

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Atorvastatin Actavis 10 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains: 10 mg of atorvastatin as atorvastatin magnesium trihydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White, oval, biconvex film-coated tablets marked with “10” on one side and “A” on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypercholesterolaemia

Atorvastatin Actavis is used as a supplement to a change in diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, or triglycerides in patients with primary hypercholesterolaemia including heterozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia (such as Frederickson's types IIa and IIb), when satisfactory results have not been obtained by a special diet or measures other than medical treatment.

Atorvastatin Actavis is also indicated to reduce total-cholesterol and LDL-cholesterol in patients 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 patients estimated to have a high risk for a first cardiovascular event (see section 5.1), as an adjunct to correction of other risk factors.

4.2 Posology and method of administration

For oral administration.

The patient should be placed on a standard cholesterol-lowering diet before receiving Atorvastatin Actavis and should continue on this diet during treatment with Atorvastatin Actavis. Doses should be determined individually according to the baseline LDL-cholesterol value, treatment objective and patient response.

The usual starting dose is 10 mg once a day. Adjustment of doses should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once a day. Doses above 20 mg/day have not been investigated in patients aged <18 years. The daily dose should be administered all at once and can be taken at any time of the day, with or without food.

Current consensus guidelines should be consulted to establish treatment goals for individual patients.

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia

An appropriate dose for most patients is 10 mg Atorvastatin Actavis a day. A response is evident within 2 weeks and maximum response is usually achieved within 4 weeks. The response is maintained during long term treatment.

Heterozygous familial hypercholesterolaemia

Initial dose is 10 mg Atorvastatin Actavis a day. Doses should be determined for each patient and adjusted at 4 week intervals up to 40 mg a day. Then the dose can be increased to either a maximum of 80 mg a day or administer 40 mg of atorvastatin once a day in combination with a bile acid sequestrant.

Homozygous familial hypercholesterolaemia

In a compassionate-use study of 64 patients there were 46 patients for whom confirmed LDL receptor information was available. From these 46 patients, the mean percent reduction in LDL-C was approximately 21%. Atorvastatin was administered at doses up to 80 mg/day.

The dose for patients with homozygous familial hypercholesterolaemia is 10-80 mg daily, in addition to other lipid lowering-treatment (e.g. LDL apheresis) 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.

Patients with impaired renal function

Renal diseases neither affect plasma concentration nor the effects of atorvastatin on blood lipids and therefore no dose adjustment is required.

Patients with impaired hepatic function

Atorvastatin Actavis should be used with caution in patients with hepatic impairment (see sections 4.4 and 5.2). Atorvastatin Actavis is contraindicated in patients with active liver disease (see section 4.3).

Elderly

Efficacy and safety of the use of recommended doses for patients over 70 years old are similar as for other adults.

Children and adolescents

The use in children should be supervised by a specialist. The experience in children is limited and restricted to a small group of patients (aged 4-17 years) with serious hyperlipidaemia such as homozygous familial hypercholesterolaemia (see section 5.1). Developmental safety data in this population have not been evaluated. The recommended initial dose for this group is 10 mg atorvastatin a day.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Active liver disease or unexplained persistent elevation of serum transaminase levels where the elevation is exceeding three times the mean upper limits.
- Myopathy.
- Pregnant and breast feeding women and women of child bearing potential not using contraceptives (see section 4.6).

4.4 Special warnings and precautions for useLiver effects

It is recommended that liver function tests be performed before the initiation of treatment, at 12 weeks after initiation of therapy or elevation of dose and periodically (e.g. six months) thereafter. Liver function tests should be performed if signs or symptoms of possible liver damage are observed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve. In case of an elevation of transaminase levels exceeding three times the mean upper limit, dose reduction is recommended or discontinuation of treatment with Atorvastatin Actavis (see section 4.8).

Atorvastatin Actavis should be used with caution in patients who consume substantial amounts of alcohol and/or have a

history of liver disease.

