Eturion® Tablets
Atorvastatin Calcium

1. NAME OF THE MEDICINAL PRODUCT

Eturion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient: atorvastatin.

The tablets for oral administration contain atorvastatin calcium equivalent to 10 mg, 20 mg, 40 mg, or 80 mg atorvastatin.

3. PHARMACEUTICAL FORM

Tablets: 10 mg, 20 mg, 40 mg, 80 mg.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Atorvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo B), and triglycerides (TG) in adults, adolescents and children aged 10 years or older with primary hypercholesterolemia, heterozygous familial hypercholesterolemia, or combined (mixed) hyperlipidemia (Fredrickson Types IIa and IIb), elevated serum TG levels (Fredrickson Type IV), and for patients with dysbetalipoproteinemia (Fredrickson Type III) when response to diet and other non-pharmacological measures is inadequate.

Atorvastatin also raises high density lipoprotein cholesterol (HDL-C) and lowers the LDL/HDL and total-C/HDL ratios.

Atorvastatin is also indicated to reduce total-C and LDL-C in adults with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

Prevention of Cardiovascular Disease

Eturion is indicated to reduce the risk of myocardial infarction (MI) in adult hypertensive patients without clinically evident coronary heart disease (CHD), but with at least three additional risk factors for CHD such as age ≥55 years, male sex, smoking, left ventricular hypertrophy, other specified abnormalities on

electrocardiogram (ECG), microalbuminuria or proteinuria, ratio of plasma total-C to HDL-C ≥6, or premature family history of CHD.

In adults with type 2 diabetes and without clinically evident CHD, but with multiple risk factors for CHD such as retinopathy, albuminuria, smoking or hypertension, Eturion is indicated to:

- Reduce the risk of MI.
- Reduce the risk of stroke.

In adults with clinically evident CHD, atorvastatin is indicated to:

- Reduce the risk of non-fatal MI.
- Reduce the risk of fatal and non-fatal stroke.
- Reduce the risk for revascularization procedures.
- Reduce the risk of hospitalization for congestive heart failure (CHF).
- Reduce the risk of angina.

4.2. Posology and method of administration

General

Before instituting therapy with atorvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise and weight reduction in obese patients, and to treat the underlying medical problems. The patient should continue on a standard cholesterol-lowering diet during treatment with atorvastatin. The recommended starting dose of atorvastatin is 10 mg 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 is 10 mg to 80 mg once daily. Atorvastatin can be administered as a single dose at any time of the day, with or without food. The doses should be individualized according to baseline LDL-C levels, the goal of therapy, and patient response. After initiation and/or upon titration of atorvastatin, lipid levels should be analyzed within 2 to 4 weeks, and dosage adjusted accordingly.

Prevention of Cardiovascular Disease (CVD)

For primary prevention, the recommended dose is 10 mg once daily. For secondary prevention, optimal dosing may range from 10 mg to 80 mg atorvastatin once daily, to be given at the discretion of the prescriber, taking into account the expected benefit and safety considerations relevant to the patient to be treated (see section **5.1. - Pharmacodynamic properties: Secondary Prevention of Cardiovascular Events**).

Primary Hypercholesterolemia and Combined (Mixed) Hyperlipidemia

The majority of patients are controlled with 10 mg atorvastatin once daily. A therapeutic response is evident within 2 weeks, and the maximum response is usually achieved within 4 weeks. The response is maintained during chronic therapy.

Homozygous Familial Hypercholesterolemia

In a compassionate-use study of patients with homozygous familial hypercholesterolemia, most patients responded to 80 mg atorvastatin with a greater than 15% reduction in LDL-C (18%-45%).

Use in Patients with Hepatic Insufficiency

See section **4.3. - Contraindications** and section **4.4. - Special warnings and precautions for use**.

Use in Patients with Renal Insufficiency

Renal disease has no influence on plasma concentrations or on LDL-C reduction with atorvastatin. Thus, no dose adjustment is required (see section **4.4. - Special warnings and precautions for use**).

Pediatric Use, Hypercholesterolemia

Pediatric use should only be carried out by physicians experienced in the treatment of pediatric hyperlipidemia and patients should be re-evaluated on a regular basis to assess progress.

For patients aged 10 years and above, the recommended starting dose of atorvastatin is 10 mg daily with titration up to 20 mg daily. Titration should be conducted according to the individual response and tolerability in pediatric patients. Safety information for pediatric patients treated with doses above 20 mg, corresponding to about 0.5 mg/kg, is limited.

Experience in pediatric patients older than 6 to less than 10 years of age is derived from open-label studies (see section **4.8. - Undesirable effects**, section **5.1. - Pharmacodynamic properties**, and section **5.2. - Pharmacokinetic properties: Special Populations**). Atorvastatin is not indicated in the treatment of patients below the age of 10 years.

Treatment experience in a pediatric population is limited to doses of atorvastatin up to 80 mg/day for one year in 8 patients with homozygous familial hypercholesterolemia. No clinical or biochemical abnormalities were reported in these patients.

Use in the Elderly

No differences in safety, efficacy or lipid treatment goal attainment were observed between elderly patients and the overall population (see section **5.2. - Pharmacokinetic properties: Special Populations**).

Use in Combination with Other Medicinal Compounds

In cases where co-administration of atorvastatin with cyclosporine, telaprevir, or the combination tipranavir/ritonavir is necessary, the dose of atorvastatin should not exceed 10 mg.

Dose of atorvastatin should not exceed 20 mg/day with concomitant use with elbasvir/grazoprevir (see section **4.4. - Special warnings and precautions for use: Skeletal Muscle Effects** and section **4.5. - Interaction with other medicinal products and other forms of interaction**).

Use of atorvastatin is not recommended in patients taking letermovir co-administered with cyclosporine.

Pharmacokinetic drug interactions that result in increased systemic concentration of atorvastatin have also been noted with other human immunodeficiency virus (HIV) protease inhibitors (lopinavir/ritonavir, saquinavir/ritonavir, darunavir/ritonavir, fosamprenavir, fosamprenavir/ritonavir and nelfinavir), hepatitis C (HCV) protease inhibitors (boceprevir, elbasvir/grazoprevir, simeprevir), clarithromycin, itraconazole, and letermovir. Caution should be used when co-prescribing atorvastatin, and appropriate clinical assessment is recommended to ensure that the lowest dose of atorvastatin necessary is employed (see section **4.4. - Special warnings and precautions for use: Skeletal Muscle Effects** and section **4.5. - Interaction with other medicinal products and other forms of interaction**).

THE FOLLOWING TREATMENT GUIDELINES MAY BE USED TO ESTABLISH TREATMENT GOALS

A. NCEP (National Cholesterol Education Program) Guidelines for Lipid Management: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal mg/dL (mmol/L)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes mg/dL (mmol/L)	LDL Level at Which to Consider Drug Therapy mg/dL (mmol/L)
CHD[a] or CHD risk equivalents (10-year risk >20%)	<100 (2.6)	≥100 (2.6)	≥130 (3.4) (100-129: drug optional)[b]
2+ risk factors (10-year risk ≤20%)	<130 (3.4)	≥130 (3.4)	10-year risk 10%-20%: ≥130 (3.4) 10-year risk <10%: ≥160 (4.1)
0-1 risk factor[c]	<160 (4.1)	≥160 (4.1)	≥190 (4.9) (160-189: LDL-lowering drug optional)

[a] CHD, coronary heart disease.
[b] Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL (2.6 mmol/L) cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.
[c] Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dL (2.2 mmol/L), non-HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL (0.8 mmol/L) higher than LDL-C goals for each risk category.

