daily for 7 days	8,28	22,00
[#]Telaprevir 750 mg every 8 hours, 10 days	20 mg single dose	7,88	10,60
[#, ‡]Saquinavir 400 mg twice daily / ritonavir 400 mg twice daily, 15 days	40 mg once daily for 4 days	3,93	4,31
[#]Elbasvir 50 mg once daily / grazoprevir 200 mg once daily, 13 days	10 mg single dose	1,94	4,34
[#]Simeprevir 150 mg once daily, 10 days	40 mg single dose	2,12	1,70
[#]Clarithromycin 500 mg twice daily, 9 days	80 mg once daily for 8 days	4,54	5,38
[#]Darunavir 300 mg twice daily / ritonavir 100 mg twice daily, 9 days	10 mg once daily for 4 days	3,45	2,25
[#]Itraconazole 200 mg once daily, 4 days	40 mg single dose	3,32	1,20
Letermovir 480 mg once daily, 10 days	20 mg single dose	3,29	2,17
[#]Fosamprenavir 700 mg twice daily / ritonavir 100 mg twice daily, 14 days	10 mg once daily for 4 days	2,53	2,84
[#]Fosamprenavir 1400 mg twice daily, 14 days	10 mg once daily for 4 days	2,30	4,04
[#]Nelfinavir 1250 mg twice daily, 14 days	10 mg once daily for 28 days	1,74	2,22
[#]Grapefruit juice, 240 ml once daily *	40 mg once daily	1,37	1,16
Diltiazem 240 mg once daily, 28 days	40 mg once daily	1,51	1,00
Erythromycin 500 mg four times daily, 7 days	10 mg once daily	1,33	1,38
Amlodipine 10 mg, single dose	80 mg once daily	1,18	0,91
Cimetidine 300 mg four times daily, 2 weeks	10 mg once daily for 2 weeks	1,00	0,89
Colestipol 10 g twice daily, 24 weeks	40 mg once daily for 8 weeks	Not used	0,74**

Maalox TC® 30 ml four times daily, 17 days	10 mg once daily for 15 days	0,66	0,67
Efavirenz 600 mg once daily, 14 days	10 mg for 3 days	0,59	1,01
#Rifampin 600 mg once daily, 7 days (co-administered) †	40 mg once daily	1,12	2,90
#Rifampin 600 mg once daily, 5 days (separated doses) †	40 mg once daily	0,20	0,60
#Gemfibrozil 600 mg twice daily, 7 days	40 mg once daily	1,35	1,00
#Fenofibrate 160 mg once daily, 7 days	40 mg once daily	1,03	1,02
#Boceprevir 800 mg three times daily, 7 days	40 mg once daily	2,32	2,66

& Ratio of treatment methods (co-administration of the drug with atorvastatin versus atorvastatin alone).

See sections "Administration details" and "Interaction with other medicinal products and other types of interaction" for information regarding clinical significance.

* There have been reports of larger increases in AUC (ratio of AUC up to 2.5) and/or C_{cmax} (ratio of C_{max} up to 1.71) with excessive intake of grapefruit juice (750 ml – 1.2 liters per day or more).

** Ratio based on a single sample taken 8–16 post dose.

† 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.

‡ The combination dose of saquinavir + ritonavir in this study is not a clinically used dose. The increase in atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore, the drug should be used with caution and at the lowest required dose.

Table 2

Effect of atorvastatin on the pharmacokinetics of co-administered medicinal products

Atorvastatin	Co-administered medicinal product and dosing regimen		
	Medicinal product/dose (mg)	*Ratio of AUC*	*Ratio of* C_{max}
80 mg once daily for 15 days	Antipyrine 600 mg single dose	1,03	0,89
80 mg once daily for 10 days	#Digoxin 0,25 mg once daily, 20 days	1,15	1,20
40 mg once daily for 22 days	Oral contraceptives once daily, 2 months – norethisterone 1 mg – ethinylestradiol 35 µg	 1,28 1,19	 1,23 1,30
10 mg once daily	Tipranavir 500 mg twice daily / ritonavir 200 mg twice daily, 7 days	1,08	0,96
10 mg once daily for 4 days	Fosamprenavir 1400 mg twice daily, 14 days	0,73	0,82
10 mg once daily for 4 days	Fosamprenavir 700 mg twice daily / ritonavir 100 mg 2 times daily, 14 days	0,99	0,94

See section "Interaction with other medicinal products and other types of interaction" for information regarding clinical significance

Atorvastatin had no clinically significant effect on prothrombin time in patients receiving long-term warfarin treatment.

Clinical characteristics.

Indications.

Prevention of cardiovascular disease in adults

In adult patients without clinically evident ischemic heart disease, but with multiple risk factors for

ischemic heart disease such as age, smoking, hypertension, low HDL, or a family history of early ischemic heart disease, Atsat® is indicated to:

-reduce the risk of myocardial infarction;

-reduce the risk of stroke;

-reduce the risk for revascularization procedures and angina.

In adult patients with type 2 diabetes mellitus and without clinically evident ischemic heart disease, but with multiple risk factors for ischemic heart disease such as retinopathy, albuminuria, smoking, or hypertension, Atsat® is indicated to:

-reduce the risk of myocardial infarction;

-reduce the risk of stroke.

In adult patients with clinically evident ischemic heart disease, Atsat® is indicated to:

-reduce the risk of non-fatal myocardial infarction;

-reduce the risk of fatal and non-fatal stroke;

-reduce the risk for revascularization procedures;

-reduce the risk of hospitalization for congestive heart failure;

-reduce the risk of angina.