Previous stroke

A post-hoc analysis of subtypes of stroke in patients without coronary heart disease, who newly had a stroke or TIA, demonstrated higher incidence of hemorrhagic stroke in patients treated with 80 mg atorvastatin compared with placebo. The increased risk was seen especially in patients with a history of hemorrhagic stroke or lacunar infarct at the start of the trial. Benefit/risk ratio for atorvastatin 80 mg has not been established for patients with history of hemorrhagic stroke or lacunar infarct. The potential risk of hemorrhagic stroke should be carefully considered before the start of the treatment (see section 5.1).

Skeletal muscle effects

Atorvastatin, as other HMG-CoA reductase inhibitors can rarely influence skeletal muscles and cause myalgia, myositis and myopathy which can devolve into rhabdomyolysis, which is a potentially fatal condition and is characterized by an elevated CPK value (exceeding ten times measured upper limits), myoglobinaemia and myoglobinuria, which can cause renal failure.

Prior to treatment initiation

Atorvastatin should be used with caution in patients predisposed for rhabdomyolysis. Creatine phosphokinase (CPK) levels should be measured prior to initiating treatment with statins in case of:

- 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

In these situations, the risk of treatment should be considered carefully with respect to the possible benefits and clinical monitoring is recommended. If the CPK values are significantly elevated, exceeding five times measured upper limits, treatment shall not be started.

Creatine phosphokinase (CPK) measurements

CPK should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CPK increase, since that makes interpretation difficult. If the CPK value is significantly high (five times measured upper limits), the measurement should be repeated after 5-7 days for confirmation.

During treatment

- The importance of immediate reporting of myalgia, cramps or fatigue, especially followed by malaise and fever, must be explained to the patients.
- If these symptoms emerge during treatment with atorvastatin CPK values should be measured and in case of elevation exceeding five times measured upper limits, treatment should be discontinued.
- If symptoms from muscles are severe or cause daily discomfort, discontinuation of treatment should be considered, even though CPK values are not over five times measured upper limits.
- If symptoms resolve and CPK values become normal, treatment with atorvastatin or another statin can be considered, with minimum dose and close monitoring.
- If significant elevation of CPK values (exceeding ten times measured upper limits) or rhabdomyolysis emerge or is suspected, treatment with atorvastatin should be discontinued.

The risk of rhabdomyolysis is increased by concurrent use of atorvastatin and certain other medicinal products which can increase atorvastatin plasma concentration such as ciclosporin, erythromycin, clarithromycin, itraconazole, ketoconazole, nefazodone, niacin, gemfibrozil, other fibrates and HIV-protease inhibitors. The risk of myopathy can also be increased during concurrent administration of atorvastatin and ezetimibe. Different treatment (that does not interact) should be considered, if possible. When concomitant treatment of these substances and atorvastatin is necessary, the benefit and the risk of the treatment should be carefully considered. A lower starting dose of atorvastatin is recommended for patients during concomitant use of products that increase atorvastatin plasma concentration. During concurrent use of ciclosporin, clarithromycin or itraconazole, a lower maximal dose of atorvastatin is recommended and these patients should be clinically monitored as appropriate (see section 4.5).

Children and adolescents

In patients aged <18 years efficacy and safety have not been studied for treatment periods >52 weeks' duration and effects on long-term cardiovascular outcomes are unknown.

The effects of atorvastatin in children aged <10 years and premenarchal girls have not been investigated.

Long term effects on cognitive development, growth and pubertal maturation are unknown.

Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). 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.

4.5 Interaction with other medicinal products and other forms of interaction

The risk of myopathy during use of HMG-CoA reductase inhibitors is increased with co-administration of ciclosporin, fibrates, macrolide antibiotics, including erythromycin, azole antifungals, HIV-protease inhibitors or niacin and has rarely led to rhabdomyolysis and renal insufficiency caused by myoglobinuria. Therefore, possible benefits and the risk involved with concurrent treatment must be considered carefully. When concomitant administration of these substances and atorvastatin is necessary, the benefit and the risk of the treatment should be considered carefully. A lower starting dose of atorvastatin is recommended for patients during co-administration of medicinal products that increase atorvastatin plasma concentration. During administration of ciclosporin, clarithromycin or itraconazole, a lower maximal dose of atorvastatin is recommended and these patients should be monitored clinically as appropriate (see section 4.4).

