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| **APPROVED****Order of the Ministry****of Health of Ukraine****No. 1922 of 10.09.2021**  |
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## INSTRUCTION

## for medical use of medicinal product

**ATORVAKOR®**

***Composition:***

*Active substance:* atorvastatin;

1 tablet contains 10.82 mg or 21.64 mg or 43.28 mg or 86.56 mg of atorvastatin calcium trihydrate as calculated on 100% substance (equivalent to atorvastatin) 10 mg or 20 mg or 40 mg or 80 mg;

*Excipients:* calcium carbonate; lactose, monohydrate; microcrystalline cellulose; sodium croscarmellose; polysorbate 80, hydroxypropyl cellulose; magnesium stearate; Opadry II 85F18422 white (polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide (E 171)).

**Pharmaceutical form**

Film-coated tablets.

*Basic physical and chemical properties:* white to off white, round, biconvex, film-coated tablets.

**Pharmacotherapeutic group**

Lipid modifying agents.HMG CoA reductase inhibitors.

АТС Code С10А А05.

***Pharmacological properties***

*Pharmacodynamics*

Atorvakor® is a synthetic lipid-lowering drug. Atorvastatin is a 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitor. This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early rate-limiting stage of cholesterol biosynthesis.

Atorvakor® is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol.

In animal models, atorvastatin lowers 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 to enhance uptake and catabolism of LDL; atorvastatin also reduces LDL production and the number of LDL particles.

Atorvastatin, as well as some of its metabolites, are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage, rather than systemic drug concentration, correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response (see Section “Posology and method of administration”).

*Pharmacokinetics*

Absorption. Atorvastatin is rapidly absorbed after oral administration. Maximum plasma concentrations (Cmax) occur within 1 to 2 hours. Extent of absorption increases in proportion to the drug dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or presystemic hepatic biotransformation. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC (area under the concentration-time curve), LDL-C reduction is similar whether Atorvakor® is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration (see Section “Posology and method of administration”).

Distribution. Mean volume of distribution of atorvastatin is approximately 381 litres. Atorvastatin is > 98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in animals, Atorvastatin is likely to be secreted in human milk (see Sections “Contraindications” and “Special warnings and precautions for use”).

Metabolism. Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of Atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *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 Section “Interaction with other medicinal products and other forms of interaction”).

Excretion. Atorvastatin and its metabolites are eliminated primarily in [bile](http://www.rxlist.com/script/main/art.asp?articlekey=2459) following hepatic and/or extrahepatic 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 a dose of Atorvastatin is recovered in urine following oral administration.

*Special populations*

Elderly. Plasma concentrations of Atorvastatin are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (age >65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults (see Section “Special warnings and precautions for use”).

Paediatric patients. The apparent oral clearance of Atorvastatin in pediatric subjects appeared similar to that of adults when scaled allometrically by body weight as the body weight was the only significant covariate in atorvastatin population pharmacokinetic model with data including pediatric heterozygous familial hypercholesterolaemia patients (ages 10 years to 17 years of age, n=29) in an open-label, 8-week study.

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

Renal impairment. Renal disease has no influence on the plasma concentrations or LDL-C reduction of Atorvastatin; thus, dose adjustment in patients with renal dysfunction is not necessary (see Sections “Special warnings and precautions for use” and “Posology and method of administration”).

Haemodialysis. While studies have not been conducted in patients with end-stage renal disease, [haemodialysis](http://www.rxlist.com/script/main/art.asp?articlekey=11433) is not expected to significantly enhance clearance of Atorvastatin since the drug is extensively bound to plasma proteins.

Hepatic impairment. In patients with chronic alcoholic [liver disease](http://www.rxlist.com/script/main/art.asp?articlekey=53394), plasma concentrations of Atorvastatin are markedly increased. Cmax and AUC are each 4-fold greater in patients with Childs-Pugh A disease. Cmax and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease (see Section “Contraindications”).