Hyperlipidemia

In adult patients

-As an adjunct to diet to reduce elevated total cholesterol, LDL-C, apolipoprotein B, and triglyceride levels, as well as to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb).

-As an adjunct to diet for the treatment of patients with elevated serum triglyceride levels (Fredrickson Type IV);

-For the treatment of patients with primary dysbetalipoproteinemia (Fredrickson Type III) who do not respond adequately to diet.

-To reduce total cholesterol and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

In children

- As an adjunct to diet to reduce total cholesterol, LDL-C, and apolipoprotein B levels in children 10 to 17 years of age with heterozygous familial hypercholesterolemia if after adequate diet therapy the following findings are present:

а) LDL-C remains ≥ 190 mg/dl (4,91 mmol/l) or

б) LDL-C remains ≥ 160 mg/dl (4,14 mmol/l) and:

• there is family history of premature cardiovascular disease or

• two or more other risk factors for cardiovascular disease are present in the pediatric patient.

Contraindications.

- Active liver disease which may include unexplained persistent elevations of liver transaminases.
- Hypersensitivity to any of the components of this medicinal product.
- Pregnancy.
- Lactation.

Interaction with other medicinal products and other types of interaction.

Atorvastatin is a substrate of CYP3A4 and transporters (e.g., OATP1B1/1B3, P-gp or BCRP). Plasma atorvastatin levels may be significantly increased upon co-administration with CYP3A4 inhibitors and transporters. Medicinal products that may increase atorvastatin exposure and the risk of myopathy and rhabdomyolysis upon co-administration, as well as recommendations regarding treatment and prevention of such risks are listed in table 3 (see sections “Administration details” and “Pharmacological properties”).

Table 3

Drug interactions that may increase the risk of myopathy and rhabdomyolysis during the use of atorvastatin

Ciclosporin or gemfibrozil

Clinical impact	Plasma atorvastatin levels increased significantly upon co-administration with ciclosporin, a CYP4A4 and OATP1B1 inhibitor (see section "Pharmacological properties"). Gemfibrozil monotherapy may cause myopathy. Concomitant use of ciclosporin or gemfibrozil with atorvastatin is associated with an increased risk of myopathy and rhabdomyolysis.
Intervention	Concomitant use of ciclosporin or gemfibrozil with atorvastatin is not recommended.
Antiviral agents	
Clinical impact	Plasma atorvastatin levels were significantly increased upon concomitant administration with many antiviral agents which are CYP3A4 inhibitors and/or transporters (e.g., BCRP, OATP1B1/1B3, P-gp, MRP2, and/or OAT2) (see section "Pharmacological properties"). Myopathy and rhabdomyolysis have been reported with concomitant use of ledipasvir + sofosbuvir with atorvastatin.
Intervention	• Concomitant use of tipranavir + ritonavir or glecaprevir + pibrentasvir with atorvastatin is not recommended. • The risk/benefit of concomitant use with atorvastatin should be assessed in patients taking lopinavir + ritonavir, or simeprevir. • In patients taking saquinavir + ritonavir, darunavir + ritonavir, fosamprenavir, fosamprenavir + ritonavir, elbasvir + grazoprevir or letermovir, the dose of atorvastatin should not exceed 20 mg. • In patients taking nelfinavir, the dose of atorvastatin should not exceed 40 mg (see section "Dosage and administration"). • The risk/benefit of concomitant use of ledipasvir + sofosbuvir with atorvastatin should be assessed. • All patients should be monitored for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration of either drug.
Examples	Tipranavir + ritonavir, glecaprevir + pibrentasvir, lopinavir + ritonavir, simeprevir, saquinavir + ritonavir, darunavir + ritonavir, fosamprenavir, fosamprenavir + ritonavir, elbasvir + grazoprevir, letermovir, nelfinavir, and ledipasvir + sofosbuvir.
Select azole antifungals or macrolide antibiotics	
Clinical impact	Atorvastatin plasma levels were significantly increased with concomitant administration of atorvastatin with select azole antifungals or macrolide antibiotics due to inhibition of CYP3A4 and/or transporters (see section "Pharmacological properties").
Intervention	In patients taking clarithromycin or itraconazole, the dose of atorvastatin should not exceed 20 mg (see section "Dosage and administration"). The risk/benefit of concomitant use of select azole antifungals or macrolide antibiotics with atorvastatin should be assessed. All patients should be monitored for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration of either drug.
Examples	Erythromycin, clarithromycin, itraconazole, ketoconazole, posaconazole, and voriconazole.
Niacin	
Clinical impact	Myopathy and rhabdomyolysis have been observed with concomitant use of lipid modifying dosages of niacin (≥1 g/day niacin) with atorvastatin.
Intervention	It should be considered whether the benefits of using lipid modifying dosages of niacin concomitantly with atorvastatin outweigh the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, patients should be monitored for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration of either drug.
Fibrates (other than gemfibrozil)	
Clinical impact	The use of fibrates as monotherapy may cause myopathy. The risk of myopathy and rhabdomyolysis is increased with concomitant use of fibrates with atorvastatin.
Intervention	It should be considered whether the benefits of using fibrates concomitantly with atorvastatin outweigh the increased risk of myopathy and rhabdomyolysis. If concomitant

	use is decided, patients should be monitored for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration of either drug.
Colchicine	
Clinical impact	Myopathy and rhabdomyolysis have been reported with concomitant use of colchicine with atorvastatin.
Intervention	The risks/benefits of concomitant use of colchicine with atorvastatin should be considered. If concomitant use is decided, patients should be monitored for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration of either drug.
Grapefruit juice	
Clinical impact	Consumption of grapefruit juice, especially in excessive amounts (more than 1.2 liters per day), can raise the plasma levels of atorvastatin and may increase the risk of myopathy and rhabdomyolysis.
Intervention	Intake of large quantities of grapefruit juice (more than 1.2 liters per day) should be avoided during the use of atorvastatin.