4.3. Contraindications

Atorvastatin is contraindicated in patients who have:

Hypersensitivity to any component of this medication

Active liver disease or unexplained persistent elevations of serum transaminases exceeding three times the upper limit of normal (ULN)

or who are:

Pregnant, breast-feeding, or of child-bearing potential who are not using adequate contraceptive measures. Atorvastatin should be administered to women of child-bearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards to the fetus.

Concomitantly treated with glecaprevir/pibrentasvir.

4.4. Special warnings and precautions for use

Hepatic Effects

As with other lipid-lowering agents of the same class, moderate (>3 x ULN) elevations of serum transaminases have been reported following therapy with atorvastatin. Liver function was monitored during pre-marketing as well as post-marketing clinical studies of atorvastatin at doses of 10 mg, 20 mg, 40 mg and 80 mg.

Persistent increases in serum transaminases (>3 x ULN on two or more occasions) occurred in 0.7% of patients who received atorvastatin in these 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.

Increases were generally not associated with jaundice or other clinical signs or symptoms. When the dosage of atorvastatin was reduced, or drug treatment interrupted or discontinued, transaminase levels returned to pre-treatment levels. Most patients continued treatment on a reduced dose of atorvastatin without sequelae.

Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggesting liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve(s). Should an increase in ALT or AST of >3 x ULN persist, reduction of dose or withdrawal of atorvastatin is recommended. Atorvastatin can cause an elevation in transaminases (see section **4.8. - Undesirable effects**).

Atorvastatin 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 atorvastatin (see section **4.3. - Contraindications**).

Skeletal Muscle Effects

Myalgia has been reported in atorvastatin-treated patients (see section **4.8. - Undesirable effects**). Myopathy, defined as muscle ache or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 x ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or if myopathy is diagnosed or suspected. The risk of myopathy is increased with concurrent administration of drugs that increase the systemic concentration of atorvastatin (see section **4.5. - Interaction with other medicinal products and other forms of interaction** and section **5.2. - Pharmacokinetic properties**). Many of these drugs inhibit cytochrome P450 3A4 (CYP 3A4) metabolism and/or drug-transport. CYP 3A4 is the primary hepatic isozyme known to be involved in the biotransformation of atorvastatin. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, HIV/HCV protease inhibitors, HCV non-structural protein 5A (NS5A)/non-structural protein 5B (NS5B) inhibitors, letermovir, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and 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. Therefore, lower starting and maintenance doses of atorvastatin should also be considered when taken concomitantly with the aforementioned drugs (see section **4.2. - Posology and method of administration**). The concurrent use of atorvastatin and fusidic acid is not recommended, therefore, temporary suspension of atorvastatin is advised during fusidic acid therapy (see section **4.5. - Interaction with other medicinal products and other forms of interaction**). Periodic CPK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. Atorvastatin may cause an elevation of CPK (see section **4.8. - Undesirable effects**).

There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins (see section **4.8. - Undesirable effects**). IMNM is clinically characterized by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment, positive anti-HMG-CoA reductase antibody and improvement with immunosuppressive agents.

As with other drugs in this class, rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria, have been reported. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects. Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or with 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).

Hemorrhagic Stroke

A post-hoc analysis of a clinical study in 4731 patients without CHD who had a stroke or transient ischemic attack (TIA) within the preceding 6 months and were initiated on atorvastatin 80 mg revealed a higher incidence of hemorrhagic stroke in the atorvastatin 80 mg group compared to placebo (55 atorvastatin vs. 33 placebo). Patients with hemorrhagic stroke on entry appeared to be at increased risk for recurrent hemorrhagic stroke (7 atorvastatin vs. 2 placebo) (see section **5.1. - Pharmacodynamic properties: Recurrent Stroke**). The potential risk of hemorrhagic stroke should be carefully considered before initiating treatment with atorvastatin in patients with recent (1 to 6 months) stroke or TIA.

Endocrine Function

Increases in hemoglobin A1c (HbA1c) and fasting serum glucose levels have been reported with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, including atorvastatin. For some patients, at high risk of diabetes mellitus, hyperglycemia was sufficient to shift them to the diabetes status. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins. Periodic monitoring of these patients is recommended.

Information for the Patient

Patients should be advised to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Adolescent females and women of child-bearing potential should be counseled on appropriate contraceptive methods while on atorvastatin therapy (see section **4.6. - Pregnancy and lactation**).

4.5. Interaction with other medicinal products and other forms of interaction

The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporine, fibric acid derivatives, lipid-modifying doses of niacin or CYP 3A4/transporter inhibitors (e.g., erythromycin and azole antifungals) (see below and also section **4.2. - Posology and method of administration: Use in Combination with Other Medicinal Compounds** and section **4.4. - Special warnings and precautions for use: Skeletal Muscle Effects**).

In the rest of the sub-sections, ‘ratio of AUC’ is defined as ‘ratio treatment (co-administered drug plus atorvastatin versus atorvastatin alone)’.

Inhibitors of CYP 3A4

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

Clarithromycin: Co-administration of atorvastatin with clarithromycin (500 mg twice daily) a known inhibitor of CYP 3A4, was associated with higher plasma concentrations of atorvastatin (see section **4.4. - Special warnings and precautions for use: Skeletal Muscle Effects**, section **4.2. - Posology and method of administration: Use in Combination with Other Medicinal Compounds** and section **5.2. - Pharmacokinetic properties: Drug Interactions - Table on Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin**).

Erythromycin: Co-administration of atorvastatin with erythromycin (500 mg four times daily), a known inhibitor of CYP 3A4, was associated with higher plasma concentrations of atorvastatin (see section **4.4. - Special warnings and precautions for use: Skeletal Muscle Effects** and section **5.2. - Pharmacokinetic properties: Drug Interactions - Table on Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin**).

Protease inhibitors: Co-administration of atorvastatin with protease inhibitors, known inhibitors of CYP 3A4, was associated with increased plasma concentrations of atorvastatin (see section **4.2. - Posology and method of administration: Use in Combination with Other Medicinal Compounds** and section **5.2. - Pharmacokinetic properties: Drug Interactions - Table on Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin**).

Diltiazem hydrochloride: Co-administration of atorvastatin (40 mg) with diltiazem (240 mg) was associated with higher plasma concentrations of atorvastatin (see section **5.2. - Pharmacokinetic properties: Drug Interactions - Table on Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin**).

Cimetidine: An atorvastatin interaction study with cimetidine was conducted, and no clinically significant interactions were seen (see section **5.2. - Pharmacokinetic properties: Drug Interactions - Table on Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin**).

Itraconazole: Concomitant administration of atorvastatin (20 mg-40 mg) with itraconazole (200 mg) was associated with an increase in atorvastatin AUC (see section **5.2. - Pharmacokinetic properties: Drug Interactions -Table on Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin**).

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 L/day) (see section **5.2. - Pharmacokinetic properties: Drug Interactions - Table on Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin**).

Transporter Inhibitors

Atorvastatin is a substrate of the hepatic transporters (see section **5.2. - Pharmacokinetic properties**).

Concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day resulted in an increase in exposure to atorvastatin (ratio of AUC: 8.7; see section **5.2. -**

Pharmacokinetic properties). Cyclosporine is an inhibitor of organic anion-transporting polypeptide 1B1 (OATP1B1), OATP1B3, multi-drug resistance protein 1 (MDR1), and breast cancer resistance protein (BCRP) as well as CYP 3A4, thus it increases exposure to atorvastatin. Do not exceed 10 mg atorvastatin daily (see section **4.2. - Posology and method of administration: Use in Combination with Other Medicinal Compounds**).

Glecaprevir and pibrentasvir are inhibitors of OATP1B1, OATP1B3, MDR1 and BCRP, thus they increase exposure to atorvastatin and concomitant use with atorvastatin is contraindicated.

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 **5.2 - Pharmacokinetic properties**). Letermovir inhibits efflux transporters P-gp, BCRP, multidrug resistance associated-protein 2 (MRP2), OAT2 and hepatic transporter OATP1B1/1B3, thus it increases exposure to atorvastatin. Do not exceed 20 mg atorvastatin daily (see section **4.2. - Posology and method of administration: Use in Combination with Other Medicinal Compounds**).

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 atorvastatin is not recommended in patients taking letermovir co-administered with cyclosporine.

Elbasvir and grazoprevir are inhibitors of OATP1B1, OATP1B3, MDR1 and BCRP, thus they increase exposure to atorvastatin. Use with caution and lowest dose necessary. Dose of atorvastatin should not exceed 20 mg/day with concomitant use with elbasvir/grazoprevir (see section **4.2. - Posology and method of administration: Use in Combination with Other Medicinal Compounds**).

Inducers of CYP 3A4

Concomitant administration of atorvastatin with inducers of CYP 3A4 (e.g., efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin (CYP 3A4 induction and inhibition of hepatocyte uptake transporter OATP1B1), 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 (see section **5.2. - Pharmacokinetic properties: Drug Interactions - Table on Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin**).

Antacids: Co-administration of atorvastatin with an oral antacid suspension containing magnesium and aluminum hydroxides decreased atorvastatin plasma concentrations (ratio of AUC: 0.66); however, LDL-C reduction was not altered.

Antipyrine: Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

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.

Digoxin: When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steady-state plasma digoxin concentrations were unaffected. However, digoxin concentrations increased (ratio of AUC: 1.15) following administration of digoxin with 80 mg atorvastatin daily. Patients taking digoxin should be monitored appropriately.

Azithromycin: Co-administration of atorvastatin (10 mg once daily) with azithromycin (500 mg once daily) did not alter the plasma concentrations of atorvastatin.

Oral contraceptives: Co-administration of atorvastatin with an oral contraceptive containing norethindrone and ethinyl estradiol increased the area under the concentration vs. time curve (AUC) values for norethindrone (ratio of AUC: 1.28) and ethinyl estradiol (ratio of AUC: 1.19). These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

Warfarin: An atorvastatin interaction study with warfarin was conducted, and no clinically significant interactions were seen.

Colchicine: Although interaction studies with atorvastatin and colchicine have not been conducted, cases of myopathy have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.

Amlodipine: In a drug-drug interaction study in healthy subjects, co-administration of atorvastatin 80 mg with amlodipine 10 mg resulted in an increase in exposure to atorvastatin (ratio of AUC: 1.18) which was not clinically meaningful.

Fusidic acid: Although interaction studies with atorvastatin and fusidic acid have not been conducted, there is an increased risk of rhabdomyolysis in patients receiving a combination of statins, including atorvastatin, and fusidic acid. The mechanism of this interaction is not known. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. 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 atorvastatin and fusidic acid should only be considered on a case by case basis and under close medical supervision. The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness.

Other Concomitant Therapy

In clinical studies, atorvastatin was used concomitantly with antihypertensive agents and estrogen replacement therapy without evidence of clinically significant adverse interactions. Interaction studies with specific agents have not been conducted.

Pediatric Population

Drug-drug interaction studies have only been performed in adults. The extent of interactions in the pediatric population is not known. The above-mentioned interactions for adults and the warnings in section **4.4. - Special warnings and precautions for use** should be taken into account for the pediatric population.

4.6. Pregnancy and lactation

Atorvastatin is contraindicated in pregnancy. Women of childbearing potential should use adequate contraceptive measures. Atorvastatin should be administered to women of child-bearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards to the fetus.

Atorvastatin is contraindicated while breast-feeding. It is not known whether this drug is excreted in human milk. Because of the potential for adverse reactions in nursing infants, women taking atorvastatin should not breast-feed.

4.7. Effects on ability to drive and use machines

None known.

4.8. Undesirable effects

Atorvastatin is generally well-tolerated. Adverse reactions have usually been mild and transient. In the atorvastatin placebo-controlled clinical trial database of 16,066 (8755 Lipitor vs. 7311 placebo) patients treated for a median period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of patients on placebo.

The most frequent (≥1%) adverse effects that may be associated with atorvastatin therapy, reported in patients participating in placebo-controlled clinical studies include:

Infections and infestations: nasopharyngitis.

Metabolism and nutrition disorders: hyperglycemia.

Respiratory, thoracic and mediastinal disorders: pharyngolaryngeal pain, epistaxis.

Psychiatric disorders: insomnia.

Nervous system disorders: headache.

Gastrointestinal disorders: nausea, diarrhea, abdominal pain, dyspepsia, constipation, flatulence.

Musculoskeletal and connective tissue disorders: arthralgia, pain in extremity, musculoskeletal pain, muscle spasms, myalgia, joint swelling.

General disorders and administration site conditions: asthenia.

Investigations: liver function test abnormal, blood creatine phosphokinase increased.

Additional adverse effects reported in atorvastatin placebo-controlled clinical trials include:

Metabolism and nutrition disorders: hypoglycemia, hyperglycemia, anorexia.

Psychiatric disorders: nightmare.

Eye disorders: vision blurred.

Ear and labyrinth disorders: tinnitus.

Nervous system disorders: peripheral neuropathy, paresthesia.

Gastrointestinal disorders: abdominal discomfort, eructation, pancreatitis, vomiting.

Hepatobiliary disorders: hepatitis, cholestasis.

Skin and subcutaneous tissue disorders: alopecia, pruritus, rash, urticaria.

Musculoskeletal and connective tissue disorders: myopathy, myositis, muscle cramps, muscle fatigue, neck pain.

Reproductive system and breast disorders: impotence.

General disorders and administration site conditions: malaise, pyrexia.

Investigations: white blood cells urine positive.

Not all effects listed above have been causally associated with atorvastatin therapy.

Pediatric Population

The clinical safety database includes safety data for 249 pediatric patients who received atorvastatin, among which 7 patients were <6 years old, 14 patients were in the age range of 6 to 9, and 228 patients were in the range of 10 to 17.

Nervous system disorders: Common: Headache.

Gastrointestinal disorders: Common: Abdominal pain.

Investigations: Common: Alanine aminotransferase increased, blood creatine phosphokinase increased.

Based on the data available, frequency, type and severity of adverse reactions in children are expected to be the same as in adults. There is currently limited experience with respect to long-term safety in the pediatric population.

Patients treated with atorvastatin had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups, regardless of causality assessment, were infections.