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

Table 1

Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin

|  |  |
| --- | --- |
| Co-administered drugs and dosing regimen | Atorvastatin |
| Dose (mg) | Ratio of AUC& | Ratio of Cmax& |
| #Cyclosporine 5.2 mg/kg/day, stable dose  | 10 mg once daily for 28 days | 8.69 | 10.66 |
| #Tipranavir 500 mg BID/Ritonavir 200mg BID, 7 days | 10 mg SD | 9.36 | 8.58 |
| #Glecaprevir 400 mg OD/Pibrentasvir 120 mg OD, 7 days | 10 mg once daily for 7 days | 8.28 | 22.00 |
| #Telaprevir 750 mg q8h, 10 days | 20 mg SD | 7.88 | 10.60 |
| #,‡Saquinavir 400 mg BID/Ritonavir 400mg BID, 15 days  | 40 mg once daily for 4 days | 3.93 | 4.31 |
| #Elbasvir 50 mg OD/ Grazoprevir 200 mg OD, 13 days | 10 mg SD | 1.94 | 4.34 |
| #Simeprevir 150 mg OD, 10 days | 40 mg SD | 2.12 | 1.70 |
| #Clarithromycin 500 mg BID, 9 days | 80 mg once daily for 8 days | 4.54 | 5.38 |
| #Darunavir 300 mg BID/Ritonavir 100 mg BID, 9 days | 10 mg once daily for 4 days | 3.45 | 2.25 |
| #Itraconazole 200 mg OD, 4 days  | 40 mg SD | 3.32 | 1.20 |
| Letermovіr 480 mg OD, 10 days  | 20 mg SD | 3.29 | 2.17 |
| #Fosamprenavir 700 mg BID/Ritonavir 100 mg BID, 14 days | 10 mg once daily for 4 days | 2.53 | 2.84 |
| #Fosamprenavir 1400 mg BID, 14 days | 10 mg once daily for 4 days | 2.30 | 4.04 |
| #Nelfinavir 1250 mg BID, 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 for 28 days  | 40 mg once daily | 1.51 | 1.00 |
| Erythromycin 500 mg QID, 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 QID, 2 weeks  | 10 mg once daily for 2 weeks | 1.00 | 0.89 |
| Colestipol 10 mg BID, 28 weeks  | 40 mg once daily for 28 weeks | Not determined | \*\* |
| Maalox TC® 30 mL QID, 17 days  | 10 mg once daily for 15 days | 0.66 | 0.67 |
| Efavirenz 600 mg OD for 14 days  | 10 mg for 3 days | 0.59 | 1.01 |
| #Rifampin 600 mg OD, 7 days (coadministered) † | 40 mg once daily | 1.12 | 2.90 |
| #Rifampin 600 mg OD, 5 days (doses separated) †  | 40 mg once daily | 0.20 | 0.60 |
| #Gemfibrozil 600 mg BID, 7 days   | 40 mg once daily | 1.35 | 1.00 |
| #Fenofibrate 160 mg OD, 7 days | 40 mg once daily | 1.03 | 1.02 |
| #Boceprevir 800 mg TID, 7 days | 40 mg once daily | 2.32 | 2.66 |

& Correlation ratio for treatment methods (concomitant use of atorvastatin compared to atorvastatin alone).

# See Sections “Interactions with other medicinal products and other forms of interaction” and “Special warnings and precautions for use” for clinical significance.

\* Greater increases in AUC (up to 2.5 fold) and/or Cmax (up to 1.71 fold) have been reported with excessive grapefruit consumption (≥750 mL - 1.2 litres per day).

 \*\* Single sample taken 8 - 16 h 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 dose of saquinavir plus ritonavir in this study is not the clinically used dose. The increase in atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore, caution should be applied and the lowest dose necessary should be used.

Table 2

Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs

|  |  |
| --- | --- |
| Atorvastatin | Co-administered drugs and dosing regimen |
| Drug/dose (mg) | Ratio of AUC | Ratio of Cmax |
| 80 mg once daily for 15 days  | Antipyrine, 600 mg once daily | 1.03 | 0.89 |
| 80 mg once daily for 14 days | #Digoxin 0.25 mg once daily, 20 days | 1.15 | 1.20 |
| 40 mg once daily for 22 days  | Oral contraceptive once daily, 2 months– norethisterone 1mg– ethinyl estradiol 35 µg | ­28 ­19 | ­23­30 |
| 10 mg once daily | Tipranavir 500 mg BID/Ritonavir 200 mg BID, 7 days | 1.08 | 0.96 |
| 10 mg once daily for 4 days | Fosamprenavir 1400 mgBID, 14 days | 0.73 | 0.82 |
| 10 mg once daily for 4 days | Fosamprenavir 700 mg BID/Ritonavir 100 mg BID, 14 days | 0.99 | 0.94 |

# See Sections “Interactions with other medicinal products and other forms of interaction” for clinical significance.

**Clinical particulars**

***Indications***

*Prevention of cardiovascular disease*

In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, [hypertension](http://www.rxlist.com/script/main/art.asp?articlekey=3846), low high density lipoprotein (HDL), or a family history of early coronary heart disease, Atorvakor® is indicated to:

- reduce the risk of myocardial infarction;

- reduce the risk of stroke;

- reduce the risk for revascularization procedures and angina.

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

* reduce the risk of myocardial infarction;
* reduce the risk of stroke.

In patients with clinically evident coronary heart disease, Atorvakor® 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 CHF;
* reduce the risk of angina.