Table 4

Drug interactions that may decrease exposure to atorvastatin.

Rifampicin	
Clinical impact	Concomitant administration of atorvastatin with rifampicin, an inducer of cytochrome P450 3A4 and inhibitor of OATP1B1, can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampicin, delayed administration of atorvastatin after administration of rifampicin has been associated with a significant reduction in atorvastatin plasma concentrations.
Intervention	Simultaneous co-administration of atorvastatin with rifampicin is recommended.

Table 5

Atorvastatin effects on other medicinal products.

Oral contraceptives	
Clinical impact	Co-administration of atorvastatin and oral contraceptives increased plasma concentrations of norethisterone and ethinylestradiol (see section “Pharmacological properties”).
Intervention	This should be considered when selecting an oral contraceptive for patients taking atorvastatin.
Digoxin	
Clinical impact	When multiple doses of atorvastatin and digoxin were co-administered, steady state plasma digoxin concentrations increased (see section “Pharmacological properties”).
Intervention	Patients taking digoxin should be monitored appropriately.

Diltiazem hydrochloride.
Co-administration of atorvastatin (40 mg) with diltiazem (240 mg) was associated with higher plasma concentrations of atorvastatin.
Cimetidine.
Studies have revealed no signs of interaction between atorvastatin and cimetidine.
Antacids.
When atorvastatin was co-administered with an antacid suspension containing magnesium and aluminium hydroxide, plasma concentrations of atorvastatin decreased by approximately 35 %. However, the hypolipidemic action of atorvastatin was not altered.
Colestipol.
Plasma concentrations of atorvastatin were lower (ratio of atorvastatin concentration 0.74) when colestipol was co-administered with atorvastatin. However, the hypolipidemic effects were greater when atorvastatin and colestipol were co-administered than when either medicinal product was given alone.
Azithromycin.

Simultaneous prescription of atorvastatin (10 mg once daily) and azithromycin (500 mg once daily) was not accompanied by changes in plasma atorvastatin concentrations.

Transporter inhibitors.

Inhibitors of transport proteins (e.g., ciclosporin, letermovir) can increase the systemic exposure of atorvastatin (see table 1). The effect of inhibition of hepatic uptake transporters on atorvastatin exposure in hepatocytes is unknown. If concomitant administration of these drugs cannot be avoided, dose reduction and clinical monitoring of atorvastatin efficacy is recommended (see table 1).

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 atorvastatin. Appropriate clinical monitoring of such patients is recommended.

Fusidic acid.

The risk of myopathy including rhabdomyolysis may be increased with concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is currently unknown. There have been reports of rhabdomyolysis (including fatal cases) in patients receiving this combination.

If treatment with systemic fusidic acid is necessary, atorvastatin treatment should be discontinued for the entire duration of the fusidic acid treatment (see section "Administration details").

Other medicinal products.

In clinical studies, concomitant administration of atorvastatin and hypotensive agents and its administration during estrogen replacement therapy was not accompanied by clinically significant adverse effects. Interaction studies with other medicinal products have not been conducted.

Administration details.

Myopathy and rhabdomyolysis

Atorvastatin may cause myopathy (muscle pain, tenderness, or weakness associated with elevated creatine kinase (CK) over 10 times the upper limit of normal) and rhabdomyolysis (with or without acute kidney injury secondary to myoglobinuria). Rare fatalities have been reported as a result of rhabdomyolysis in patients treated with statins, including atorvastatin.

Risk factors for myopathy

Risk factors for myopathy include the age of 65 years or greater, uncontrolled hypothyroidism, renal impairment, concomitant use with certain other drugs, and higher atorvastatin doses (see section "Interaction with other medicinal products and other types of interaction").

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 resistance 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 + ritonavir, or glecaprevir + pibrentasvir with atorvastatin is not recommended. Atorvastatin dosage modifications are recommended for patients taking certain anti-virals, azole antifungals, or macrolide antibiotics (see section "Dosage and administration"). Myopathy/rhabdomyolysis have been reported with atorvastatin co-administered with lipid modifying doses (>1 g/day) of niacin, fibrates, colchicine, and ledipasvir + sofosbuvir. It should be considered whether the benefit of using these products outweighs the increased risk of myopathy and rhabdomyolysis (see section "Interaction with other medicinal products and other types of interaction").

Concomitant intake of large quantities of grapefruit juice (more than 1.2 liters per day) is not recommended in patients taking atorvastatin (see section "Interaction with other medicinal products and other types of interaction").

Atorvastatin should be discontinued if markedly elevated CK levels are observed or if myopathy is either diagnosed or suspected. Muscle symptoms and CK elevations resolve after discontinuation of atorvastatin.

Atorvastatin should be temporarily discontinued 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; uncontrolled epilepsy).

Patients should be informed of the risk of myopathy and rhabdomyolysis when starting the treatment or increasing the atorvastatin dosage. Patients should be instructed 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), autoimmune myopathy, associated with statin use. 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. The risks of IMNM should be closely evaluated before initiating treatment with other statins. If another statin has been initiated, monitoring of signs and symptoms of IMNM is required.