No clinically significant effect on growth and sexual maturation was observed in a 3-year study in children ages 6 and above based on the assessment of overall maturation and development, assessment of Tanner Stage, and measurement of height and weight. The safety and tolerability profile in pediatric patients was similar to the known safety profile of atorvastatin in adult patients.

Post-marketing Experience

In post-marketing experience, the following additional undesirable effects have been reported:

Blood and lymphatic system disorders: thrombocytopenia;

Immune system disorders: allergic reactions (including anaphylaxis);

Injury, poisoning and procedural complications: tendon rupture;

Metabolism and nutrition disorders: weight gain;

Nervous system disorders: hypoesthesia, amnesia, dizziness, dysgeusia;

Gastrointestinal disorders: pancreatitis;

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema, erythema multiforme, bullous rashes;

Musculoskeletal and connective tissue disorders: rhabdomyolysis, immune-mediated necrotizing myopathy, myositis, back pain;

General disorders and administration site conditions: chest pain, peripheral edema, fatigue.

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

4.9. Overdose

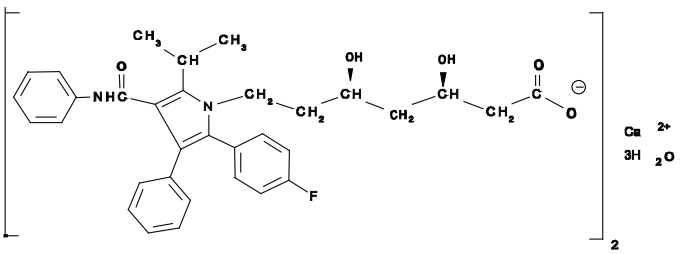
There is no specific treatment for atorvastatin overdose. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Atorvastatin calcium is a synthetic lipid-lowering agent, which is an inhibitor of HMG-CoA reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate limiting step in cholesterol biosynthesis.

The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca \bullet 3H_2O$ and its molecular weight is 1209.42. Its structural formula is:



Atorvastatin calcium is a white to off-white crystalline powder, practically insoluble in aqueous solutions of pH 4 and below. It is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile; slightly soluble in ethanol; and freely soluble in methanol.

Mechanism of Action

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts HMG-CoA to mevalonate, a precursor of sterols, including cholesterol. In patients with homozygous and heterozygous familial hypercholesterolemia, non-familial forms of hypercholesterolemia, and mixed dyslipidemia, atorvastatin reduces total-C, LDL-C, and apo B. Atorvastatin also reduces very-low-density lipoprotein cholesterol (VLDL-C) and TG and produces variable increases in HDL-C.

Triglycerides and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, IDL, and remnants can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk

factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular (CV) morbidity and mortality has not been determined.

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 for enhanced uptake and catabolism of LDL.

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

In a dose-response study, atorvastatin (10 mg-80 mg) reduced total-C (30%-46%), LDL-C (41%-61%), apo B (34%-50%), and TG (14%-33%). These results are consistent in patients with heterozygous familial hypercholesterolemia, non-familial forms of hypercholesterolemia, and mixed hyperlipidemia, including patients with non-insulin-dependent diabetes mellitus.

In patients with isolated hypertriglyceridemia, atorvastatin reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C. In patients with dysbetalipoproteinemia, atorvastatin reduces intermediate density lipoprotein cholesterol (IDL-C).

In patients with Fredrickson Types IIa and IIb hyperlipoproteinemia pooled from 24 controlled trials, the median percent increases from baseline in HDL-C for atorvastatin (10 mg-80 mg) were 5.1% to 8.7% in a non-dose-related manner. Additionally, analysis of this pooled data demonstrated significant dose-related decreases in total-C/HDL-C and LDL-C/HDL-C ratios, ranging from -29% to -44% and -37% to -55%, respectively.

Atorvastatin and some of its metabolites are pharmacologically active in humans. The primary site of action of atorvastatin is the liver, which is the principal site of cholesterol synthesis and LDL clearance. LDL-C reduction correlates better with drug dose than it does with systemic drug concentration. Individualization of drug dosage should be based on therapeutic response (see section **4.2. - Posology and method of administration**).

The effects of atorvastatin on ischemic events and total mortality were studied in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering study (MIRACL). This multicenter, randomized, double-blind, placebo-controlled study followed 3086 patients with acute coronary syndromes; unstable angina or non-Q wave MI. Patients were treated with standard care, including diet, and either atorvastatin 80 mg daily or placebo for a median duration of 16 weeks. The final LDL-C, total-C, HDL-C and TG levels were 72 mg/dL, 147 mg/dL, 48 mg/dL, and 139 mg/dL, respectively, in the atorvastatin group, and 135 mg/dL, 217 mg/dL, 46 mg/dL, and 187 mg/dL, respectively, in the placebo group. Atorvastatin significantly reduced the risk of ischemic events and death by 16%. The risk of

experiencing rehospitalization for angina pectoris with documented evidence of myocardial ischemia was significantly reduced by 26%. Atorvastatin reduced the risk of ischemic events and death to a similar extent across the range of baseline LDL-C. In addition, atorvastatin reduced the risk of ischemic events and death to similar extents in patients with non-Q wave MI and unstable angina, as well as in males and females and in patients ≤65 years of age and >65 years of age.

Prevention of Cardiovascular Complications

In the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA), the effect of atorvastatin on fatal and non-fatal CHD was assessed in 10,305 hypertensive patients 40 to 80 years of age (mean age 63 years), without a previous MI and with total-C levels <6.5 mmol/L (251 mg/dL). Additionally, all patients had at least three of the following CV risk factors: male gender (81.1%), age >55 years (84.5%), smoking (33.2%), diabetes (24.3%), history of CHD in a first-degree relative (26%), total-C:HDL >6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypertrophy (14.4%), prior cerebrovascular event (9.8%), specific ECG abnormality (14.3%), proteinuria/albuminuria (62.4%). In this double-blind, placebo-controlled study, patients were treated with anti-hypertensive therapy (goal BP <140/90 mm Hg for non-diabetic patients, <130/80 mm Hg for diabetic patients) and allocated to either atorvastatin 10 mg daily (n=5168) or placebo (n=5137). As the effect of atorvastatin treatment compared to placebo exceeded the significance threshold during an interim analysis, the ASCOT-LLA was terminated early at 3.3 years instead of 5 years. Additionally, blood pressure was well controlled and similar in patients assigned atorvastatin and placebo. These changes persisted throughout the treatment period.

Atorvastatin reduced the rate of the following events:

Event	**Risk Decrease (%)**	**No. of Events (Atorvastatin vs. Placebo)**	**p-value**
Coronary events (fatal CHD[a] plus non-fatal MI[b])	36%	100 vs. 154	0.0005
Total CV events and revascularization procedures	20%	389 vs. 483	0.0008
Total coronary events	29%	178 vs. 247	0.0006
Fatal and non-fatal stroke*	26%	89 vs. 119	0.0332

[a] Coronary Heart Disease
[b] Myocardial Infarction
* Although the reduction of fatal and non-fatal strokes did not reach a pre-defined significance level (p=0.01), a 26% relative risk reduction was observed.