*Hyperlipidaemia in adult patients*

* As an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDLC in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidaemia (Fredrickson Types IIa and IIb).
* As an adjunct to diet for the treatment of patients with elevated serum TG 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-C 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-C, LDL-C, and apo B levels in children, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:
1. LDL-C remains ≥190 mg/dL (4.91 mmol/L) or
2. LDL-C remains ≥160 mg/dL (4.14 mmol/L) and:
* there is a positive family history of premature cardiovascular disease or
* two or more other cardiovascular disease risk factors are present in the paediatric patient.

***Contraindications***

* Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels.
* Hypersensitivity to any of the drug excipients.
* Pregnancy and lactation.

***Interactions with other medicinal products and other forms of interaction***

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 Р450 3А4 CYP 3A4 inhibitors (e.g., clarithromycin, HIV protease inhibitors, and itraconazole) (see “Pharmacological properties” and “Special warnings and precautions for use”).

*Potent CYP 3A4 inhibitors.*Atorvakor® is metabolized by cytochrome P450 3A4. Concomitant administration of Atorvakor® with potent CYP 3A4 inhibitors can lead to increase in plasma concentrations of Atorvastatin (see Table 1 and detailed information below). The extent of interaction and potentiation of effects depend on the variability of effect on CYP 3A4. Co-administration of potent CYP3A4 inhibitors (e.g. cyclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and some antivirals used in the treatment of HCV (e.g. elbasvir/grazoprevir) and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir) should be avoided if possible. In cases where co-administration of these medicinal products with atorvastatin cannot be avoided lower starting and maximum doses of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended (see Table 1).

Moderate CYP3A4 inhibitors (e.g. erythromycin, diltiazem, verapamil and fluconazole) may increase plasma concentrations of atorvastatin (see Table 1). An increased risk of myopathy has been observed with the use of erythromycin in combination with statins. Interaction studies evaluating the effects of amiodarone or verapamil on atorvastatin have not been conducted. Both amiodarone and verapamil are known to inhibit CYP3A4 activity and co-administration with atorvastatin may result in increased exposure to atorvastatin. Therefore, a lower maximum dose of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended when concomitantly used with moderate CYP3A4 inhibitors. Appropriate clinical monitoring is recommended after initiation or following dose adjustments of the inhibitor.

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

*Clarithromycin.* Atorvastatin AUC was significantly increased with concomitant administration of Atorvastatin 80 mg with clarithromycin (500 mg twice daily) compared to that of Atorvastatin alone (see “Pharmacological properties”). Therefore, in patients taking clarithromycin, caution should be used when the Atorvakor® dose exceeds 20 mg (see “Special warnings and precautions for use” and “Posology and method of administration”).

*Combination of protease inhibitors.* Atorvastatin AUC was significantly increased with concomitant administration of Atorvastatin with several combinations of protease inhibitors (see “Pharmacological properties”). Therefore, in patients taking tipranavir plus ritonavir, or glecaprevir plus pibrentasvir, concomitant use of Atorvakor® should be avoided. In patients taking lopinavir plus ritonavir or simeprevir, the lowest dose necessary should be used when prescribing Atorvakor®. In patients taking saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, or elbasvir plus grazoprevir the dose of Atorvakor® should not exceed 20 mg. In patients taking nelfinavir, the dose of Atorvakor® should not exceed 40 mg and close clinical monitoring is recommended (see “Special warnings and precautions for use” and “Posology and method of administration”).

*Itraconazole.* Atorvastatin AUC was significantly increased with concomitant administration of Atorvakor® 40 mg with itraconazole 200 mg (see “Pharmacological properties”). Therefore, in patients taking itraconazole, caution should be used when the Atorvakor® dose exceeds 20 mg (see “Special warnings and precautions for use” and “Posology and method of administration”).

*Cyclosporine.* Atorvastatin is a substrate of the hepatic transporters. Metabolites of atorvastatin are substrates of OATP1B1. Inhibitors of the OATP1B1 (e.g., cyclosporine) can increase the bioavailability of Atorvastatin. Atorvastatin AUC was significantly increased with concomitant administration of Atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day compared to that of Atorvastatin alone (see “Pharmacological properties”). The co-administration of Atorvakor® with cyclosporine should be avoided (see “Special warnings and precautions for use”).

*Letermovir.* Concomitant administration of atorvastatin 20 mg and letermovir 480 mg daily resulted in an increase in exposure to atorvastatin (ratio of AUC: 3.29) (see Section “Pharmacokinetics”).

Letermovir inhibits efflux transporters P-gp, BCRP, MRP2, OAT2 and hepatic transporter OATP1B1/1B3, thus it increases exposure to atorvastatin. Do not exceed 20 mg of Atorvakor® daily (see Section “Posology and method of administration”).