Hepatic dysfunction

Statins, as well as some other hypolipidemic agents, have been associated with abnormal liver function tests. Persistent increases (to more than 3 times the upper limit of normal that has occurred twice or more) in serum transaminases were observed in approximately 0.7 % of patients receiving atorvastatin in clinical trials. The incidence of such abnormalities was 0.2 %, 0.2 %, 0.6 % and 2.3 % for 10, 20, 40 and 80 mg dosages, respectively.

One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical symptoms. Upon dose reduction, interruption, or discontinuation of atorvastatin, transaminase levels returned to or near pretreatment levels without negative outcomes. 18 of 30 patients with persistent elevations of liver function tests continued treatment with a reduced dose of atorvastatin.

Liver function tests should be performed before the initiation of treatment with atorvastatin and repeated as clinically indicated. There have been rare post-marketing 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, therapy should be promptly discontinued. If an alternate etiology is not found, the drug should not be restarted.

Atorvastatin should be used with caution in patients who abuse alcohol and/or have a history of liver disease. Atorvastatin is contraindicated in case of active liver disease or unexplained persistent transaminase elevations (see section “Contraindications”).

Endocrine function

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

Statins interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair the adrenal reserve. The effects of statins on male fertility have not been studied in adequate numbers of patients. The effects, if any, of atorvastatin on the “hypothalamic-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.

Use in patients with a recent stroke or transient ischemic attack

In a post-hoc analysis of the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial where 4731 adult patients, without ischemic heart disease and with a history of stroke or transient ischemic attack within the preceding 6 months, were treated with atorvastatin at a dose of 80 mg, a higher incidence of hemorrhagic stroke was seen in the atorvastatin 80 mg group compared to placebo (55 cases, 2.3 % in the atorvastatin group vs. 33 cases, 1.4 % in the placebo group; HR: 1.68, 95 % CI: 1.09, 2.59; p=0.0168). The incidence of fatal hemorrhagic stroke was similar across all treatment groups (17 vs. 18 for the atorvastatin and placebo groups, respectively). The incidence of non-fatal hemorrhagic stroke was significantly higher in the atorvastatin group (38, 1.6 %) as compared to the placebo group (16, 0.7 %). Some baseline characteristics, including hemorrhagic and lacunar stroke on study entry, were associated with a higher incidence of hemorrhagic stroke in the atorvastatin group (see section “Adverse reactions”).

Of 39828 of atorvastatin-treated patients in clinical trials, 15813 (40 %) were over 65 years old and 2800 (7 %) were over 75 years old. No overall differences in the safety or effectiveness of the drug were

observed between these patients and younger patients, in the same way that no differences were observed in response to treatment between elderly patients and younger patients according to other clinical experience, although greater responsiveness of some elderly patients cannot be ruled out. Since old age (over 65 years of age) is a predisposing factor for myopathy, caution should be exercised when prescribing atorvastatin in elderly patients.

Hepatic impairment

Atorvastatin is contraindicated in patients with active liver disease including unexplained persistent elevation of serum transaminases (see sections "Contraindications" and "Pharmacological properties").

Before the treatment

Atorvastatin should be prescribed with caution in patients with predisposing factors for rhabdomyolysis. CK levels should be measured in patients predisposed to rhabdomyolysis before initiating statin treatment in the following situations:

- 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 alcohol abuse.

For elderly patients (over 70 years of age), the necessity of such measurements should be considered, according to the presence of other predisposing factors for rhabdomyolysis.

Increased drug plasma concentrations are possible, in particular, in case of interaction (see section "Interaction with other medicinal products and other types of interaction") and use in special groups of patients (see section "Pharmacokinetics"), including patients with hereditary disorders.

In such situations, the risks of treatment should be considered in relation to the possible benefits, and clinical monitoring of patients should be performed. If CK levels are significantly elevated (over 5 times the ULN) at baseline, treatment should not be initiated.

Creatine kinase measurement

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

During treatment

Patients must be instructed to promptly report muscle pain, cramps, or weakness, especially if accompanied by malaise or fever.

If such symptoms occur during treatment with atorvastatin, the patient's CK levels should be measured. If CK levels are found to be significantly elevated over 5 times the ULN), treatment should be discontinued.

Discontinuation of treatment should also be considered if muscular symptoms are severe and cause daily discomfort, even if the CK levels are elevated to under 5 times the ULN.

If symptoms resolve and CK levels return to normal, re-introduction of atorvastatin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.

Atorvastatin must be discontinued if clinically significant elevation of CK levels (over 10 times the ULN) occurs, or if rhabdomyolysis is diagnosed (or suspected).

Concomitant use with other medicinal products

The risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of atorvastatin. These include potent inhibitors of CYP 3A4 or transport proteins (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole, letermovir and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir. The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivates, boceprevir, erythromycin, niacin and ezetimibe, telaprevir, or combination of telaprevir/ritonavir. If possible, alternative (not interacting with atorvastatin) medicinal products should be considered instead of these medicinal products.