Cytochrome P450 3A4 inhibitor

Atorvastatin is metabolised by cytochrome P450 3A4. Interactions can occur during concurrent administration of atorvastatin and a cytochrome P450 3A4 inhibitor (e.g. ciclosporin, macrolide antibiotics, including erythromycin and clarithromycin, nefazodone, azole antifungals, including itraconazole and HIV protease inhibitors). Special precaution is therefore required during concurrent administration of atorvastatin and these medicinal products because it can result in elevated plasma concentration of atorvastatin (see also section 4.4).

Transport protein inhibitors

Atorvastatin and its metabolites are substrates of OATP1B1 transporters. Concomitant use of 10 mg atorvastatin and 5.2 mg/kg/day of ciclosporin resulted in 7.7-fold increasing in atorvastatin exposure. When concurrent administration of atorvastatin and ciclosporin is necessary, the atorvastatin dose should not be higher than 10 mg.

Erythromycin, clarithromycin

Erythromycin and clarithromycin are known inhibitors of the enzyme system cytochrome P450 3A4. Concurrent administration of 80 mg atorvastatin once a day and erythromycin (500 mg four times a day) resulted in 33% increase in exposure of atorvastatin total activity. Concurrent administration of 10 mg atorvastatin daily and clarithromycin (500 mg twice a day) resulted in 3.4-fold increase in exposure of atorvastatin. When concurrent administration of atorvastatin and clarithromycin is necessary, lower maintenance doses are recommended for atorvastatin. At doses higher than 40 mg, suitable clinical monitoring of the patients is recommended.

Itraconazole

Concomitant administration of atorvastatin 40 mg and itraconazole 200 mg daily resulted in a 2.5-3.3 fold increase in exposure to atorvastatin. In cases where co-administration of itraconazole with atorvastatin is necessary, the maintenance dose of atorvastatin should not exceed 40 mg daily. Patients who normally require 80 mg of atorvastatin should either reduce their doses during concomitant itraconazole treatment, or alternatively (for short courses of this antifungal medicinal product) where not practical, a temporary suspension of treatment with atorvastatin may be considered.

Protease inhibitors

Co-administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P 450 3A4, was associated with an approximately two fold increase in plasma concentration of atorvastatin. Lipid levels should be monitored to ensure that the lowest dose necessary of atorvastatin is used.

Diltiazemhydrochloride

Concurrent administration of 40 mg atorvastatin and 240 mg diltiazem resulted in 51% increase in exposure of atorvastatin. Appropriate clinical monitoring is recommended for these patients after initiation of diltiazem and after dose adjustments.

Ezetimibe

The use of ezetimibe as monotherapy is associated with myopathy. The risk of myopathy can therefore be increased with concurrent administration of ezetimibe and atorvastatin.

Grapefruit juice

Grapefruit juice contains one or more CYP3A4 inhibitors and can cause elevation in plasma concentration of medicinal products metabolised by CYP3A4. AUC for atorvastatin increased by 37% and AUC of the active orthohydroxy metabolite decreased by 20.4% following intake of 1 glass (240 ml) of grape fruit juice. A large amount of grape fruit juice (exceeding 1.2 l a day for five days) however causes a 2.5-fold increase in the AUC for atorvastatin and a 1.3-fold increase in AUC for the active substances (atorvastatin and metabolites). Drinking large amounts of grape fruit juice is therefore not recommended during atorvastatin treatment.

Cytochrome P450 3A4 inducers

Concurrent administration of atorvastatin and cytochrome P450 3A4 inducers (e.g. efavirenz, rifampin or St. John's Wort) can result in various decrease of plasma concentration of atorvastatin. Due to the double interaction mechanism of rifampin (cytochrome P450 3A induction and blocking of the transport protein OATP1B1 in the hepatocytes), it is recommended to administer atorvastatin and rifampin at the same time since the administration of atorvastatin after administration of rifampin has been connected with significant reduction of plasma concentration of atorvastatin.