The magnitude of CYP3A- and OATP1B1/1B3-mediated drug interactions on co-administered drugs may be different when letermovir is co-administered with cyclosporine. Use of Atorvakor® is not recommended in patients taking letermovir co-administered with cyclosporine.

*Glecaprevir and pibrentasvir, elbasvir and grazoprevir.* Concomitant use of glecaprevir and pibrentasvir or elbasvir and grazoprevir may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy.

Coadministration of glecaprevir and pibrentasvir with atorvastatin increase plasma concentrations of atorvastatin by 8.3-fold due in part to BCRP, OATP1B1/1B3, and CYP3A inhibition; therefore, coadministration of Atorvakor® in patients receiving concomitant medications with products containing glecaprevir and pibrentasvir is not recommended.

Coadministration of elbasvir and grazoprevir with atorvastatin increase plasma concentrations of atorvastatin by 1.9-fold due in part to BCRP, OATP1B1/1B3, and CYP3A inhibition; therefore, the dose of Atorvakor® should not exceed 20 mg daily in patients receiving concomitant medications with products containing elbasvir and grazoprevir (see “Pharmacokinetics”, “Special warnings and precautions for use” and “Posology and method of administration”).

Medical recommendations for the use of interacting drugs are given in Table 3 (see Sections “Pharmacological properties”, “Special warnings and precautions for use” and “Posology and method of administration”).

Table 3

Drug Interactions Which Increase the Risk of Myopathy/Rhabdomyolysis

|  |  |
| --- | --- |
| Interacting drugs | Medical recommendations for use |
| Cyclosporine, tipranavir + ritonavir, glecaprevir + pibrentasvir, letermovir when co-administered with cyclosporine | Avoid the use of atorvastatin |
| Clarithromycin, itraconazole, saquinavir + ritonavir\*, darunavir + ritonavir, fosamprenavir, fosamprenavir + ritonavir, elbasvir + grazoprevir, letermovir | Do not exceed the atorvastatin dose of 20 mg/day |
| Nelfinavir  | Do not exceed the atorvastatin dose of 40 mg/day |
| Lopinavir + ritonavir, simeprevir, fibric acid derivatives, erythromycin, azole antifungal agents, lipid-modifying doses of niacin, colchicine | Caution should be applied and the lowest dose necessary should be used |

\*The lowest dose necessary should be used.

*Gemfibrozil.* Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are coadministered with gemfibrozil, concomitant administration of Atorvakor® with gemfibrozil should be avoided (see “Special warnings and precautions for use”).

*Other fibrates.* Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of other fibrates, Atorvakor® should be administered with caution when used concomitantly with other fibrates (see Section “Special warnings and precautions for use”).

*Niacin.* The risk of skeletal muscle effects may be enhanced when Atorvakor® is used in combination with niacin; a reduction in Atorvakor® dosage should be considered in this setting (see Section “Special warnings and precautions for use”).

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

*Diltiazem hydrochloride.* Co-administration of atorvastatin (40 mg) and diltiazem (240 mg) may increase plasma concentrations of atorvastatin.

*Cimetidine.* During interaction studies atorvastatin and cimetidine interaction were not detected.

*Antacids.* Oral co-administration of atorvastatin and antacid suspension of magnesium and aluminium hydroxides is accompanied by decrease in the concentration of atorvastatin in the blood plasma by approximately 35%. The hypolipidemic effect of atorvastatin did not change.

*Colestipol.* Plasma concentrations of atorvastatin were lower (ratio of concentration: 0.74) when colestipol was administered with atorvastatin. However, lipid effects were greater when atorvastatin and colestipol were co-administered than when either drug was given alone.

*Azithromycin.* Co-administration of atorvastatin (10 mg once a day) and azithromycin (500 mg once a day) was not accompanied by changes in the concentration of atorvastatin in the blood plasma.

*Transport protein inhibitors.* Inhibitors of transport proteins (e.g. cyclosporine, letermovir) can increase the systemic exposure of atorvastatin (see Table 1). The effect of inhibition of hepatic uptake transporters on atorvastatin concentrations in hepatocytes is unknown. If concomitant administration cannot be avoided, a dose reduction and clinical monitoring for efficacy is recommended (see Table 1).

*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 these patients is recommended.
*Fusidic acid.* The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.

If treatment with systemic fusidic acid is necessary, atorvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment (see “Special warnings and precautions for use”).

*Digoxin.* When multiple doses of Atorvakor® and digoxin were co-administered, steady state plasma digoxin concentrations increased (see “Pharmacokinetics”). Patients taking digoxin should be monitored appropriately.

