

Atoris

Atorvastatin

COMPOSITION

Atoris film-coated tablets 10 mg

Each film-coated tablet contains 10 mg of atorvastatin as atorvastatin calcium.

Atoris film-coated tablets 20 mg

Each film-coated tablet contains 20 mg of atorvastatin as atorvastatin calcium .

Atoris film-coated tablets 40 mg

Each film-coated tablet contains 40 mg of atorvastatin as atorvastatin calcium .

PRODUCT DESCRIPTION

10 mg tablets: White, round, slightly convex, film-coated tablet, bevel-edged.

20 mg tablets: White, round, slightly convex, film-coated tablet, bevel-edged.

40 mg tablets: White, round, slightly convex, film-coated tablet, bevel-edged.

THERAPEUTIC INDICATIONS

Hypercholesterolemia

Atoris is indicated as an adjunct to diet for reduction of elevated total cholesterol (total-C), LDL-cholesterol (LDL-C), apolipoprotein B, and triglycerides in adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (Corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other nonpharmacological measures is inadequate.

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

Prevention of cardiovascular disease

Prevention of cardiovascular events in adult patients estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors.

POSOLOGY AND METHOD OF ADMINISTRATION

Posology

The patient should be placed on a standard cholesterol-lowering diet before receiving Atoris and should continue on this diet during treatment with Atoris.

The dose should be individualised according to baseline LDL-C levels, the goal of therapy, and patient response.

The usual starting dose is 10 mg once a day. Adjustment of dose should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once a day.

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia

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

Heterozygous familial hypercholesterolaemia

Patients should be started with Atoris 10 mg daily. Doses should be individualised and adjusted every 4 weeks to 40 mg daily. Thereafter, either the dose may be increased to a maximum of 80 mg daily or a bile acid sequestrant may be combined with 40 mg atorvastatin once daily.

Homozygous familial hypercholesterolaemia

Only limited data are available.

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

Prevention of cardiovascular disease

In the primary prevention trials the dose was 10 mg/day. Higher doses may be necessary in order to attain (LDL-) cholesterol levels according to current guidelines.

Renal impairment

No adjustment of dose is required.

Hepatic impairment

Atoris should be used with caution in patients with hepatic impairment. Atoris is contraindicated in patients with active liver disease.

Use in the elderly

Efficacy and safety in patients older than 70 using recommended doses are similar to those seen in the general population.

Paediatric use

Hypercholesterolaemia:

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

For patients with Heterozygous Familial Hypercholesterolemia aged 10 years and above, the recommended starting dose of atorvastatin is 10 mg per day. The dose may be increased to 80 mg daily, according to the response and tolerability. Doses should be individualised according to the recommended goal of therapy. Adjustments should be made at intervals of 4 weeks or more. The dose titration to 80 mg daily is supported by study data in adults and by limited clinical data from studies in children with Heterozygous Familial Hypercholesterolemia.

There are limited safety and efficacy data available in children with Heterozygous Familial Hypercholesterolemia between 6 to 10 years of age derived from open-label studies. Atorvastatin is not indicated in the treatment of patients below the age of 10 years. Currently available data are described in sections Undesirable effects, Pharmacodynamic properties and Pharmacokinetic properties but no recommendation on a posology can be made.

Other pharmaceutical forms/strengths may be more appropriate for this population.

Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors

In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the hepatitis C protease inhibitor (telaprevir), therapy with Atoris should be avoided.

In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing Atoris and the lowest dose necessary employed.

In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, therapy with Atoris should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed.

In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, therapy with Atoris should be limited to 40 mg and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed.

In patients taking hepatitis C antiviral agents elbasvir/grazoprevir or letermovir for cytomegalovirus infection prophylaxis concomitantly with atorvastatin, the dose of atorvastatin should not exceed 20 mg/day.

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

Method of administration

Atoris is for oral administration. Each daily dose of atorvastatin is given all at once and may be given at any time of day with or without food.

CONTRAINDICATIONS

Atoris is contraindicated in patients:

- With hypersensitivity to the active substance or to any of the excipients of this medicinal product.
- With active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal.
- During pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures.
- Treated with the hepatitis C antivirals glecaprevir/pibrentasvir.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Liver effects

Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggestive of liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve. Should an increase in transaminases of greater than 3 times the upper limit of normal (ULN) persist, reduction of dose or withdrawal of Atoris is recommended.

Atoris should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)

In a post-hoc analysis of stroke subtypes in patients without coronary heart disease (CHD) who had a recent stroke or transient ischemic attack (TIA) there was a higher incidence of hemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior hemorrhagic stroke or lacunar infarct at study entry. For patients with prior hemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain, and the potential risk of hemorrhagic stroke should be carefully considered before initiating treatment.

Skeletal muscle effects

Atorvastatin, like other HMG-CoA reductase inhibitors, may in rare occasions affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis, a potentially life-threatening condition characterised by markedly elevated creatine kinase (CK) levels (> 10 times ULN), myoglobinaemia and myoglobinuria which may lead to renal failure.