In cases where co-administration of these medicinal products with atorvastatin is necessary, the benefits and the risks of concurrent treatment should be carefully considered. When patients are receiving

medicinal products that increase the plasma atorvastatin concentrations, it is recommended to reduce the dose of atorvastatin to a minimum. In addition, in the case of potent CYP 3A4 inhibitors, a lower starting dose of atorvastatin should be considered. Appropriate clinical monitoring of these patients is also recommended.
Atorvastatin must not be co-administered with systemic 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 for the entire 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 "Interaction with other medicinal products and other types of interaction"). 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 7 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 atorvastatin and fusidic acid should only be considered on a case-by-case basis and under close medical supervision.
Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins (especially with long-term therapy). Presenting features can include dyspnea, non-productive cough, and deterioration in general well-being (fatigue, weight loss and fever). If it is suspected that a patient has developed interstitial lung disease, statin therapy should be discontinued.
Therapy with lipid-altering agents should be a component of complex therapy in patients with a significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Drug therapy should be used in addition to a diet restricted in saturated fat and cholesterol when the response to diet and other nonpharmacological measures has been inadequate. In patients with ischemic heart disease or several risk factors for ischemic heart disease atorvastatin may be initiated simultaneously with following a diet.
Limitations of administration
Atorvastatin has not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons (Fredrickson types I and V).
Myasthenia gravis/ocular myasthenia
In few cases, statins have been reported to induce *de novo* or aggravate pre-existing myasthenia gravis or ocular myasthenia (see section "Adverse reactions"). The drug Atsat® should be discontinued in case of aggravation of symptoms. There have been reports of recurrences when the same or a different statin was administered.
Excipients.
The drug contains lactose. In case of known intolerance to some sugars, contact a doctor before taking this medicinal product.
This medicinal product contains less than 1 mmol of sodium (23 mg)/dose, therefore, it is essentially sodium-free.

Use during pregnancy or breastfeeding.
Pregnancy.
Risk assessment
Atorvastatin is contraindicated in pregnant women, since the safety of its use in pregnant women is not established and there is no obvious benefit of lipid-lowering drugs during pregnancy. Since HMG-CoA-reductase inhibitors reduce cholesterol synthesis and possibly the synthesis of other biologically active substances that are cholesterol derivatives, atorvastatin may have a detrimental effect on the fetus. Atsat® should be discontinued as soon as pregnancy is established (see section "Contraindications").
The estimated background risk for significant congenital malformations and miscarriages for this population is unknown. In the overall US population, the estimated background risk for significant congenital malformations and miscarriages in clinically recognized pregnancies is between 2–4 % and 15–20 %, respectively.
Contraception

Atorvastatin may harm the fetus when used by a pregnant woman. Women of reproductive age should be informed about the need to use effective contraception during treatment with this drug.
Clinical data
Limited published data from observational studies, meta-analyzes, and clinical trials on the use of atorvastatin calcium did not indicate an increased risk of severe congenital malformations or miscarriages. There were rare reports of congenital anomalies after intrauterine exposure of other HMG-CoA reductase inhibitors. A prospective observation of approximately 100 cases of pregnancy in women treated with simvastatin or lovastatin showed that the incidence of congenital fetal abnormalities, miscarriages, and fetal death/stillbirths did not exceed the frequency expected for the general population. The number of cases is sufficient to exclude ≥ 3–4 fold increase in congenital abnormalities of fetal development versus background frequency. In 89 % of pregnant women, who were prospectively monitored, drug treatment began before pregnancy and stopped during the first trimester after pregnancy had been diagnosed.
Breastfeeding
Atorvastatin is contraindicated during breastfeeding. There is no information on the effect of the drug on the breastfed child or on lactation. It is not known whether atorvastatin penetrates into breast milk, but it has been shown that another drug of this class penetrates into breast milk; atorvastatin is present in rat milk. Since statins are potentially capable of causing serious adverse reactions in breastfed children, women who require treatment with atorvastatin should not breastfeed their children (see section "Contraindications").

Effect on reaction rate when driving motor transport or using other mechanisms.
The drug has negligible effect on the reaction rate when driving motor transport or using other mechanisms.

Dosage and administration.
Hyperlipidemia and mixed dyslipidemia
The recommended initial dose of atorvastatin is 10 or 20 mg 1 time per day. For patients who require a significant reduction in LDL cholesterol (over 45 %), therapy may be initiated at a dosage of 40 mg 1 time per day. The dose range of atorvastatin is from 10 to 80 mg 1 time per day. The single drug dose can be administered regardless of food intake and time. Initial and maintenance doses of atorvastatin should be titrated individually, depending on the treatment goals and response. After the initiation of treatment and/or after atorvastatin dose titration, lipid levels should be analyzed over a period of 2 to 4 weeks and the dose adjusted accordingly.
Heterozygous familial hypercholesterolemia in pediatric patients (10 to 17 years of age)
The recommended starting dose of atorvastatin is 10 mg/day, the usual dose range is 10 to 20 mg orally once daily. Doses should be individualized according to the recommended goal of therapy. Dose adjustments should be made at intervals of 4 weeks or more.
Homozygous familial hypercholesterolemia.
The dosage of atorvastatin in patients with homozygous familial hypercholesterolemia is from 10 to 80 mg daily. Atorvastatin should be administered as an adjunct to other hypolipidemic methods of treatment (e.g., LDL apheresis) or if lipid-lowering treatment methods are unavailable.
Simultaneous hypolipidemic therapy.
Atorvastatin may be used with bile acid sequestrants. The combination of HMG-CoA reductase inhibitors (statins) and fibrates should generally be used with caution (see section “Administration details”, “Interaction with other medicinal products and other forms of interaction”).
Dosage in patients with renal impairment
Renal disease does not affect the blood plasma concentrations nor LDL-C reduction of atorvastatin administration; thus, dosage adjustment in patients with renal dysfunction is not necessary (see section “Administration details”, “Pharmacokinetics”).
Dosage in patients taking cyclosporine, clarithromycin, itraconazole, letermovir or certain protease inhibitors
Treatment with atorvastatin should be avoided in patients taking cyclosporine or HIV protease inhibitors tipranavir + ritonavir, or the hepatitis C protease inhibitor glecaprevir + pibrentasvir, or letermovir if ciclosporin is co-administered. In patients with HIV taking lopinavir + ritonavir, atorvastatin should be