*Oral contraceptives.* Co-administration of atorvastatin and an oral contraceptive increased AUC values for norethisterone and ethinyl estradiol (see “Pharmacological properties”). These increases should be considered when selecting an oral contraceptive for a woman taking Atorvakor®.

*Warfarin.* Atorvakor® had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

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

*Other medicinal products.* Clinical studies have shown that co-administration of atorvastatin and antihypertensive drugs and its use in the course of estrogen replacement therapy is not accompanied by clinically significant adverse effects. No drug interaction studies have been conducted.

***Special warnings and precautions for use***

*Skeletal muscles*

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

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

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.

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

The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of medicinal products listed in Table 3. Physicians considering combined therapy with Atorvakor® and any of these products should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Lower starting and maintenance doses of atorvastatin should be considered when taken concomitantly with the aforementioned drugs (see “Interaction with other medicinal products and other forms of interaction”). Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

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

*Hepatic impairment*

Statins, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Persistent increases in serum transaminases >3 x ULN (which occurred 2 times or more) were reported 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 the 10 mg, 20 mg, 40 mg, and 80 mg doses 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 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 LFT elevations continued treatment with a reduced dose of atorvastatin.

It is recommended that liver enzyme tests be obtained prior to initiating therapy with Atorvakor® and repeated as clinically indicated. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including atorvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with Atorvakor®, promptly interrupt therapy. If an alternate etiology is not found, do not restart Atorvakor®.

Atorvakor® should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of Atorvakor® (see “Contraindications”).

*Endocrine function*

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

Statins interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma [cortisol](http://www.rxlist.com/script/main/art.asp?articlekey=2850) concentration or impair adrenal reserve. The effects of statins on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if a statin is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

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

In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study where atorvastatin 80 mg vs. placebo was administered in 4,731 subjects without CHD who had a stroke or TIA within the preceding 6 months, a higher incidence of hemorrhagic stroke was seen in the atorvastatin 80 mg group compared to placebo (55, 2.3% atorvastatin vs. 33, 1.4% placebo; Hazard Ratio (HR): 1.68, 95% Confidence Interval (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 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 “Undesirable effects”).

Of the 39,828 patients who received atorvastatin in clinical studies, 15,813 (40%) were ≥65 years old and 2,800 (7%) were ≥75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older adults cannot be ruled out. Since advanced age (≥65 years) is a predisposing factor for myopathy, Atorvakor® should be prescribed with caution in the elderly.

*Hepatic insufficiency*

Atorvakor® is contraindicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels (see Sections “Pharmacological properties” and “Contraindications”).

*Before treatment*

Atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A CK level should be measured before starting 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 where substantial quantities of alcohol are consumed.
In elderly (age > 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis.

An increase in plasma levels may occur particularly with interactions (see Section *“*Interaction with other medicinal products and other forms of interaction”) and in special populations including genetic subpopulations.

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended. If CK levels are significantly elevated (> 5 times ULN) at baseline, treatment should not be started.

*Creatine kinase measurement*

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

*During treatment*

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

If such symptoms occur whilst a patient is receiving treatment with atorvastatin, their CK levels should be measured. If these levels are found to be significantly elevated (> 5 times ULN), treatment should be stopped.

If muscular symptoms are severe and cause daily discomfort, even if the CK levels are elevated to ≤ 5 x ULN, treatment discontinuation should be considered.

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

Atorvastatin must be discontinued if clinically significant elevation of CK levels (> 10 x ULN) occur, or if rhabdomyolysis is diagnosed or suspected.

*Concomitant treatment with other medicinal products*

Risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of atorvastatin such as potent inhibitors of CYP3A4 or transport proteins (e.g. cyclosporine, 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 derivatives, boceprevir, erythromycin, niacin and ezetimibe, telaprevir, or the combination of tipranavir/ritonavir. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products.

In cases where co-administration of these medicinal products with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. When patients are receiving medicinal products that increase the plasma concentration of atorvastatin, a dose of atorvastatin should be decreased to the lowest dose. In addition, in the case of potent CYP3A4 inhibitors, a lower starting dose of atorvastatin should be considered and appropriate clinical monitoring of these patients is recommended.

Atorvastatin must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination (see “Interaction with other medicinal products and other forms 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 seven days after the last dose of fusidic acid.

In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for co-administration of Atorvakor® 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 dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Excipients

Atorvakor® contains lactose. If the patient is intolerant of some sugars, medical consultation is needed before taking this drug.

Atorvakor® contains less than 1 mmol/dose sodium, i.e. is essentially “sodium free”.

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Drug therapy is recommended as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacological measures alone has been inadequate. In patients with CHD or multiple risk factors for CHD, Atorvakor® can be started simultaneously with diet.

*Limitations of use*

Atorvakor® has not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons (Fredrickson Types I and V).

