

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Atacor 10 mg film-coated tablets
Atacor 20 mg film-coated tablets
Atacor 40 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains: 10 mg, 20 mg or 40 mg atorvastatin (as atorvastatin calcium).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

10 mg: White, round, biconvex, 7 mm, film-coated tablets.

20 mg: White, round, biconvex, 9 mm, film-coated tablets.

40 mg: White, oval, biconvex, 8.2 x 17 mm, film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Atacor 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, 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 medication.

In combination therapy with e.g. other LDL-cholesterol reducing medicinal products or if satisfactory results have not been obtained by other measures of reducing total cholesterol and LDL-cholesterol in patients with homozygous familial hypercholesterolaemia.

4.2 Posology and method of administration

The patient should be placed on a standard cholesterol-lowering diet before receiving Atacor and should continue following this diet during treatment with Atacor. 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 dosage should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once a day. The daily dose should be administered all at once and can be taken at any time of the day, with or without food.

Treatment objectives for patients with a confirmed coronary disease or other patients at increased risk of ischemia are LDL-cholesterol <3 mmol/l (or <115 mg/dl) and total cholesterol <5 mmol/l (or <190 mg/dl).

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia

An appropriate dose for most patients is 10 mg Atacor 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

The initial dose is 10 mg Atacor 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 else, 40 mg of atorvastatin once a day can be administered in combination with a bile acid sequestrant.

Homozygous familial hypercholesterolaemia

In a clinical study in 64 patients, 46 of whom had homozygous familial hypercholesterolaemia, atorvastatin was administered in up to 80 mg doses. For these 46 patients the mean reduction of LDL-cholesterol was 21%.

Patients with homozygous familial hypercholesterolaemia who had not been responsive to alternative treatments received atorvastatin in 10-80 mg doses a day concurrently with other blood lipid lowering-treatment (e.g. other LDL-cholesterol reducing medicinal products).

Patients with impaired renal function

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

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.

Experience of the use of the medicinal product in children is limited and restricted to a small group of patients (aged 4-17 years) with serious hyperlipidaemia such as homozygous familial hypercholesterolaemia. The recommended initial dose for this group is 10 mg atorvastatin a day. Based on response and tolerance the dose can be increased to 80 mg a day. Information regarding safety with respect to maturation for this group has not been evaluated.

4.3 Contraindications

Atacor is contraindicated in:

- Patients with a history of hypersensitivity to the active substance or to any of the excipients.
- Patients with an active liver disease or unexplained persistent elevation of serum transaminase levels where the elevation exceeds three times the mean upper limits.
- Patients with myopathy.
- Pregnant and breast feeding women.
- Women of child bearing potential not using contraceptives.

4.4 Special warnings and precautions for use

Liver effects

Liver function tests should be performed before the initiation of treatment and periodically during treatment. 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 or discontinuation of treatment with Atacor is recommended (see section 4.8).

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

Skeletal muscle effects

Like other HMG-CoA reductase inhibitors, atorvastatin can very rarely influence skeletal muscles and cause myalgia, myositis and myopathy which can evolve 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 insufficiency.

Prior to treatment initiation:

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

- Renal impairment
- Hypothyroidism
- History of genetic myopathy.
- History of myopathy in relation to prior use of statins or fibrates.
- Liver impairment and/or excessive alcohol use.
- Elderly patients (70 years and older). Requirements for such a measurement shall be evaluated with respect to the above.

In these cases the risk involved with the treatment must be considered carefully with respect to the possible benefits and potential risk. Thorough clinical monitoring is recommended. If the CPK value is significantly high (exceeding five times measured upper limits) treatment should not be initiated.

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 (exceeding 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 if 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 significant elevation (exceeding five times measured upper limits), treatment should be discontinued.
- If muscle symptoms 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 rhabdomyolysis is suspected, treatment with atorvastatin should be discontinued.

The risk of rhabdomyolysis is increased by concurrent use of atorvastatin and medicinal products such as cyclosporin, erythromycin, clarithromycin, itraconazole, ketoconazole, nefazodone, niacin, gemfibrozil, other fibrates and HIV-protease inhibitors (see section 4.5 and section 4.8).