Verapamil and amiodarone

Interaction studies with atorvastatin and verapamil and amiodarone have not been conducted. Both verapamil and amiodarone inhibit CYP3A4 activity and co-administration with atorvastatin may result in increased exposure to atorvastatin. Lipid levels should be monitored to ensure that the lowest dose necessary of atorvastatin is used.

Concurrent use of other medicinal products*Gemfibrozil/fibrates*

The administration of fibrates as monotherapy is associated with myopathy. Risk of atorvastatin induced myopathy can be increased during concurrent administration of fibrates (see section 4.4). Concomitant administration of 600 mg gemfibrozil twice daily resulted in 24% increase in the exposure of atorvastatin.

Digoxin

Repeated administration of digoxin and atorvastatin 10 mg at the same time did not influence the steady state plasma concentration of digoxin. Digoxin concentration however increased by ca. 20% during concurrent use of digoxin and atorvastatin 80 mg a day. This interaction can be explained by inhibition of the P-glycoprotein (membrane transferring protein). Patients treated with digoxin should be monitored carefully.

Oral contraceptives

Concurrent use of atorvastatin and oral contraceptives increased the plasma concentration of norethisterone and ethinyl oestradiol. This should be considered when selecting oral contraceptive doses.

Colestipol

Plasma concentration of atorvastatin and its active metabolites decreased (approx. 25%) when colestipol was administered with atorvastatin. However, lipid effects were greater when atorvastatin and colestipol were administered together than when either medicinal product was administered alone.

Antacids

Concurrent administration of atorvastatin and oral antacid liquid formulations containing magnesium and aluminium hydroxides decreased plasma concentration of atorvastatin and its active metabolites by approx. 35%; reduction of LDL-cholesterol was however not altered.

Warfarin

Concurrent use of atorvastatin and warfarin caused a minor decrease in prothrombin time during the first days of treatment, but returned to normal within 15 days. Nevertheless patients receiving warfarin should be closely monitored when atorvastatin is added to their treatment.

Phenazone

Concurrent use of repeated doses of atorvastatin and phenazone resulted in little or no visible effect on the clearance of phenazone.

Cimetidine

In the one study available of interactions between cimetidine and atorvastatin no interaction was seen.

Amlodipine

An interaction study on healthy voluntary subjects showed that concomitant administration of atorvastatin 80 mg and amlodipine 10 mg resulted in 18% increase in the exposure of atorvastatin.

Other interactions

In clinical studies no clinically significant interactions were observed when atorvastatin was administered together with antihypertensives or hypoglycemic agents.

4.6 Fertility, pregnancy and lactation

Atorvastatin Actavis is contraindicated in pregnancy and while breast-feeding. Women of child bearing potential must use effective contraceptive measures during treatment. Safety of atorvastatin use during pregnancy and lactation has not been established (see section 4.3).

Animal studies indicate that HMG-CoA reductase inhibitors can influence the embryonic and foetal development. Maturation of rat offspring was delayed and post-natal survival was reduced after administering atorvastatin to the mother in doses higher than 20 mg/kg/day (clinical systemic exposure).

In rats the concentration of atorvastatin and its active metabolites is similar in plasma and milk. It is not known whether atorvastatin or its metabolites are excreted into breast milk in humans.

4.7 Effects on ability to drive and use machines

Atorvastatin has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The most frequent adverse events that can be expected are symptoms from the gastrointestinal system, including constipation, flatulence, dyspepsia, abdominal pain, usually resolving during continued treatment. Less than 2% of patients were discontinued from clinical trials due to side effects related to atorvastatin.

The following list of adverse events is based on results from clinical studies and post marketing reports.

Estimated frequency of events is as follows: Common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$).

Blood and lymphatic system disorders

Uncommon: Thrombocytopenia.

Nervous system disorders

Common: Headache, dizziness, paraesthesia, hypoesthesia.

Uncommon: Peripheral neuropathy.

Very rare: Taste disturbances.

Eye disorders

Very rare: Sight disturbances.

Ear and labyrinth disorders

Uncommon: Tinnitus.

Very rare: Impaired hearing.

Respiratory, thoracic and mediastinal disorders

Frequency not known: Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4).

Gastrointestinal disorders

Common: Abdominal pain, constipation, flatulence, dyspepsia, nausea, diarrhea.