Physicians considering combined therapy with atorvastatin and fibrates, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-modifying doses of niacin (≥ 1 g/day) should carefully weigh the potential benefits and risks and should carefully monitor patients for 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. Temporary suspension of atorvastatin may be appropriate during fusidic acid therapy.

There have been very rare reports of a immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterized by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

Before the 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
- Situations where an increase in plasma levels may occur, such as interactions and 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.

Whilst on 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. ciclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole, letermovir and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, tipranavir/ritonavir, etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivatives, antivirals for the treatment of hepatitis C (HCV) (e.g. boceprevir, telaprevir, elbasvir/grazoprevir, ledipasvir/sofosbuvir), erythromycin, niacin and ezetimibe. 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 lower maximum dose of atorvastatin is recommended. 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.

The concurrent use of atorvastatin and fusidic acid is not recommended, therefore, temporary suspension of atorvastatin may be considered during fusidic acid therapy.

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.

Myasthenia Gravis/ Ocular Myasthenia

In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia. Atoris should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

Paediatric use

No clinically significant effect on growth and sexual maturation was observed in a 3-year study based on the assessment of overall maturation and development, assessment of Tanner Stage, and measurement of height and weight.

Diabetes Mellitus

Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30kg/m², raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Atoris contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

INTERACTION WITH OTHER MEDICINAL PRODUCTS

Concurrent use of fibrates may cause severe myositis and myoglobinuria.

The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin or cytochrome P450 3A4 inhibitors (eg erythromycin and azole antifungals).

Inhibitors of cytochrome P450 3A4

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

Transporter Inhibitors

Atorvastatin is metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin. Inhibitors of the OATP1B1 (e.g. cyclosporine) can increase the bioavailability of atorvastatin. Concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day resulted in a 7.7 fold increase in exposure to atorvastatin. Use of atorvastatin is not recommended in patients taking letermovir co-administered with ciclosporin.

Erythromycin/Clarithromycin

Co-administration of atorvastatin and erythromycin (500 mg four times daily), or clarithromycin (500 mg twice daily) known inhibitors of cytochrome P450 3A4, was associated with higher plasma concentrations of atorvastatin.

Protease inhibitors

Co-administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with increased plasma concentrations of atorvastatin.

Diltiazem hydrochloride

Co-administration of atorvastatin (40mg) with diltiazem (240mg) was associated with higher plasma concentrations of atorvastatin.

Cimetidine

No clinically significant interactions were seen.

Itraconazole

Concomitant administration of atorvastatin (20 to 40 mg) and itraconazole (200 mg) was associated with an increase in atorvastatin AUC.

Grapefruit juice

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

Inducers of cytochrome P450 3A

Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (eg efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, (cytochrome P450 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.

Antacids

Co-administration of atorvastatin with an oral antacid suspension containing magnesium and aluminum hydroxides, decreased atorvastatin plasma concentrations approximately 35%; 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 (approximately 25%) 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 approximately 20% 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) and azithromycin (500 mg once daily) did not alter the plasma concentrations of atorvastatin.

Oral Contraceptives

Co-administration with an oral contraceptive containing norethindrone and ethinyl estradiol increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

Warfarin

No clinically significant interactions were seen.

Amlodipine

Co-administration of atorvastatin 80 mg and amlodipine 10 mg resulted in an 18% increase in exposure to atorvastatin which was not clinically meaningful.

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.

Fusidic Acid

Although interaction studies with atorvastatin and fusidic acid have not been conducted, severe muscle problems such as rhabdomyolysis have been reported in post-marketing experience with this combination. Patients should be closely monitored and temporary suspension of atorvastatin treatment may be appropriate.

Other Concomitant Therapy

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.

PREGNANCY AND LACTATION

Women of childbearing potential

Women of child-bearing potential should use appropriate contraceptive measures during treatment.

Pregnancy

Atoris is contraindicated during pregnancy. Safety in pregnant women has not been established. No controlled clinical trials with atorvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. Animal studies have shown toxicity to reproduction.

Maternal treatment with atorvastatin may reduce the fetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia.

For these reasons, Atoris should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with Atoris should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant.

Breastfeeding

It is not known whether atorvastatin or its metabolites are excreted in human milk. In rats, plasma concentrations of atorvastatin and its active metabolites are similar to those in milk. Because of the potential for serious adverse reactions, women taking Atoris should not breast-feed their infants. Atorvastatin is contraindicated during breastfeeding.

Fertility

In animal studies atorvastatin had no effect on male or female fertility.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

UNDESIRABLE EFFECTS

Atorvastatin is generally well-tolerated. Adverse reactions have usually been mild and transient.