used at the lowest necessary dose. In patients taking clarithromycin, itraconazole, elbasvir + grazoprevir, or in patients with HIV taking a combination of saquinavir + ritonavir, darunavir + ritonavir, fosamprenavir, fosamprenavir + ritonavir or letermovir, the therapeutic dose of atorvastatin should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest necessary dose of atorvastatin is applied. In patients taking the HIV protease inhibitor nelfinavir, therapy with atorvastatin should be limited to a dose of 40 mg (see section "Administration details" and "Interaction with other medicinal products and other forms of interaction").

Children.
Heterozygous familial hypercholesterolemia
The safety and efficacy of atorvastatin have been established in children 10 to 17 years of age with heterozygous familial hypercholesterolemia as an adjunct to the diet to reduce total cholesterol, LDL and apolipoprotein B levels when, after an adequate trial of diet therapy, the following findings are present:
• LDC cholesterol ≥ 190 mg/dL (4.91 mmol/l) or
• LDC cholesterol ≥ 160 mg/dL (4.14 mmol/l) and
o family history of familial hypercholesterolemia or premature cardiovascular disease in first- or second-degree relatives or
o there are two or more other risk factors for cardiovascular disease.

Indications for the use of atorvastatin have been confirmed on the basis of studies:
- A 6-month placebo-controlled clinical trial involving 187 boys and postmenarchal girls from 10 to 17 years of age. Patients treated with atorvastatin at a dose of 10 mg or 20 mg daily had an adverse reaction profile similar to that in patients receiving placebo. In this limited controlled study, there was no significant effect of the drug on growth or sexual maturation in boys or on the duration of the menstrual cycle in girls.
- A three-year, open-label, uncontrolled trial involving 163 children from 10 to 15 years of age with heterozygous familial hypercholesterolemia who were titrated to achieve a target LDL-C level of < 130 mg/dl (3.36 mmol/l). The safety and efficacy of atorvastatin in lowering LDL cholesterol are generally consistent with those observed for adult patients, despite limitations of the uncontrolled study design.

Postmenarchal girls should be advised regarding contraception, if appropriate for the patient.
The long-term efficacy of atorvastatin therapy initiated in childhood to reduce morbidity and mortality in adulthood has not been established.
The safety and efficacy of atorvastatin have not been established for children under 10 years of age with heterozygous familial hypercholesterolemia.
Homozygous familial hypercholesterolemia
The clinical efficacy of the drug at doses up to 80 mg/day for 1 year was evaluated in an uncontrolled study in patients with homozygous familial hypercholesterolemia, which included 8 children.

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

Adverse reactions.
Due to the fact that clinical trials are conducted under different conditions, adverse reaction rates observed in the clinical trials of a medicinal product cannot be directly compared to the rates in the clinical trials of another medicinal product, and may not reflect the rates observed in clinical practice.
According to an atorvastatin clinical trial of 16,066 patients (8,755 received atorvastatin and 7,311 received placebo; age range 10–93 years, 39 % women, 91 % caucasians, 3 % blacks, 2 % asians, 4 % other) with a median treatment duration of 53 weeks, 9.7 % of patients receiving atorvastatin and 9.5 % of patients receiving placebo discontinued the drug due to adverse reactions, regardless of causality.

The five most common adverse reactions in patients treated with atorvastatin that led to discontinuation of treatment and occurred at a rate greater than in the placebo group were: myalgia (0.7 %), diarrhea (0.5 %), nausea (0.4 %), elevated alanine aminotransferase (0.4 %), and elevated hepatic enzymes (0.4 %).
In patients treated with atorvastatin in placebo-controlled trials (n=8,755), the most commonly reported adverse reactions (the incidence of 2 % or more, and greater than in the placebo group) regardless of causality, were: nasopharyngitis (8.3 %), arthralgia (6.9 %), diarrhea (6.8 %), pain in extremities (6.0 %), and urinary tract infection (5.7 %).
Table 6 summarizes the frequency of clinical adverse reactions, regardless of causality, reported in 2 % or more and at a rate greater than in the placebo group in patients treated with atorvastatin (n=8,755), from 17 placebo-controlled trials

Table 6.
Clinical adverse reactions occurring in 2 % or more in patients treated with any dose of atorvastatin and at an incidence greater than in the placebo group, regardless of causality (% of patients).