Uncommon: Anorexia, vomiting.

Skin and subcutaneous tissue disorders

Common: Rash, pruritus.

Uncommon: Urticaria.

Very rare: Angioedema, bullous eruptions (including erythema multiforme, Steven-Johnsons syndrome and toxic epidermal necrolysis).

Musculoskeletal and connective tissue disorders

Common: Myalgia, arthralgia, back pain.

Uncommon: Myopathy, muscle spasms.

Rare: Myositis, rhabdomyolysis.

Very rare: Rupture of tendons.

Endocrine disorders

Uncommon: Alopecia, hyper- or hypoglycaemia, pancreatitis.

General disorders and administration site conditions

Common: Asthenia, chest pain, peripheral oedema, fatigue.

Uncommon: Malaise, weight gain.

Immune system disorders

Common: Allergic reactions.

Very rare: Anaphylaxis.

Hepatobiliary disorders

Rare: Hepatitis, cholestatic jaundice.

Very rare: Liver failure.

Reproductive system and breast disorders

Uncommon: Impotence.

Very rare: Gynecomastia.

Frequency not known: Sexual dysfunction.

Psychiatric disorders

Common: Insomnia.

Uncommon: Amnesia.

Frequency not known: Depression, sleep disturbances, including nightmares

Investigations

Elevation of serum transaminases has been reported in patients receiving atorvastatin as with other HMG-CoA reductase inhibitors. These alterations were most often mild and transient and discontinuation of treatment was not necessary. Elevation of serum transaminases of clinical significance (exceeding three times mean values of upper limits) was observed in 0.8% of patients receiving atorvastatin. These elevations were dose dependent and resolved in all patients.

In clinical studies increase in serum creatine phosphokinase (CPK) was observed (exceeding three times mean values of upper limits) in 2.5% of patients receiving atorvastatin which is similar as with other HMG-CoA reductase inhibitors. Values exceeding ten times the upper mean values were observed in 0.4% of patients receiving atorvastatin (see section 4.4).

4.9 Overdose

No specific treatment for Atorvastatin Actavis overdose is available. In case of an overdose the patient should be treated symptomatically and supportive measures instituted if required. Liver function should be monitored and serum CPK-values. Due to extensive binding to plasma proteins, haemodialysis is not expected to enhance significantly atorvastatin clearance.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: HMG-CoA reductase inhibitors, ATC code: C 10 A A 05

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzymeA to mevalonate, a precursor of sterols, including cholesterol. Triglycerides and cholesterol in the liver are incorporated into VLDL (very low density lipoproteins) and released into the blood for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolised primarily through the high affinity LDL receptor.

Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver. Atorvastatin also increases the number of hepatic LDL receptors on the cell surface in the liver, which results in 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 hypercholesterolemia, a population that has not usually responded to lipid-lowering medical treatment.

Atorvastatin has been shown to reduce total cholesterol (30-46%), LDL-cholesterol (41-61%), apolipoprotein B (34-50%) and triglycerides (14-33%), but to cause variable increases in HDL cholesterol and apolipoprotein A1 in dose related studies. These results apply to patients with heterozygous familial hypercholesterolaemia, non familial hypercholesterolaemia and mixed hyperlipidaemia, including patients with non-insulin dependent diabetes mellitus.

Reductions in total-cholesterol, LDL-cholesterol and apolipoprotein B have been proved to reduce risk for cardiovascular events and cardiovascular mortality. Mortality and morbidity studies with atorvastatin have not yet completed.

Atherosclerosis

In the REVERSAL (Reversing Atherosclerosis with Aggressive Lipid-Lowering Study), the effect of aggressive lipid lowering with atorvastatin 80 mg and lipid lowering to standard levels with pravastatin 40 mg on coronary atherosclerosis was assessed by intravascular ultrasound (IVUS), during angiography, in patients with coronary heart disease.

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), there was no progression of atherosclerosis.

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).

The effect of intensive lipid reduction on cardiovascular end-points (e.g. the need for revascularisation, non-fatal myocardial infarction, coronary death) was not investigated in this study.