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 by concurrent use of cyclosporin, fibrates, macrolide antibiotics including erythromycin, azole antifungals or niacin and has

very rarely led to rhabdomyolysis and renal insufficiency caused by myoglobinuria. Possible benefits and the risk involved with concurrent treatment must be considered carefully (see section 4.4).

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

Erythromycin, clarithromycin: Concurrent administration of atorvastatin, 10 mg once a day and erythromycin (500 mg four times a day) or clarithromycin (500 mg twice a day), known cytochrome P450 3A4 inhibitors, resulted in a higher plasma concentration of atorvastatin. When administered concurrently with atorvastatin, clarithromycin caused a 56% increase in the C_{max} of atorvastatin and an 80% increase in its AUC.

P-glycoprotein inhibitors: Atorvastatin and its metabolites are substrates of P-glycoprotein. P-glycoprotein inhibitors (e.g. cyclosporin) can increase the bioavailability of atorvastatin.

Itraconazole: Concurrent administration of atorvastatin 40 mg and itraconazole 200 mg a day resulted in a threefold increase in the AUC of atorvastatin.

Protease inhibitors: Concurrent use of atorvastatin and protease inhibitors which are known CYP3A4 inhibitors resulted in an increased plasma concentration of atorvastatin.

Grapefruit juice: Contains one or more CYP3A4 inhibitors and can cause elevation in plasma concentration of medicinal products metabolised by CYP3A4. The AUC for atorvastatin increased by 37% and the AUC of the active orthohydroxy metabolite decreased by 20.4% following intake of 240 ml of grapefruit juice. A large amount of grapefruit 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 HMG-Co A reductase inhibitors (atorvastatin and active metabolites). Drinking large amounts of grapefruit juice is therefore not recommended during atorvastatin treatment.

Cytochrome P450 3A4 inducers: The effects of cytochrome P450 3A4 inducers (e.g. rifampicine or phenytoin) on atorvastatin are not known. Possible interactions with other substrates of this isoenzyme are not known, but should be considered in case of medicinal products with a narrow therapeutic index, e.g. class III antiarrhythmics, including amiodarone.

Concurrent use of other medicinal products:

Gemfibrozil/fibrates: The risk of atorvastatin induced myopathy can increase during concurrent administration of fibrates. In vitro studies indicate that gemfibrozil inhibits glucuronization of atorvastatin and can therefore possibly cause increased plasma concentration of atorvastatin (see also section 4.4).

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 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 concentration of norethisterone and ethinyl oestradiol. These increased concentrations 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, lipidaemic effects were greater when atorvastatin and colestipol were administered together than when either drug was administered alone.

Antacids: Concurrent administration of atorvastatin and oral antacid liquid formulations containing magnesium and aluminium hydroxides decreased atorvastatin plasma concentrations 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 atorvastatin and phenazone for some time resulted in little or no visible effect on the clearance of phenazone.

Cimetidine: In one study of interactions between cimetidine and atorvastatin no interaction was seen.

Amlodipine: Concurrent use of atorvastatin 80 mg and amlodipine 10 mg did not influence pharmacokinetic properties of atorvastatin at steady state.

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

4.6 Pregnancy and lactation

Atacor is contraindicated in pregnancy and while breast feeding. Women of child bearing potential have to use effective contraceptive measures during treatment.

Safety of atorvastatin use during pregnancy and lactation has not been established.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

Estimated frequency of events is as follows: Common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1.000$, $< 1/100$); rare ($\geq 1/10.000$, $< 1/1.000$); very rare ($< 1/10.000$).

Gastrointestinal disorders:

Common: Constipation, flatulence, dyspepsia, nausea, diarrhoea.

Uncommon: Anorexia, vomiting.

Blood and lymphatic system disorders:

Uncommon: Thrombocytopenia.

Immune system disorders:

Common: Hypersensitivity.

Very rare: Anaphylaxis.