Adverse reaction*	Any dose N=8755	10 mg N=3908	20 mg N=188	40 mg N=604	80 mg N=4055	Placebo N=7311
Nasopharyngitis	8.3	12.9	5.3	7	4.2	8.2
Arthralgia	6.9	8.9	11.7	10.6	4.3	6.5
Diarrhea	6.8	7.3	6.4	14.1	5.2	6.3
Pain in extremity	6	8.5	3.7	9.3	3.1	5.9
Urinary tract infection	5.7	6.9	6.4	8	4.1	5.6
Dyspepsia	4.7	5.9	3.2	6	3.3	4.3
Nausea	4	3.7	3.7	7.1	3.8	3.5
Musculoskeletal pain	3.8	5.2	3.2	5.1	2.3	3.6
Muscle spasms	3.6	4.6	4.8	5.1	2.4	3
Myalgia	3.5	3.6	5.9	8.4	2.7	3.1
Insomnia	3	2.8	1.1	5.3	2.8	2.9
Pharyngolaryngeal pain	2.3	3.9	1.6	2.8	0.7	2.1

* Adverse reaction > 2 % in any dose greater than in the placebo group

Other adverse reactions reported in placebo-controlled studies include:
General disorders: malaise, pyrexia.
Gastrointestinal disorders: gastrointestinal discomfort, eructation, flatulence, hepatitis, cholestasis.
Musculoskeletal disorders: musculoskeletal pain, muscle fatigue, neck pain, joint swelling, tendinopathy (sometimes complicated by rupture).
Metabolism and nutrition disorders: transaminases increased, abnormal liver function tests, blood alkaline phosphatase increased, increased creatine phosphokinase, hyperglycemia.
Nervous system disorders: nightmares.
Respiratory system disorders: epistaxis.
Skin and appendages: urticaria.
Eye disorders: blurred vision, visual disturbance.
Ear and labyrinth disorders: tinnitus.
Urogenital system disorders: leukocyturia.
Reproductive system and breast disorders: gynecomastia.
All adverse reactions are listed according to organ systems and frequency: very common (≥ 1/10), common (≥1/100 – <1/10), uncommon (≥1/1 000 – <1/100), rare (≥1/10000 – <1/1000), very rare (<1/10 000), frequency unknown (cannot be estimated from the available data).
Nervous system disorders: common – headache; uncommon – dizziness, paresthesia, hypoesthesia, dysgeusia, amnesia; rare – peripheral neuropathy.
Gastrointestinal tract disorders: common – constipation; uncommon – pancreatitis, vomiting.

Musculoskeletal and connective tissue disorders: common – arthralgia, back pain; rare – myopathy, myositis, rhabdomyolysis.
General disorders: uncommon – asthenia, chest pain, peripheral edema, fatigue.
Metabolism disorders: uncommon – hypoglycemia, weight gain, anorexia.
Hepatobiliary disorders: very rare – hepatic failure.
Skin and subcutaneous tissue disorders: uncommon – skin rash, pruritus, alopecia; rare – angioedema, bullous dermatitis (including erythema multiforme), Stevens-Jonhson syndrome and toxic epidermal necrolysis.
Respiratory, thoracic and mediastinal disorders: common – pharyngolaryngeal pain.
Blood and lymphatic system disorders: rare – thrombocytopenia.
Immune system disorders: common – allergic reactions; very rare – anaphylaxis.
Eye disorders: uncommon – blurred vision.
Laboratory investigations: common – abnormal liver function tests, increased blood CPK; uncommon – positive white blood cells in the urine.
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 significant (over 3 times the upper limit of normal) elevations in serum transaminases was observed in 0.8 % patients taking atorvastatin. These elevations were dose-dependent and were reversible in all patients.
Elevated serum creatine kinase levels over 3 times the upper limit of normal were observed in 2.5 % of patients receiving atorvastatin. This is similar to observations with other HMG-CoA reductase inhibitors in clinical trials. Levels over 10 times the upper limit of normal were observed in 0.4 % of atorvastatin-treated patients.
Adverse reactions observed in clinical trials: urinary tract infection, diabetes mellitus, stroke.
In ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) involving 10,305 patients (age range 40–80 years, 19 % women; 94.6 % Caucasians, 2.6 % Blacks, 1.5 % South Asians, 1.3 % mixed/other) treated with atorvastatin at a dose of 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with atorvastatin was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.
In CARDS (Collaborative Atorvastatin Diabetes Study) involving 2,838 patients (age range 39–77 years, 32 % women; 94.3 % Caucasians, 2.4 % South Asians, 2.3 % Afro-Caribbean, 1.0 % other) with type 2 diabetes mellitus treated with atorvastatin at a dose of 10 mg daily (n=1,428) or placebo (n=1,410), no difference was observed in the overall frequency of adverse reactions or serious adverse reactions between the treatment groups during a median follow-up of 3.9 years. No cases of rhabdomyolysis were reported.
In TNT (Treating to New Targets Study) involving 10,001 patients (age range 29–78 years, 19 % women; 94.1 % Caucasians, 2.9 % Blacks, 1.0 % Asians, 2.0 % other) with clinically evident ischemic heart disease treated with atorvastatin at a dose of 10 mg daily (n=5006) or atorvastatin at a dose of 80 mg daily (n=4995), there were more serious adverse reactions and discontinuations due to adverse reactions in the high-dose atorvastatin group (92, 1.8 %; 497, 9.9 %, respectively) as compared to the low-dose group (69, 1.4 %; 404, 8.1 %, respectively) during a median follow-up of 4.9 years. Persistent transaminase elevations (over 3 times the upper limit of normal, twice within 4 to 10 days) were observed in 62 (1.3 %) individuals receiving atorvastatin 80 mg, and in 9 (0.2 %) individuals receiving atorvastatin 10 mg. Elevations of CK (over 10 times the upper limit of normal) were low overall, but were higher in the high-dose atorvastatin treatment group (13, 0.3 %) compared to the low-dose atorvastatin group (6, 0.1 %).
In IDEAL (Incremental Decrease in Endpoints through Aggressive Lipid Lowering Study) involving 8,888 patients (age range 26–80 years, 19 % women; 99.3 % Caucasians, 0.4 % Asians, 0.3 % Blacks, 0.04 % other) treated with atorvastatin at a dose of 80 mg/day (n=4439) or simvastatin at a dose of 20–40 mg daily (n=4449), there was no difference in the overall frequency of adverse reactions or serious adverse reactions between the treatment groups during a median follow-up of 4.8 years.
In SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) involving 4,731 patients (age range 21–92 years, 40 % women; 93.3 % Caucasians, 3.0 % Blacks, 0.6 % Asians, 3.1 % other) without clinically evident ischemic heart disease but with a history of stroke or transient ischemic attack (TIA) within the previous 6 months treated with atorvastatin at a dose of 80 mg (n=2365) or placebo (n=2366) for a median follow-up of 4.9 years, there was a higher incidence of persistent elevations of