In the atorvastatin group, LDL-cholesterol was reduced to a mean value of 2.04 mmol/l $\pm$ 0.8 (78.9 mg/dl $\pm$ 30) from baseline value 3.98 mmol/l $\pm$ 0.7.

In the pravastatin group, LDL-cholesterol was reduced to a mean value of 2.85 mmol/l $\pm$ 0.7 (110 mg/dl $\pm$ 26) from baseline value 3.89 mmol/l $\pm$ 0.7 (150 mg/dl $\pm$ 26) (p<0.0001). Atorvastatin also significantly reduced mean TC by 34.1% (pravastatin: -18.4%, p<0.0001), mean TG levels by 20% (pravastatin: -6.8%, p<0.0009, and mean apolipoprotein B by 39.1% (pravastatin: -22.0%, p<0.0001).

Atorvastatin increased mean HDL-cholesterol 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).

The study results were obtained with 80 mg doses of atorvastatin and can therefore not be extrapolated to lower doses.

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

The effect of intensive lipid lowering with atorvastatin on cardiovascular mortality and morbidity was not investigated in this study. Therefore, the clinical significance of these imaging results with regard to the primary and secondary prevention of cardiovascular events is unknown.

Heterozygous familial hypercholesterolaemia in paediatric patients

In a double-blind, placebo controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolaemia (FH) or severe hypercholesterolaemia were randomised 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 $\geq$ 4.91 mmol/l or 2) a baseline LDL-C $\geq$ 4.14 mmol/l and positive family history of FH or documented premature cardiovascular disease in a first- or second degree relative. The mean baseline LDL-C value was 5.65 mmol/l (range: 3.58-9.96 mmol/l) in the atorvastatin group compared to 5.95 mmol/l (range: 4.14-8.39 mmol/l) in placebo group. The dose of atorvastatin (once daily) was 10 mg for the first 4 weeks and up-titrated to 20 mg if the LDL-C level was $>$ 3.36 mmol/l. The number of atorvastatin-treated patients who required up-titration to 20 mg after week 4 during the double-blind phase was 80 (57.1%).

Atorvastatin significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26 week double-blind phase (see Table 1).

TABLE 1. Lipid Lowering effects of atorvastatin in adolescent boys and girls with heterozygous familial hypercholesterolaemia or severe hypocholesterolaemia (mean percent change from baseline at endpoint in intention- to-treat-population						
DOSES	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

The mean achieved LDL-C value was 3.38 mmol/l (range: 1.81 6.26 mmol/l) in the atorvastatin group compared to 5.91 mmol/l (range: 3.93 9.96 mmol/l) in the placebo group during the 26-week double-blind phase.

In this limited controlled study, there was no detectable effect on growth or sexual maturation in boys or on menstrual length in girls. Atorvastatin has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age. The safety and efficacy of doses above 20 mg have not been studied in controlled trials in children. The long-term efficacy of atorvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

Prevention of cardiovascular disease

The effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in a randomized, double-blind, placebo-controlled study, the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA).

Patients were hypertensive, 40-79 years of age, with no previous myocardial infarction or treatment for angina, and with TC levels ≤6.5 mmol/l (251 mg/dl). All patients had at least 3 of the pre-defined cardiovascular risk factors: male gender, age ≥55 years, smoking, diabetes, history of CHD in a first-degree relative, TC:HDL-C>6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria. Not all included patients were estimated to have a high risk for a first cardiovascular event.

Patients were treated with anti-hypertensive therapy (either amlodipine or atenolol-based regimen) and either atorvastatin 10 mg daily (n=5168) or placebo (n=5137).

The absolute and relative risk reduction effect of atorvastatin was as follows:

Events	Relative risk reduction (%)	No. of events (atorvastatin vs. placebo)	Absolute risk reduction ¹ (%)	p-value
Fatal CHD and non-fatal MI	36%	100 vs. 154	1.1%	0.0005
Total cardiovascular events and revascularisation procedures	20%	389 vs. 483	1.9%	0.0008
Total coronary events	29%	178 vs. 247	1.4%	0.0006

¹Based on difference in crude events rates occurring over a median follow-up of 3.3 years.
CHD = coronary heart disease; MI = myocardial infarction.