The primary endpoint examined in ASCOT was the rate of fatal coronary heart disease or non-fatal (symptomatic and silent) myocardial infarction. These coronary events occurred in 1.9% of atorvastatin treated patients compared to 3% of placebo treated subjects, a relative risk reduction of 36% (p=0.0005) (Table above). There was no significant difference between groups for cardiovascular mortality (hazard ratio: 0.90, 95% CI: 0.66-1.23, p=0.51) and all-cause mortality (hazard ratio: 0.87, 95% CI: 0.71-1.06, p=0.17).

In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of atorvastatin on fatal and non-fatal CVD was assessed in 2838 patients with type 2 diabetes 40 to 75 years of age, without prior history of CVD and with LDL ≤4.14 mmol/L (160

mg/dL) and TG ≤6.78 mmol/L (600 mg/dL). Additionally, all patients had at least one of the following risk factors: hypertension, current smoking, retinopathy, microalbuminuria or macroalbuminuria.

In this randomized, double-blind, multicenter, placebo-controlled trial, patients were treated with either atorvastatin 10 mg daily (n=1428) or placebo (n=1410) for a median follow-up of 3.9 years. As the effect of atorvastatin treatment on the primary endpoint reached the pre-defined stopping rules for efficacy, CARDS was terminated 2 years earlier than anticipated.

The absolute and relative risk reduction effects of atorvastatin are as follows:

Event	**Relative Risk Reduction (%)**	**No. of Events (atorvastatin vs. placebo)**	**p-value**
Major CV events (fatal and non-fatal AMI, silent MI, acute CHD death, stroke, CABG, PTCA, revascularization procedure, unstable angina)	37%	83 vs. 127	0.0010
MI (fatal and non-fatal AMI, silent MI)	42%	38 vs. 64	0.0070
Stroke (fatal and non-fatal)	48%	21 vs. 39	0.0163
CABG, PTCA or other coronary revascularization procedure	31%	24 vs. 34	0.1557
Unstable angina	22%	8 vs. 10	0.5991
Acute CHD death (excluding confirmed acute MI)	-	10 vs. 5	0.2211

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CHD = coronary heart disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

There was no evidence of a difference in the treatment effect by patient's gender, age, or baseline LDL-C level.

A relative risk reduction in death of 27% (82 deaths in the placebo group compared to 61 deaths in the treatment arm) has been observed with a borderline statistical significance (p=0.0592).

The overall incidence of adverse events or serious adverse events was similar between the treatment groups.

Atherosclerosis

In the Reversing Atherosclerosis with Aggressive Lipid-Lowering (REVERSAL) study, the effect of atorvastatin 80 mg and pravastatin 40 mg on coronary atherosclerosis was assessed by intravascular ultrasound (IVUS), during angiography, in patients with CHD. In this randomized, double-blind, multicenter, controlled clinical trial, IVUS was performed at baseline and at 18 months in 502 patients. In the atorvastatin group (n=253), the median percent change, from baseline, in total atheroma volume (the primary study criteria) was -0.4% (p=0.98) in the atorvastatin group and +2.7% (p=0.001) in the pravastatin group (n=249). When compared to pravastatin, the effects of atorvastatin were statistically significant (p=0.02).

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

Study results were obtained with the 80 mg dose strength. Therefore, they cannot be extrapolated to the lower dose strengths.

The safety and tolerability profiles of the two treatment groups were comparable.

Recurrent Stroke

In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, the effect of atorvastatin 80 mg daily or placebo on stroke was evaluated in 4731 patients who had a stroke or TIA within the preceding 6 months and no history of CHD. Patients were 60% male, 21 to 92 years of age (mean age 63 years), and had an average baseline LDL of 133 mg/dL (3.4 mmol/L). The mean LDL-C was 73 mg/dL (1.9 mmol/L) during treatment with atorvastatin and 129 mg/dL (3.3 mmol/L) during treatment with placebo. Median follow-up was 4.9 years.

Atorvastatin 80 mg reduced the risk of the primary endpoint of fatal or non-fatal stroke by 15% (hazard ratio [HR] 0.85; 95% CI, 0.72-1.00; p=0.05 or HR 0.84; 95% CI, 0.71-0.99; p=0.03 after adjustment for baseline factors) compared to placebo. All-cause mortality was 9.1% (216/2365) for atorvastatin vs. 8.9% (211/2366) for placebo. In a post-hoc analysis, atorvastatin 80 mg reduced the incidence of ischemic stroke (218/2365, 9.2% vs. 274/2366, 11.6%, p=0.01) and increased the incidence of hemorrhagic stroke (55/2365, 2.3% vs. 33/2366, 1.4%, p=0.02) compared to placebo. The incidence of non-fatal hemorrhagic stroke was significantly greater in the atorvastatin group (38 atorvastatin vs. 16 placebo) while the incidence of fatal hemorrhagic stroke was similar between groups (17 atorvastatin vs. 18 placebo). The risk of hemorrhagic stroke was increased in patients who entered the study with a hemorrhagic stroke and had a recurrent hemorrhagic stroke (7 atorvastatin vs. 2 placebo).

All-cause mortality was 15.6% (7/45) for atorvastatin vs. 10.4% (5/48) in the subgroup of patients with prior hemorrhagic stroke.

Secondary Prevention of Cardiovascular Events

In the Treating to New Targets Study (TNT), the effect of atorvastatin 80 mg/day vs. atorvastatin 10 mg/day on the reduction in CV events was assessed in 10,001 subjects (94% white, 81% male, 38% ≥65 years) with clinically evident CHD who had achieved a target LDL-C level <130 mg/dL after completing an 8-week, open-label, run-in period with atorvastatin 10 mg/day. Subjects were randomly assigned to either

10 mg/day or 80 mg/day of atorvastatin and followed for a median duration of 4.9 years. The primary endpoint was the time-to-first occurrence of any of the following major cardiovascular events (MCVE): death due to CHD, non-fatal MI, resuscitated cardiac arrest, and fatal and non-fatal stroke. The mean LDL-C, total-C, TG, non-HDL and HDL cholesterol levels at 12 weeks were 73 mg/dL, 145 mg/dL, 128 mg/dL, 98 mg/dL and 47 mg/dL, respectively, during treatment with 80 mg atorvastatin and 99 mg/dL, 177 mg/dL, 152 mg/dL, 129 mg/dL and 48 mg/dL, respectively, during treatment with 10 mg atorvastatin.

Treatment with atorvastatin 80 mg/day significantly reduced the rate of MCVE (434 events in the 80 mg/day group vs. 548 events in the 10 mg/day group) with a relative risk reduction of 22%.