hepatic transaminases (over 3 times the upper limit of normal, twice within 4–10 days) in the atorvastatin group (0.9 %) compared to the placebo group (0.1 %). Creatine kinase elevations (over 10 times the upper limit of normal) were rare but were higher in the atorvastatin group (0.1 %) compared to the placebo group (0.0 %). Diabetes mellitus was reported as an adverse reaction in 144 patients (6.1 %) in the atorvastatin group and in 89 subjects (3.8 %) in the placebo group (see section "Administration details").
In a post-hoc analysis, atorvastatin at a dose of 80 mg reduced the incidence of ischemic stroke (218/2365, 9.2 % vs. 274/2366, 11.6 %) and increased the incidence of hemorrhagic stroke (55/2365, 2.3 % vs. 33/2366, 1.4 %) compared to placebo. The incidence of fatal hemorrhagic stroke was similar between groups (17 cases in the atorvastatin group vs. 18 cases in the placebo group). The incidence of non-fatal hemorrhagic stroke was significantly greater in the atorvastatin group (38 cases of non-fatal hemorrhagic stroke) as compared to the placebo group (16 cases of non-fatal hemorrhagic stroke). Subjects who entered the study with a history of hemorrhagic stroke were at increased risk for hemorrhagic stroke (7 (16 %) atorvastatin vs. 2 (4 %) placebo).
There were no significant differences between the treatment groups for all-cause mortality: 216 (9.1 %) in the atorvastatin 80 mg/day group vs. 211 (8.9 %) in the placebo group. The proportion of subjects who experienced cardiovascular death was numerically smaller in the atorvastatin 80 mg group (3.3 %) than in the placebo group (4.1 %). The proportion of subjects who experienced non-cardiovascular death was numerically larger in the atorvastatin 80 mg group (5.0 %) than in the placebo group (4.0 %).
Adverse reactions in clinical trials of atorvastatin in children
In a 26-week controlled study in boys and postmenarchal girls with heterozygous familial hypercholesterolemia (10 to 17 years of age) (n = 140, 31 % female; 92 % caucasians, 1.6 % blacks, 1.6 % asians, 4.8 % other), the safety and tolerability profile of atorvastatin at doses of 10 to 20 mg daily, as an adjunct to diet to reduce total cholesterol, LDL cholesterol, and apolipoprotein B levels, was generally similar to that of placebo.
Post-marketing experience.
The following adverse reactions have been identified during post-approval 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, regardless of causality assessment, include: anaphylaxis, angioedema, bullous rashes (including exudative erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis), rhabdomyolysis, myositis, fatigue, tendon rupture, fatal and non-fatal hepatic failure, dizziness, depression, peripheral neuropathy, pancreatitis, and interstitial lung disease.
There have been rare reports of immune-mediated necrotizing myopathy associated with statin use (see section "Administration details").
There have been rare post-marketing reports of cognitive impairment (such as memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive disorders have been reported with all statins. These disorders generally did not qualify as severe adverse reactions, and were reversible upon discontinuation of statins, with variable times to symptom onset (1 day to several years) and symptom resolution (median of 3 weeks).
The following adverse reactions were reported with some statins: sexual dysfunction, isolated cases of interstitial lung disease, particularly in long-term treatment.
The following adverse reactions were observed in post-marketing observational studies.
Blood and lymphatic system disorders: thrombocytopenia.
Immune system disorders: allergic reactions, anaphylaxis (including anaphylactic shock).
Metabolism and nutrition disorders: weight gain.
Nervous system disorders: headache, hypoesthesia, dysgeusia, myasthenia gravis.
Gastrointestinal disorders: abdominal pain.
Ear and labyrinth disorders: tinnitus.
Eye disorders: ocular myasthenia.
Skin and subcutaneous tissue disorders: urticaria.
Musculoskeletal and connective tissue disorders: arthralgia, back pain.
General disorders: chest pain, peripheral edema, malaise, fatigue.

Laboratory investigations: elevated alanine aminotransferase activity, elevated blood creatine phosphokinase activity.

Reporting of suspected adverse reactions.

Reporting adverse reactions after the registration of the medicinal product is of great importance. It allows to monitor the correlation of the benefits and risks related to the use of the medicinal product. Healthcare and pharmaceutical professionals, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of efficacy of the medicinal product through the Automated pharmacovigilance information system available at: https://aisf.dec.gov.ua.

Shelf life.

3 years.

Storage conditions.

Store in the original package at a temperature not more than 25 ºC.
Keep out of reach of children.

Package.

14 tablets are in a blister; 2 or 4 or 6 blisters are in a carton box.

Conditions of supply.

By prescription.

Manufacturer.

LLC “KUSUM PHARM”.

Address of manufacturer and manufacturing site.

40020, Ukraine, Sumy region, Sumy, Skryabina Str. 54.

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