Total mortality and cardiovascular mortality were not significantly reduced (185 vs. 212 events, p=0.17 and 74 vs. 82 events, p=0.51). In the subgroup analyses by gender (81% males, 19% females), a beneficial effect of atorvastatin was seen in males but could not be established in females possibly due to the low event rate in the female subgroup. Total mortality and cardiovascular mortality were numerically higher in the female patients (38 vs. 30 and 17 vs. 12), but this was not statistically significant. There was significant treatment interaction by antihypertensive baseline therapy. The primary endpoint (fatal CHD and non-fatal MI) was significantly reduced by atorvastatin in patients treated with Amlodipine (HR 0.47 (0.32-0.69), p=0.00008), but not in those treated with atenolol (HR 0.83 (0.59-1.17), p=0.287).

The effect of atorvastatin on fatal and non-fatal cardiovascular disease was also assessed in a randomized, double-blind, multicenter, placebo-controlled trial, the Collaborative Atorvastatin Diabetes Study (CARDS) in patients with type 2 diabetes, 40-75 years of age, without prior history of cardiovascular disease, and with LDL-cholesterol ≤ 4.14 mmol/l (160 mg/dl) and TG ≤ 6.78 mmol/l (600 mg/dl). All patients had at least 1 of the following risk factors: hypertension, current smoking, retinopathy, microalbuminuria or macroalbuminuria.

Patients were treated with either atorvastatin 10 mg daily (n=1428) or placebo (n=1410) for a median follow-up of 3.9 years.

The absolute and relative risk reduction effect of atorvastatin was as follows:

Events	Relative risk reduction (%)	No. of events (atorvastatin vs. placebo)	Absolute risk reduction ¹ (%)	p-value
Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularisation, stroke)	37%	83 vs. 127	3.2%	0.0010
MI (fatal and non-fatal, AMI, silent MI)	42%	38 vs. 64	1.9%	0.0070
Strokes (fatal and non-fatal)	48%	21 vs. 39	1.3%	0.0163

¹Based on difference in crude events rates occurring over a median follow-up of 3.9 years.

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-cholesterol level.

A favourable trend was observed regarding the mortality rate (82 deaths in the placebo group vs. 61 deaths in the atorvastatin group, p=0.0592).

Previous stroke

In the study “stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)”, the effect of atorvastatin 80 mg daily on stroke in 4731 patients with no known coronary heart disease (CHD) who have had a stroke or an ischemic attack (TIA) within the last 6 months was evaluated and compared with placebo. Of the patient group 60% were males, 21-92 years old (mean 63 years) with a mean LDL-cholesterol level 3.4 mmol/l (133 mg/dl) at the initiation of the treatment. The mean LDL-cholesterol level was 1.9 mmol/l (73 mg/dl) for the atorvastatin group and 3.3 mmol/l (129 mg/dl) for the placebo group. The mean of follow-up was 4.9 years.

A reduction seen for atorvastatin 80 mg in the primary endpoint for fatal or non-fatal stroke was 15% (HR 0.85; 95% CI, 0.72-1.00; p=0.05 or 0.84; 95% CI, 0.71-0.99; p=0.03 after adjustment of some factors at baseline) compared to placebo. Total mortality (all causes) was 9.1% (216/2365) for atorvastatin compared to 8.9% (211/2366) for placebo.

A post-hoc analysis for atorvastatin 80 mg showed a reduced incidence of ischemic stroke (218/2365, 9.2% versus 274/2366, 11.6%, p=0.01) and increased incidence of haemorrhagic stroke (55/2365, 2.3% versus 33/2366, 1.4%, p=0.02) compared to placebo.

- The risk of haemorrhagic stroke was increased in patients with a history of haemorrhagic stroke when joining the study (7/45 for atorvastatin compared with 2/48 for placebo; HR 4.06; 95% CI, 0.84-19.57) and the risk for ischemic stroke was similar for both groups (3/45 for atorvastatin compared with 2/48 for placebo; HR 1.64; 95% CI, 0.27-9.82).