*Use during pregnancy and in nursing women*

*Pregnancy*

Atorvakor® is contraindicated for use in pregnant women since safety in pregnant women has not been established and there is no apparent benefit of lipid lowering drugs during pregnancy. Because HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, Atorvakor® may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant, Atorvakor® should be discontinued immediately (see Section “Contraindications”).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

*Contraception*

Atorvakor® may cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with atorvastatin.

Clinical data

Limited published data on atorvastatin calcium from observational studies, meta-analyses and case reports have not shown an increased risk of major congenital malformations or miscarriage. Rare reports of congenital anomalies have been received following intrauterine exposure to other HMG-CoA reductase inhibitors. In a review of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or lovastatin, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate to exclude a ≥3 to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified.

*Lactation*

Atorvakor® use is contraindicated during breastfeeding. There is no available information on the effects of the drug on the breastfed infant or the effects of the drug on milk production. It is not known whether atorvastatin is present in human milk, but it has been shown that another drug in this class passes into human milk and atorvastatin is present in rat milk. Because of the potential for serious adverse reactions in a breast fed infant, advise women that breastfeeding is not recommended during treatment with Atorvakor® (see Section “Contraindications”).

*Effects on ability to drive and use machines*

Atorvakor® has negligible influence on the ability to drive and use machines.

***Posology and method of administration***

*Hyperlipidaemia and mixed dyslipidaemia*

The recommended starting dose of Atorvakor® is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of Atorvakor® is 10 to 80 mg once daily. Atorvakor® can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of Atorvakor® should be individualized according to patient characteristics such as goal of therapy and response. After initiation and/or upon titration of Atorvakor®, lipid levels should be analysed within 2 to 4 weeks and dosage adjusted accordingly.

*Heterozygous familial hypercholesterolemia in paediatric patients (10 - 17 years of age)*

The recommended starting dose of Atorvakor® is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy. Adjustments should be made at intervals of 4 weeks or more.

*Homozygous familial hypercholesterolemia*

The dosage of Atorvakor® in patients with homozygous familial hypercholesterolemia is 10 to 80 mg daily. Atorvakor® should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

*Concomitant lipid-lowering therapy*

Atorvakor® may be used with bile acid resins. The combination of HMG-CoA reductase inhibitors ([statins](http://www.rxlist.com/statins/drugs-condition.htm)) and fibrates should generally be used with caution (see Sections “Interaction with other medicinal products and other forms of interaction” and “Special warnings and precautions for use”).
*Dosage in patients with renal impairment*

Renal disease does not affect the plasma concentrations nor LDL-C reduction of Atorvakor®; thus, dosage adjustment in patients with renal dysfunction is not necessary (see Sections “Pharmacokinetics” and “Special warnings and precautions for use”).

*Dosage in patients taking cyclosporine, clarithromycin, itraconazole, letermovir or certain protease inhibitors*

In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the hepatitis C protease inhibitor (glecaprevir plus pibrentasvir, or letermovir) therapy with Atorvakor® should be avoided. In patients with HIV taking lopinavir plus ritonavir, the lowest dose Atorvakor® should be employed. In patients taking clarithromycin, itraconazole, elbasvir plus grazoprevir, and in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir or letermovir, therapy with Atorvakor® should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of Atorvakor® is employed. In patients taking the HIV protease inhibitor nelfinavir, therapy with Atorvakor® should be limited to 40 mg. in concomitant use of atorvastatin with other protease inhibitors, an appropriate clinical assessment is recommended to ensure that the lowest dose necessary of Atorvakor® is employed (see Sections “Interaction with other medicinal products and other forms of interaction” and “Special warnings and precautions for use”).

*Paediatric patients*

*Heterozygous familial hypercholesterolemia*

The safety and efficacy of atorvastatin have been established in children aged 10 to 17 years with heterozygous familial hypercholesterolemia as an adjunct to a diet to lower total cholesterol, LDL and apolipoprotein B levels when, after an adequate attempt at diet therapy:

• LDL-C is ≥190 mg/dL (4.91 mmol/L) or

• LDL-C is ≥160 mg/dL (4.14 mmol/L) and

o positive family history of familial hypercholesterolemia or documented premature cardiovascular disease in a first- or second-degree relative or

o having two or more other risk factors for cardiovascular disease.

Use of atorvastatin for this indication is supported by evidence from:

• A placebo-controlled clinical trial of 6 months duration in 187 boys and postmenarchal girls, 10 years to 17 years of age. Patients treated with 10 mg or 20 mg daily atorvastatin had an adverse reaction profile generally similar to that of patients treated with placebo. In this limited controlled study, there was no significant effect on growth or sexual maturation in boys or on menstrual cycle length in girls.