Most frequent adverse effects associated with atorvastatin therapy

Infections and infestations: nasopharyngitis

Metabolism and nutrition disorders: hyperglycemia

Respiratory, thoracic and mediastinal disorders: pharyngolaryngeal pain, epistaxis

Gastrointestinal disorders: nausea, diarrhea, dyspepsia, flatulence

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

Investigations: liver function test abnormal, blood creatine phosphokinase increased

Additional adverse effects reported with atorvastatin therapy

Psychiatric disorders: nightmare

Eye disorders: vision blurred

Ear and labyrinth disorders: tinnitus

Gastrointestinal disorders: abdominal discomfort, eructation

Hepatobiliary disorders: hepatitis, cholestasis

Skin and subcutaneous tissue disorders: urticaria

Musculoskeletal and connective tissue disorders: muscle fatigue, neck pain, immune-mediated necrotizing myopathy, muscle rupture, lupus-like syndrome

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 Patients

Paediatric patients aged from 10 to 17 years of age 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 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 paediatric patients was similar to the known safety profile of atorvastatin in adult patients.

The clinical safety database includes safety data for 520 paediatric patients who received atorvastatin, among which 7 patients were < 6 years old, 121 patients were in the age range of 6 to 9, and 392 patients were in the age range of 10 to 17. Based on the data available, the frequency, type and severity of adverse reactions in children is similar to adults.

Additional undesirable effects have been reported in post-marketing experience

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, myasthenia gravis

Eye disorders: ocular myasthenia

Gastrointestinal disorders: Pancreatitis

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

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

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

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

Increases in HbA1c and fasting serum glucose levels have been reported with statins. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins.

OVERDOSE

Specific treatment is not available for atorvastatin overdose. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Liver function tests should be performed and serum CK levels should be monitored. Due to extensive atorvastatin binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: HMG-CoA-reductase inhibitors, ATC code: C10AA05

Atorvastatin 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. Triglycerides and cholesterol in the liver are incorporated into very low-density lipoproteins (VLDL) and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolized primarily through the receptor with high affinity to LDL (LDL receptor).

Atorvastatin lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG-CoA reductase and subsequently cholesterol biosynthesis in the liver and increases 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-C in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering medicinal products.

Atorvastatin has been shown to reduce concentrations of total-C (30% – 46%), LDL-C (41% – 61%), apolipoprotein B (34% – 50%), and triglycerides (14% – 33%) while producing variable increases in HDL-C and apolipoprotein A1 in a dose response study. These results are consistent in patients with heterozygous familial hypercholesterolaemia, nonfamilial forms of hypercholesterolaemia, and mixed hyperlipidaemia, including patients with noninsulin-dependent diabetes mellitus.

Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce risk for cardiovascular events and cardiovascular mortality.

PHARMACOKINETIC PROPERTIES

Absorption

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (C_{max}) occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. After oral administration, atorvastatin film-coated tablets are 95% to 99% bioavailable compared to the oral solution. The absolute bioavailability of atorvastatin is approximately 12% 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

Distribution

Mean volume of distribution of atorvastatin is approximately 381 l. Atorvastatin is $\geq 98\%$ bound to plasma proteins.

Biotransformation

Atorvastatin is metabolized by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolized via glucuronidation. *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.

Excretion

Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, atorvastatin does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is approximately 20 to 30 hours due to the contribution of active metabolites.

Atorvastatin is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporters multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin.

Special populations

Elderly: Plasma concentrations of atorvastatin and its active metabolites are higher in healthy elderly subjects than in young adults while the lipid effects were comparable to those seen in younger patient populations.

Paediatric: Apparent oral clearance of atorvastatin in paediatric subjects appeared similar to adults when scaled allometrically by body weight. Consistent decreases in LDL-C and TC were observed over the range of atorvastatin and o-hydroxyatorvastatin exposures.

Gender: Concentrations of atorvastatin and its active metabolites in women differ from those in men (Women: approx. 20% higher for C_{max} and approx. 10% lower for AUC). These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.

Renal insufficiency: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin and its active metabolites.

Hepatic insufficiency: Plasma concentrations of atorvastatin and its active metabolites are markedly increased (approx. 16-fold in C_{max} and approx. 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh B).

SLCO1B1 polymorphism: Hepatic uptake of all HMG-CoA reductase inhibitors including atorvastatin, involves the OATP1B1 transporter. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of atorvastatin, which may lead to an increased risk of rhabdomyolysis. Polymorphism in the gene encoding OATP1B1 (SLCO1B1 c.521CC) is associated with a 2.4-fold higher atorvastatin exposure (AUC) than in individuals without this genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients. Possible consequences for the efficacy are unknown.

SHELF LIFE

2 years.

SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30 °C.
Store in the original package.

PRESENTATION

Blister pack: 90 film-coated tablets in a box.

PRODUCT REGISTRATION HOLDER

PAHANG PHARMACY SDN. BHD.
Lot 5979, Jalan Teratai, 5 ½ Miles, Off Jalan Meru, 41050 Klang, Selangor, Malaysia

MANUFACTURER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

DATE OF REVISION OF THE TEXT

June 2025