- The risk of haemorrhagic stroke was increased in patients who joined the study with a history of a lacunar infarct (20/708 for atorvastatin compared to 4/701 for placebo; HR 4.99; 95% CI, 1.17-14.61) but the risk for ischemic stroke reduced also in these patients (79/708 for atorvastatin compared to 102/701 for placebo; HR 0.76; 95% CI; 0.57-1.02). It is possible that the total risk for a stroke is increased in patient with a history of lacunar infarct taking atorvastatin 80 mg daily.

The total mortality (all causes) was 15.6% (7/45) for atorvastatin compared to 10.4% (5/48) for the placebo group for patients with a history of a hemorrhagic stroke. The total mortality was 10.9% (77/708) for atorvastatin compared to 9.1% (64/701) for placebo in a subgroup of patients with a history of lacunar infarct.

5.2 Pharmacokinetic properties

Absorption

Atorvastatin is rapidly absorbed following oral administration; maximum plasma concentration ($C_{\max}$) is obtained within 1-2 hours. Extent of absorption increases in proportion to the atorvastatin dose. Bioavailability of atorvastatin following intake of film-coated tablets is 95-99% compared to the bioavailability of atorvastatin solutions. Absolute bioavailability is about 12% and systemic availability of the active HMG-CoA reductase inhibitor is about 30%. The low systemic availability is due 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.

Metabolism

Atorvastatin is metabolised by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these compounds are further metabolised by glucuronisation. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approx. 70% of inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Excretion

Atorvastatin is excreted primarily in bile following hepatic and/or extrahepatic metabolism. The medicinal product does however not appear to undergo significant enterohepatic recirculation. Mean plasma metabolism half-life of atorvastatin in humans is approx. 14 hours. Due to the active metabolites the half-life of inhibitory activity for HMG-CoA reductase is approximately 20-30 hours.

Special patient groups

- Elderly: Concentration of atorvastatin and its active metabolites in plasma is higher in healthy elderly individuals than in those who are younger, but the blood lipid effects are similar in both age groups.
- Children and adolescents: Pharmacokinetic data for children below 18 years is not available.
- Gender: Concentrations of atorvastatin and its active metabolites differ in women (maximum plasma concentration is about 20% higher and AUC about 10% lower) from those in men. This difference is not of clinical relevance, and the difference in effects on blood lipids between men and women is not significant.
- Renal impairment: Renal diseases neither affect plasma concentration nor blood lipid effects of atorvastatin and its active metabolites.
- Hepatic impairment: Plasma concentration of atorvastatin and its active metabolites increases significantly ($C_{\max}$ approx. 16-fold and AUC 11-fold) in patients with chronic alcoholic liver disease (Childs-Pugh B).

5.3 Preclinical safety data

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 as determined by total inhibitory activity.

In a 2-year study in mice, incidences of hepatocellular adenoma in males and hepatocellular carcinomas in females were increased at the maximum dose used, and the maximum dose used was 250-fold higher than the highest human dose used on a mg/kg body-weight basis. Systemic exposure was 6 to 11-fold higher based on $AUC_{(0-24)}$.

Atorvastatin did not demonstrate mutagenic or clastogenic potential in 4 *in vitro* tests with or without metabolic activation and 1 *in vivo* assay.

In animal studies atorvastatin had no effect on male or female fertility at doses of up to 175 mg/kg and 225 mg/kg/day, respectively, and was not teratogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Mannitol

Microcrystalline cellulose

Crospovidone

Sodium carbonate anhydrous

Povidone K29-32

Magnesium stearate

Coating:

Hypromellose

Titanium dioxide (E 171)

Macrogol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/Aluminium blisters.

White tablet container (HDPE) with silica gel desiccant, closed with snap-on cap (LDPE) with a tamper evident ring.

Pack sizes:

Blisters: 10, 20, 28, 30, 50, 98 and 100 film-coated tablets.

Tablet container: 30, 100, 250 and 500 film-coated tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavikurvegi 76-78
220 Hafnarfjordur
Iceland

8 MARKETING AUTHORISATION NUMBER

PA 1380/23/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th September 2009

10 DATE OF REVISION OF THE TEXT

July 2011