• A three year open-label uncontrolled trial that included 163 pediatric patients 10 to 15 years of age with HeFH who were titrated to achieve a target LDL-C <130 mg/dL (3.36 mmol/L). The safety and efficacy of atorvastatin in lowering LDL-C appeared generally consistent with that observed for adult patients, despite limitations of the uncontrolled study design.

Advise postmenarchal girls of contraception recommendations, 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 in pediatric patients younger than 10 years of age with HeFH.

*Homozygous familial hypercholesterolemia*

Clinical efficacy of atorvastatin with dosages up to 80 mg/day for 1 year was evaluated in an uncontrolled study of patients with HoFH including 8 pediatric patients.

***Overdose***

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

***Undesirable effects***

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

In the atorvastatin placebo-controlled clinical trial database of 16,066 patients (8755 atorvastatin vs. 7,311 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 on atorvastatin and 9.5% of the patients on placebo discontinued due to adverse reactions regardless of causality. The five 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%).

The most commonly reported adverse reactions (incidence >2% and greater than placebo) regardless of causality, in patients treated with atorvastatin in placebo controlled trials (n=8,755) were: nasopharyngitis (8.3%), arthralgia (6.9%), diarrhea (6.8%), pain in extremity (6.0%), and urinary tract infection (5.7%).

Table 4 below summarizes the frequency of clinical adverse reactions, regardless of causality, reported in >2% and at a rate greater than placebo in patients treated with atorvastatin (n=8,755), from seventeen placebo-controlled trials.

Table 4

Clinical Adverse Reactions Occurring in >2% in Patients Treated With Any Dose of Atorvastatin and at an Incidence Greater Than Placebo Regardless of Causality (% of Patients)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Adverse reaction\* | Any dose, n=8,755  | 10 mg, n=3,908 | 20 mg, n=188  | 40 mg, n=604  | 80 mg, n=4,055 | Placebo, n=7,311 |
| 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 reactions occurring in >2% in patients treated with any dose of atorvastatin and at an incidence greater than placebo regardless of causality.

Other adverse reactions reported in placebo-controlled studies include:

*General disorders:* malaise, pyrexia.

*Gastrointestional disorders:* abdominal discomfort, eructation, flatulence, hepatitis, cholestasis.

*Musculoskeletal disorders:* musculoskeletal pain, muscle fatigue, neck pain, joint swelling, tendinopathy (sometimes complicated by a rupture of the tendon).

*Metabolism and nutrition disorders:* transaminases increase, liver function test abnormal, blood alkaline phosphatase increase, creatine phosphokinase increase, hyperglycemia.

*Nervous system disorders:* nightmare.

*Respiratory disorders:* epistaxis.

*Skin and subcutaneous tissue disorders:* urticaria.

*Eye disorders:* blurred vision, visual impairment.

*Ear and labyrinth disorders:* tinnitus.

*Urinary tract disorders:* white blood cells urine positive.

*Reproductive system and breast disorders:* gynaecomastia.

Frequencies were defined as follows: common (>1/100 to <1/10); uncommon (>1/1,000 to <1/100), rare (> 1/10,000, <1/1,000), very rare (<1/10,000).

*Nervous system disorders:* common: headache; uncommon: dizziness, paresthesia, hypoaesthesia, dysgeusia, amnesia; rare: peripheral neuropathy.

*Gastrointestional disorders:* common: constipation; uncommon: pancreatitis, vomiting.

*Musculoskeletal, connective tissue and bone disorders:* common: joint pain, back pain; rare: myopathy, myositis, rhabdomyolysis, muscle rupture; very rare: lupus-like syndrome.

*General disorders:* uncommon: asthenia, chest pain, peripheral edema, fatigue.

*Metabolism and nutrition disorders:* uncommon: hypoglycemia, weight gain, anorexia.

*Liver/biliary disorders:* very rare: hepatic insufficiency.

*Skin and subcutaneous tissue disorders:* uncommon: rash, pruritus, alopecia; rare: angioedema, bullous dermatitis (including erythema multiforme), Stevens-Johnson 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.

*Investigations:* common: liver function test abnormal, blood creatine kinase increased; uncommon: white blood cells urine positive.

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

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

Clinical trial adverse experiences:

urinary tract infections, diabetes, stroke.

In the study involving 10,305 participants (age range 40–80 years, 19% women; 94.6% Caucasians, 2.6% Africans, 1.5% South Asians, 1.3% mixed/other) treated with atorvastatin 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 the study involving 2,838 subjects (age range 39–77 years, 32% women; 94.3% Caucasians, 2.4% South Asians, 2.3% Afro-Caribbean, 1% other) with type 2 diabetes treated with atorvastatin 10 mg daily (n=1,428) or placebo (n=1,410), 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 3.9 years. No cases of rhabdomyolysis were reported.