Endocrine disorders:

Uncommon: Alopecia, hyper- or hypoglycaemia, pancreatitis.

Psychiatric disorders:

Common: Insomnia.

Uncommon: Amnesia.

Nervous system disorders.

Common: Headache, dizziness, paraesthesia, hypoesthesia.

Uncommon: Peripheral neuropathy.

Hepatobiliary disorders:

Rare: Hepatitis, cholestatic jaundice.

Ear and labyrinth disorders:

Uncommon: Tinnitus.

Skin and subcutaneous tissue disorders:

Common: Rash, pruritus.

Uncommon: Urticaria.

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

Musculoskeletal disorders:

Common: Myalgia, arthralgia.

Uncommon: Myopathy.

Rare: Myositis, rhabdomyolysis.

Reproductive system:

Uncommon: Impotence.

General disorders:

Common: Fatigue, chest pain, back pain, peripheral oedema.

Uncommon: Malaise, weight gain.

Investigations:

As is also the case with other HMG-CoA reductase inhibitors, elevation of serum transaminases has been reported in patients receiving atorvastatin. 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 Atacor overdose is available. In case of an overdose the patient should be treated symptomatically and supportive measures should be instituted if required. Liver function should be monitored and serum CPK values also. Due to its extensive binding to plasma proteins haemodialysis is not expected to increase atorvastatin clearance significantly.

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-coenzyme A 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 blood 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 increased 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 reduces LDL-cholesterol significantly in patients with homozygous familial hypercholesterolaemia. The latter patient category does not usually respond to blood lipid reducing treatments.

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.

It has been confirmed that lowering total cholesterol, LDL-cholesterol and apolipoprotein B results in a reduction in the risk of heart attacks and fatalities. Investigations of the influence of atorvastatin on diseases and death rate are ongoing.

In a prophylactic follow up study Early Recurrent Ischaemic Events in Acute coronary Syndromes (MIRACL) administration of atorvastatin 80 mg to 3,086 patients (atorvastatin n=1538; placebo=1548) with acute coronary disease, including angina, was evaluated. Treatment was initiated 24-96 hours after the patient arrived at the hospital. Risk of re-admittance due to angina with clear signs of cardiac ischemia was reduced significantly by 26% (p=0.018).

5.2 Pharmacokinetic properties

Absorption: Atorvastatin is rapidly absorbed following oral administration with maximum plasma concentration (C_{max}) being 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. 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 however does 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: Pharmacokinetic data for children 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 influence neither 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 times higher than the highest human dose (80 mg/day) on a mg/kg body weight basis and 8 to 16 times 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 doses used, which were 250 times higher than the highest human dose used on a mg/kg body weight basis. The effects on the mice were 6 to 11 times greater based on AUC (0-24). Atorvastatin demonstrated neither mutagenic effects nor malformations of reproductive organs in four *in vitro* studies and one *in vivo* assay. In animal studies atorvastatin affected neither male fertility, in administered doses of up to 175 mg/kg a day, nor female fertility, in administered doses of up to 225 mg/kg a day, and did not cause malformation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Mannitol

Cellulose, microcrystalline

Calcium carbonate

Povidone (type K-30)

Croscarmellose sodium

Sodium laurylsulfate

Silica colloidal, anhydrous

Magnesium stearate

Tablet coat:

Hypromellose

Titanium dioxide (E 171)

Macrogol 6000.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blisters (aluminium/aluminium): 4, 7, 10, 14, 20, 28, 30, 50, 56, 84, 98, 100, 200 (10 x 20), 500 for all strengths.

Containers (HDPE) with snap-on cap (LDPE): 10, 20, 30, 50, 100, 200 for all strengths.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Actavis Group hf
Reykjavíkurvegi 76-78
220 Hafnarfjörður
Iceland

8. MARKETING AUTHORISATION NUMBER(S)

Atacor, 10 mg film-coated tablets: MA651/00501

Atacor, 20 mg film-coated tablets: MA651/00502

Atacor, 40 mg film-coated tablets: MA651/00503

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27th March 2007

10. DATE OF REVISION OF THE TEXT