Overview of Efficacy Results in TNT

Significant Endpoint	**Atorvastatin 10 mg (N=5006)**		**Atorvastatin 80 mg (N=4995)**		**HR[a] (95% CI)**
PRIMARY ENDPOINT[*]	N	%	N	%	
First major CV endpoint	548	10.9	434	8.7	0.78 (0.69-0.89)
Components of the Primary Endpoint					
CHD death	127	2.5	101	2.0	0.80 (0.61-1.03)
Non-fatal, non-procedure related MI	308	6.2	243	4.9	0.78 (0.66-0.93)
Resuscitated cardiac arrest	26	0.5	25	0.5	0.96 (0.56-1.67)
Stroke (fatal and non-fatal)	155	3.1	117	2.3	0.75 (0.59-0.96)
SECONDARY ENDPOINTS[**]					
First CHF with hospitalization	164	3.3	122	2.4	0.74 (0.59-0.94)
First PVD endpoint	282	5.6	275	5.5	0.97 (0.83-1.15)
First CABG or other coronary revascularization procedure[b]	904	18.1	667	13.4	0.72 (0.65-0.80)
First documented angina endpoint[b]	615	12.3	545	10.9	0.88 (0.79-0.99)
All-cause mortality	282	5.6	284	5.7	1.01 (0.85-1.19)
Components of All-Cause Mortality					
CV death	155	3.1	126	2.5	0.81 (0.64-1.03)
Non-CV death	127	2.5	158	3.2	1.25 (0.99-1.57)
Cancer death	75	1.5	85	1.7	1.13 (0.83-1.55)
Other non-CV death	43	0.9	58	1.2	1.35 (0.91-2.00)
Suicide, homicide and other traumatic non-CV death	9	0.2	15	0.3	1.67 (0.73-3.82)

[a] Atorvastatin 80 mg: atorvastatin 10 mg.
[b] Component of other secondary endpoints.
[*] MCVE =death due to CHD, non-fatal MI, resuscitated cardiac arrest, and fatal and non-fatal stroke.
[**] Secondary endpoints not included in primary endpoint.
HR=hazard ratio; CHD=coronary heart disease; CI=confidence interval; MI=myocardial infarction; CHF=congestive heart failure; CV=cardiovascular; PVD=peripheral vascular disease; CABG=coronary artery bypass graft.
Confidence intervals for the secondary endpoints were not adjusted for multiple comparisons.

There was no significant difference between the treatment groups for all-cause mortality: 282 (5.6%) in the atorvastatin 10 mg/day group vs. 284 (5.7%) in the atorvastatin 80 mg/day group. The proportions of subjects who experienced CV death, including the components of CHD death and fatal stroke were numerically smaller in the atorvastatin 80 mg group than in the atorvastatin 10 mg treatment group. The proportions of subjects who experienced non-CV death were numerically larger in the atorvastatin 80 mg group than in the atorvastatin 10 mg treatment group.

In the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study (IDEAL), treatment with atorvastatin 80 mg/day was compared to treatment with simvastatin 20 mg/day to 40 mg/day in 8888 subjects up to 80 years of age with a history of CHD to assess whether reduction in CV risk could be achieved. Patients were mainly male (81%), white (99%) with an average age of 61.7 years, and an average LDL-C of 121.5 mg/dL at randomization; 76% were on statin therapy. In this prospective, randomized, open-label, blinded endpoint (PROBE) trial with no run-in period, subjects were followed for a median duration of 4.8 years. The mean LDL-C, total-C, TG, HDL and non-HDL-C levels at Week 12 were 78 mg/dL, 145 mg/dL, 115 mg/dL, 45 mg/dL and 100 mg/dL, respectively, during treatment with 80 mg atorvastatin and 105 mg/dL, 179 mg/dL, 142 mg/dL, 47 mg/dL and 132 mg/dL, respectively, during treatment with 20 mg to 40 mg simvastatin.

There was no significant difference between the treatment groups for the primary endpoint; the rate of first major coronary event (fatal CHD, non-fatal MI and resuscitated cardiac arrest): 411 (9.3%) in the atorvastatin 80 mg/day group vs. 463 (10.4%) in the simvastatin 20 mg/day to 40 mg/day group, HR 0.89, 95% CI (0.78 -1.01), p=0.07.

There were no significant differences between the treatment groups for all-cause mortality: 366 (8.2%) in the atorvastatin 80 mg/day group vs. 374 (8.4%) in the simvastatin 20 mg/day to 40 mg/day group. The proportions of subjects who experienced CV or non-CV death were similar for the atorvastatin 80 mg group and the simvastatin 20 mg to 40 mg group.

There were more serious adverse events and discontinuations due to adverse events 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). 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 CPK (≥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%).

Heterozygous Familial Hypercholesterolemia in Pediatric Patients

The following pediatric-exclusive studies have been completed with atorvastatin.

In an open-label, single-arm study, 271 male and female Heterozygous Familial Hypercholesterolemia (HeFH) children 6-15 years of age were enrolled and treated with atorvastatin for up to 3 years. Inclusion in the study required confirmed HeFH and a baseline LDL-C level ≥4 mmol/L (approximately 152 mg/dL). The study included 139 children at Tanner 1 development stage (generally ranging from 6-10 years of age). The dosage of atorvastatin (once daily) was initiated at 5 mg (chewable tablet) in children less than 10 years of age. Children age 10 and above were initiated at 10 mg atorvastatin (once daily). All children could titrate to higher doses to achieve a target of <3.35 mmol/L LDL-C. The mean weighted dose for children aged 6 to 9 years was 19.6 mg and the mean weighted dose for children aged 10 years and above was 23.9 mg.

The mean (+/- SD) baseline LDL-C value was 6.12 (1.26) mmol/L which was approximately 233 (48) mg/dL. See table below for final results.

The data were consistent with no drug effect on any of the parameters of growth and development (i.e., height, weight, BMI, Tanner stage, Investigator assessment of Overall Maturation and Development) in pediatric and adolescent subjects with HeFH receiving atorvastatin treatment over the 3-year study. There was no Investigator-assessed drug effect noted in height, weight, BMI by age or by gender by visit.

Lipid-lowering Effects of Atorvastatin in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia (mmol/L)

Timepoint	N	TC (S.D.)	LDL-C (S.D.)	HDL-C (S.D.)	TG (S.D.)	Apo B (S.D.)[#]
Baseline	271	7.86 (1.30)	6.12 (1.26)	1.314 (0.2663)	0.93 (0.47)	1.42 (0.28)[**]
Month 30	206	4.95 (0.77)[*]	3.25 (0.67)	1.327 (0.2796)	0.79 (0.38)[*]	0.90 (0.17)[*]
Month 36/ET	240	5.12 (0.86)	3.45 (0.81)	1.308 (0.2739)	0.78 (0.41)	0.93 (0.20)[***]

TC = total cholesterol; LDL-C = low density lipoprotein cholesterol-C; HDL-C = high density lipoprotein cholesterol-C; TG = triglycerides; Apo B = apolipoprotein B; S.D. = Standard Deviation; "Month 36/ET" included final visit data for subjects who ended participation prior to the scheduled 36 month timepoint as well as full 36 month data for subjects completing the 36 month participation; "*" = Month 30 N for this parameter was 207; "**" = Baseline N for this parameter was 270; "***" = Month 36/ET N for this parameter was 243; "#"=g/L for Apo B.

In a double-blind, placebo-controlled study followed by an open-label phase, 187 boys and post-menarchal girls 10 to 17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia or severe hypercholesterolemia were randomized to atorvastatin (n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level ≥190 mg/dL or 2) a baseline LDL-C ≥160 mg/dL and positive family history of familial hypercholesterolemia or documented premature CVD in a first- or second-degree relative. The mean baseline LDL-C value was 218.6 mg/dL (range: 138.5-385.0 mg/dL) in the atorvastatin group compared to 230.0 mg/dL (range: 160.0-324.5 mg/dL) in the placebo group. The dosage of atorvastatin (once daily) was 10 mg for the first 4 weeks and up-titrated to 20 mg if the LDL-C level was >130 mg/dL. The number of atorvastatin-treated patients who required up-titration to 20 mg after Week 4 during the double-blind phase was 78 (55.7%).