In the study involving 10,001 subjects (age range 29–78 years, 19% women; 94.1% Caucasians, 2.9% Blacks, 1.0% Asians, 2.0% other) with clinically evident CHD treated with atorvastatin 10 mg daily (n=5,006) or atorvastatin 80 mg daily (n=4,995), 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 (≥3 x ULN twice within 4–10 days) occurred in 62 (1.3%) individuals with atorvastatin 80 mg and in nine (0.2%) individuals with atorvastatin 10 mg. Elevations of CK (≥10 x ULN) 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 the study involving 8,888 subjects (age range 26–80 years, 19% women; 99.3% Caucasians, 0.4% Asians, 0.3% Blacks, 0.04% other) treated with atorvastatin 80 mg/day (n=4,439) or simvastatin 20–40 mg daily (n=4,449), 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 the study involving 4,731 subjects (age range 21–92 years, 40% women; 93.3% Caucasians, 3.0% Blacks, 0.6% Asians, 3.1% other) without clinically evident CHD but with a stroke or TIA within the previous 6 months treated with atorvastatin 80 mg (n=2,365) or placebo (n=2,366) for a median follow-up of 4.9 years, there was a higher incidence of persistent hepatic transaminase elevations (≥3 x ULN twice within 4–10 days) in the atorvastatin group (0.9%) compared to placebo (0.1%). Elevations of CK (>10 x 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 144 subjects (6.1%) in the atorvastatin group and 89 subjects (3.8%) in the placebo group (see “Special warnings and precautions for use”).

In a post-hoc analysis, atorvastatin 80 mg reduced the incidence of ischemic stroke (218/2,365, 9.2% vs. 274/2,366, 11.6%) and increased the incidence of hemorrhagic stroke (55/2,365, 2.3% vs. 33/2,366, 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). Subjects who entered the study with a hemorrhagic stroke appeared to be 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 proportions of subjects who experienced cardiovascular death were numerically smaller in the atorvastatin 80 mg group (3.3%) than in the placebo group (4.1%). The proportions of subjects who experienced non-cardiovascular death were numerically larger in the atorvastatin 80 mg group (5.0%) than in the placebo group (4.0%).

Adverse reactions from clinical studies of atorvastatin in pediatric patients:

In a 26-week controlled study in boys and postmenarchal girls with HeFH (ages 10 years to 17 years) (n=140, 31% female; 92% Caucasians, 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 TC, LDL-C, and apo B levels, was generally similar to that of placebo.

*Post-marketing experience of atorvastatin*

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

Adverse reactions associated with atorvastatin therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic oedema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), rhabdomyolysis, myositis, fatigue, tendon rupture, fatal and non-fatal hepatic failure, dizziness, depression, peripheral neuropathy, pancreatitis and interstitial lung disease.

There have been rare reports of immune-mediated necrotizing myopathy associated with statin use (see Section “Special warnings and precautions for use”).

There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins and were not considered serious adverse reactions. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

The following adverse effects were described with some statins: sexual disorders; single cases of interstitial lung disease, especially during prolonged treatment.

The following adverse reactions have been identified during postapproval use of Atorvastatin.

*Blood and lymphatic system disorders:* thrombocytopenia.

*Immune system disorders:* allergic reactions, anaphylaxis including anaphylactic shock.

*Metabolism and nutrition disorders:* weight increased.

*Nervous system disorders:* headache, hypoesthesia, dysgeusia.

*Gastrointestinal disorders:* abdominal pain.

*Ear disorders:* tinnitus.

*Skin and subcutaneous tissue:* urticaria.

*Musculoskeletal and connective tissue disorders:* arthralgia, back pain; rare: muscle rupture; very rare: lupus syndrome.

*General disorders:* chest pain, peripheral swelling, malaise, fatigue.

*Investigations:* alanine aminotransferase increased, blood creatine phosphokinase increased.

***Shelf-life***

2 years.

Do not use after expiry date indicated on the carton.

**Storage**

Store in the original package below 25 °C.

Keep out of reach of children.

**Nature and contents of container**

Tablets 10 mg: No.30 (10х3), No.60 (10х6) in blisters inserted into a carton.

Tablets 20 mg: No.30 (10х3), No.40 (10х4) in blisters inserted into a carton.

Tablets 40 mg: No.30 (10х3) in blisters inserted into a carton.

Tablets 80 mg: No.30 (6х5) in blisters inserted into a carton.

Prescription status

Prescription only.

**Manufacturer**

JSC Farmak.

**Location**

74, Kyrylivska str., Kyiv, Ukraine, 04080

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