Atorvastatin significantly decreased plasma levels of total-C, LDL-C, TG, and apo B during the 26-week double-blind phase (see Table below).

Lipid-lowering Effects of Atorvastatin in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia

(Mean Percent Change from Baseline at Endpoint in Intention-to-Treat Population)

DOSAGE	**N**	**Total-C**	**LDL-C**	**HDL-C**	**TG**	**Apo B**
Placebo	47	-1.5	-0.4	-1.9	1.0	0.7

Atorvastatin	140	-31.4	-39.6	2.8	-12.0	-34.0

Total-C=total cholesterol; LDL-C=low density lipoprotein cholesterol; HDL-C=high density lipoprotein cholesterol; TG=triglycerides; Apo B=apolipoprotein B

The mean achieved LDL-C value was 130.7 mg/dL (range: 70.0-242.0 mg/dL) in the atorvastatin group compared to 228.5 mg/dL (range: 152.0-385.0 mg/dL) in the placebo group during the 26-week double-blind phase. In this 1-year study, there was no detectable effect on growth or sexual maturation in boys or on menstrual cycle length in girls.

An 8-week, open-label study to evaluate pharmacokinetics, pharmacodynamics, and safety and tolerability of atorvastatin was conducted in 39 patients, 6 to 17 years of age with genetically confirmed heterozygous familial hypercholesterolemia and baseline LDL-C ≥4 mmol/L. Cohort A included 15 patients, 6 to 12 years of age and at Tanner Stage 1. Cohort B included 24 patients, 10 to 17 years of age and at Tanner Stage ≥2.

The initial dose of atorvastatin was 5 mg daily of a chewable tablet in Cohort A and 10 mg daily of a tablet formulation in Cohort B. The atorvastatin dose was permitted to be doubled if a patient had not attained target LDL-C of <3.35 mmol/L at Week 4 and if atorvastatin was well tolerated.

Mean values for LDL-C, TC, VLDL-C, and Apo B decreased by Week 2 among all patients. For patients whose dose was doubled, additional decreases were observed as early as 2 weeks, at the first assessment, after dose escalation. The mean percent decreases in lipid parameters were similar for both cohorts, regardless of whether patients remained at their initial dose or doubled their initial dose. At Week 8, on average, the percent change from baseline in LDL-C and TC was approximately 40% and 30%, respectively, over the range of exposures.

The long-term efficacy of atorvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

An additional pediatric study of atorvastatin vs. colestipol in patients with hypercholesterolemia aged 10-18 years demonstrated that atorvastatin (N=25) caused a significant reduction in LDL-C at Week 26 ($p < 0.05$) compared with colestipol (N=31).

A compassionate use study in patients with severe hypercholesterolemia (including homozygous hypercholesterolemia) included 46 pediatric patients treated with atorvastatin titrated according to response (some subjects received 80 mg atorvastatin per day). The study lasted 3 years: LDL-C was lowered by 36%.

5.2. Pharmacokinetic properties

Pharmacokinetics and Metabolism

Absorption: Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. The extent of absorption and plasma

atorvastatin concentrations increases in proportion to atorvastatin dose. Atorvastatin tablets are 95% to 99% bioavailable compared to solutions. The absolute bioavailability of atorvastatin 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 hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9% respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for C_{max} and AUC) following evening drug administration compared to morning. However, LDL-C reduction is the same regardless of the time of day of drug administration (see section **4.2. - Posology and method of administration**).

Distribution: Mean volume of distribution of atorvastatin is approximately 381 Liters. Atorvastatin is ≥98% bound to plasma proteins. A red blood cell/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells.

Metabolism: Atorvastatin is extensively metabolized to ortho- and para-hydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and para-hydroxylated 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 hepatic CYP 3A4, consistent with increased plasma concentrations of atorvastatin in humans following co-administration with erythromycin, a known inhibitor of this isozyme. *In vitro* studies also indicate that atorvastatin is a weak inhibitor of CYP 3A4. Atorvastatin co-administration did not produce a clinically significant effect in plasma concentrations of terfenadine, a compound predominantly metabolized by CYP 3A4; therefore, it is unlikely that atorvastatin will significantly alter the pharmacokinetics of other CYP 3A4 substrates (see section **4.5. - Interaction with other medicinal products and other forms of interaction**). In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion: Atorvastatin and its metabolites are eliminated primarily in bile 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.

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 of the efflux transporters MDR1 and BCRP, which may limit the intestinal absorption and biliary clearance of atorvastatin.

Special Populations

Elderly: Plasma concentrations of atorvastatin are higher (approximately 40% for C_{max} and 30% for AUC) in healthy, elderly subjects (aged ≥65 years) than in young adults. The ACCESS study specifically evaluated elderly patients with respect to reaching their National Cholesterol Education Program (NCEP) treatment goals. The study included 1087 patients under 65 years of age, 815 patients over 65 years of age, and 185 patients over 75 years of age. No differences in safety, efficacy or lipid treatment goal attainment were observed between elderly patients and the overall population.

Pediatric: In an open-label, 8-week study, Tanner Stage 1 (N=15) and Tanner Stage ≥2 (N=24) pediatric patients (ages 6-17 years) with heterozygous familial hypercholesterolemia and baseline LDL-C ≥4 mmol/L were treated with 5 mg or 10 mg of chewable or 10 mg or 20 mg of film-coated atorvastatin tablets once daily, respectively. Body weight was the only significant covariate in atorvastatin population PK model. Apparent oral clearance of atorvastatin in pediatric subjects appeared similar to adults when scaled allometrically by body weight. Consistent decreases in LDL-C and total-C were observed over the range of atorvastatin and o-hydroxyatorvastatin exposures.

Gender: Plasma concentrations of atorvastatin in women differ (approximately 20% higher for C_{max} and 10% lower for AUC) from those in men. However, there were no clinically significant differences in lipid effects between men and women.

Renal Insufficiency: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin. Thus, dose adjustment in patients with renal dysfunction is not necessary (see section **4.2. - Posology and method of administration**).

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

Hepatic Insufficiency: Plasma concentrations of atorvastatin are markedly increased (approximately 16-fold in C_{max} and 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh Class B) (see section **4.3. - Contraindications**).

Drug Interactions: The effect of co-administered drugs on the pharmacokinetics of atorvastatin as well as the effect of atorvastatin on the pharmacokinetics of co-administered drugs are summarized below (see section **4.4. - Special warnings and precautions for use**, and section **4.5. - Interaction with other medicinal products and other forms of interaction**).

Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin

Co-administered Drug and Dosing Regimen	**Atorvastatin**		
	Dose (mg)	**Ratio of AUC[&]**	**Ratio of C_{max}[&]**
[#]Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QD[a] for 28 days	8.7	10.7
[#]Tipranavir 500 mg BID[b]/ritonavir 200 mg BID[b], 7 days	10 mg, SD[c]	9.4	8.6

Co-administered Drug and Dosing Regimen	Atorvastatin		
[#]Glecaprevir 400 mg QD[a]/Pibrentasvir 120 mg QD[a], 7 days	10 mg QD[a] for 7 days	8.3	22.0
[#]Telaprevir 750 mg q8h[f], 10 days	20 mg SD[c]	7.9	10.6
[#]Elbasvir 50 mg QD[a]/grazoprevir 200 mg QD[a], 13 days	10 mg SD[c]	1.95	4.3
[#]Boceprevir 800 mg TID[d], 7 days	40 mg SD[c]	2.3	2.7
[#]Simeprevir 150 mg QD[a], 10 days	40 mg SD[c]	2.12	1.7
[#]Lopinavir 400 mg BID[b]/ritonavir 100 mg BID[b], 14 days	20 mg QD[a] for 4 days	5.9	4.7
[#,‡]Saquinavir 400 mg BID[b]/ritonavir 400 mg BID[b], 15 days	40 mg QD[a] for 4 days	3.9	4.3
[#]Clarithromycin 500 mg BID[b], 9 days	80 mg QD[a] for 8 days	4.5	5.4
[#]Darunavir 300 mg BID[b]/ritonavir 100 mg BID[b], 9 days	10 mg QD[a] for 4 days	3.4	2.2
[#]Itraconazole 200 mg QD[a], 4 days	40 mg SD[c]	3.3	1.20
[#]Letermovir 480 mg QD, 10 days[a]	20 mg SD[c]	3.29	2.17
[#]Fosamprenavir 700 mg BID[b]/ritonavir 100 mg BID[b], 14 days	10 mg QD[a] for 4 days	2.5	2.8
[#]Fosamprenavir 1400 mg BID[b], 14 days	10 mg QD[a] for 4 days	2.3	4.0
[#]Nelfinavir 1250 mg BID[b], 14 days	10 mg QD[a] for 28 days	1.74	2.2
[#]Grapefruit juice, 240 mL QD[a]*	40 mg SD[c]	1.37	1.16
Diltiazem 240 mg QD[a], 28 days	40 mg SD[c]	1.51	1.00
Erythromycin 500 mg QID[e], 7 days	10 mg SD[c]	1.33	1.38
Amlodipine 10 mg, single dose	80 mg SD[c]	1.18	0.91
Cimetidine 300 mg QID[e], 2 weeks	10 mg QD[a] for 2 weeks	1.00	0.89
Colestipol 10 g BID[b], 24 weeks	40 mg QD[a] for 8 weeks	NA	0.74**
Maalox TC® 30 mL QID[e], 17 days	10 mg QD[a] for 15 days	0.66	0.67
Efavirenz 600 mg QD[a], 14 days	10 mg for 3 days	0.59	1.01
[#]Rifampin 600 mg QD[a], 7 days (co-administered)[†]	40 mg SD[c]	1.12	2.9
[#]Rifampin 600 mg QD[a], 5 days (doses separated)[†]	40 mg SD[c]	0.20	0.60
[#]Gemfibrozil 600 mg BID[b], 7 days	40 mg SD[c]	1.35	1.00
[#]Fenofibrate 160 mg QD[a], 7 days	40 mg SD[c]	1.03	1.02

[&] Represents ratio treatments (co-administered drug plus atorvastatin vs. atorvastatin alone).

[#] See section **4.4. - Special warnings and precautions for use** and section **4.5. - Interaction with other medicinal products and other forms of interaction** for clinical significance.

* Greater increases in AUC (ratio of AUC up to 2.5) and/or C_{max} (ratio of C_{max} up to 1.71) have been reported with excessive grapefruit consumption (≥750 mL-1.2 L/day).

** Ratio based on a 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/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 exercised and the lowest dose necessary should be used.

[a] Once daily

[b] Twice daily
[c] Single dose
[d] Three times daily
[e] Four times daily
[f] Every 8 hours

Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs

Atorvastatin	Co-administered Drug and Dosing Regimen		
	Drug/Dose (mg)	**Ratio of AUC[&]**	**Ratio of C_{max}[&]**
80 mg QD[a] for 15 days	Antipyrine, 600 mg SD[c]	1.03	0.89
80 mg QD[a] for 10 days	Digoxin 0.25 mg QD[a], 20 days[#]	1.15	1.20
40 mg QD[a] for 22 days	Oral contraceptive QD[a], 2 months - Norethindrone 1 mg - Ethinyl estradiol 35 µg	 1.28 1.19	 1.23 1.30
10 mg SD[c]	Tipranavir 500 mg BID[b]/ritonavir 200 mg BID[b], 7 days	1.08	0.96
10 mg QD[a] for 4 days	Fosamprenavir 1400 mg BID[b], 14 days	0.73	0.82
10 mg QD[a] for 4 days	Fosamprenavir 700 mg BID[b]/ritonavir 100 mg BID[b], 14 days	0.99	0.94

[&] Represents ratio treatments (co-administered drug plus atorvastatin vs. atorvastatin alone).
[#] See section **4.5. - Interaction with other medicinal products and other forms of interaction** for clinical significance.
[a] Once daily
[b] Twice daily
[c] Single dose

5.3. Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility - Atorvastatin was not carcinogenic in rats. The maximum dose used was 63-fold higher than the highest human dose (80 mg/day) on a mg/kg body-weight basis and 8- to 16-fold higher based on $AUC_{(0-24)}$ values. In a 2-year study in mice, the incidences of hepatocellular adenomas in males and hepatocellular carcinomas in females were increased at the maximum dose used, which was 250-fold higher than the highest human dose, on a mg/kg body-weight basis. Systemic exposure was 6- to 11-fold higher based on $AUC_{(0-24)}$.

All other chemically similar drugs in this class have induced tumors in both mice and rats at multiples of 12 to 125 times their highest recommended clinical doses, on a mg/kg body-weight basis.

Atorvastatin did not demonstrate mutagenic or clastogenic potential in four *in vitro* tests with and without metabolic activation or in one *in vivo* assay. It was negative in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, and in the *in vitro* hypoxanthine-guanine phosphoribosyltransferase (HGPRT) forward mutation assay in Chinese hamster lung cells. Atorvastatin did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay and was negative in the *in vivo* mouse micronucleus test.

No adverse effects on fertility or reproduction were observed in male rats given doses of atorvastatin up to 175 mg/kg/day or in female rats given doses up to 225 mg/kg/day. These doses are 100 to 140 times the maximum recommended human dose on a mg/kg basis. Atorvastatin caused no adverse effects on sperm or semen parameters, or on reproductive organ histopathology in dogs given doses of 10 mg/kg, 40 mg/kg, or 120 mg/kg for 2 years.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Calcium carbonate, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, polysorbate 80, hydroxypropyl cellulose, magnesium stearate, film-coating material (hydroxypropyl methylcellulose, polyethylene glycol 8000, titanium dioxide, talc), simethicone emulsion (simethicone, polysorbate 65, methylcellulose, polyoxyl 8 stearate, glycerol monostearate, xanthan gum, benzoic acid, sorbic acid, sulfuric acid, purified water).

6.2. Incompatibilities

Not relevant.

6.3. Shelf-life

See shelf-life on outer carton.

6.4. Special precautions for storage

See storage condition on outer carton.

6.5. Nature and content of container

10 mg film-coated tablets in blister-pack of 30’s and 100’s
20 mg film-coated tablets in blister-pack of 30’s and 100’s
40 mg film-coated tablets in blister-pack of 30’s and 100’s
80 mg film-coated tablets in blister-pack of 30’s and 100’s

Not all presentations may be available locally.

6.6. Special precautions for disposal and other handling

None.

7. PRODUCT OWNER

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