Space for Pharmacode

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ATOCOR
Atorvastatin

QUALITATIVE AND QUANTITATIVE COMPOSITION

Atorvastatin tablet 10 mg

Each film-coated tablet contains Atorvastatin calcium equivalent to 10 mg Atorvastatin.

Atorvastatin tablet 20 mg

Each film-coated tablet contains Atorvastatin calcium equivalent to 20 mg Atorvastatin.

Atorvastatin tablet 40 mg

Each film-coated tablet contains Atorvastatin calcium equivalent to 40 mg Atorvastatin.

Excipients

Basic butylated methacrylate copolymer, Lactose monohydrate, Microcrystalline cellulose, Methanol, Crospovidone, Sodium bicarbonate, Sodium lauryl sulphate, Hydroxypropyl cellulose, Opadry OY-58900 white, Isopropyl alcohol, Methylene chloride, Magnesium stearate

PHARMACEUTICAL FORM

Atorvastatin tablet 10 mg

White to off-white, capsule shaped, biconvex film-coated tablets debossed with "RDY" on one side and "121"on other side.

Atorvastatin tablet 20 mg

White to off-white, capsule shaped, biconvex film-coated tablets debossed with "RDY" on one side and "122" on other side.

Atorvastatin tablet 40 mg

White to off-white, capsule shaped, biconvex film-coated tablets debossed with "RDY" on one side and "123"on other side.

CLINICAL INFORMATION

Indications

For the treatment of:

Hypercholesterolemia

- As an adjunct to diet to reduce elevated total cholesterol (total-C), LDL-C, apolipoprotein B, and triglycerides (TG levels) and to increase HDL-C in patients with primary hypercholesterolaemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb)
- As an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV)
- For the treatment of patients with primary dysbetalipoproteinemia (Fredrickson Type III) who do not respond adequately to diet
- To reduce total-C and LDL-C in patients with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable
- As an adjunct to diet to reduce total-C, LDL-C, and apolipoprotein B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolaemia if after an adequate trial of diet therapy the following findings are present:
  a. LDL-C remains ≥190 mg/dL
  b. LDL-C remains ≥160 mg/dL and:
- there is a positive family history of premature cardiovascular disease
- two or more other CVD risk factors are present in the paediatric patient

Prevention of Cardiovascular Disease

In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, atorvastatin is indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke
- Reduce the risk for revascularization procedures and angina

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

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke

In patients with clinically evident coronary heart disease, atorvastatin is indicated to:

- Reduce the risk of non-fatal myocardial infarction
- Reduce the risk of fatal and non-fatal stroke
- Reduce the risk for revascularization procedures
- Reduce the risk of hospitalization for CHF
- Reduce the risk of angina

Therapy with lipid-altering agents should be only one component of multiple-risk-factor intervention in individuals at a significantly increased risk for atherosclerotic vascular disease due to hypercholesterolaemia. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol only when the response to diet and other non pharmacological measures has been inadequate. In patients with CHD or multiple risk factors for CHD, atorvastatin can be started simultaneously with diet.

Dosage and Administration

Atorvastatin can be administered as a single dose at any time of the day, with or without food.

Route of Administration

For oral use

Adults

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

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.

Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb)

The recommended starting dose of atorvastatin is 10 mg or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of atorvastatin is 10 mg to 80 mg once daily.

Homozygous Familial Hypercholesterolaemia (FH)

The dosage of atorvastatin in patients with homozygous FH 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.

Children

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

There is limited experience in children between 6 -10 years of age.

Atorvastatin is not indicated in the treatment of patients below the age of 10 years.

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

Elderly

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

Renal impairment

No adjustment of dose is required *(see Section Warnings and Precautions)*.

Hepatic impairment

Atorvastatin should be used with caution in patients with hepatic impairment (*see Section Warnings and Precautions*). Atorvastatin is contraindicated in patients with active liver disease *(see Section Contraindications)*.

Contraindications

Atorvastatin is contraindicated in:

- hypersensitivity to the active substance or to any of the excipients of this medicinal product
- active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal
- pregnancy *(see Section Pregnancy and Lactation)*
- breast-feeding women, and in women of child-bearing potential not using appropriate contraceptive measures *(see Section Pregnancy and Lactation)*.

Warnings and Precautions

Liver effects

It is recommended that liver function tests should be performed before the initiation of Atocor, and thereafter when clinically indicated. 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 atorvastatin is recommended (*see Section Adverse Reactions*).

Atorvastatin 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 haemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior haemorrhagic stroke or lacunar infarct at study entry. For patients with prior haemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain and the potential risk of haemorrhagic 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, 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.

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 re-measured within 5 to 7 days later to confirm the results.

Before the treatment

Atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A creatine kinase (CK) level should be measured before starting 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 (*see Section 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.

Whilst on treatment

- Patients must be asked to promptly report muscular pain, weakness or cramps 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 CK levels are elevated to ≤5 times 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 times ULN) occur, or if rhabdomyolysis is diagnosed or suspected.

Increased risk of rhabdomyolysis

Risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medications that may increase the plasma concentration of atorvastatin such as potent inhibitors of CYP3A4 or transport proteins (eg. ciclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole , and HIV-protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivates, erythromycin, niacin and ezetimibe. If possible alternative (non-interacting) therapies should be considered instead of these medicinal products.

Concomitant treatment with other medicinal products

Co-administration of strong CYP3A4 inhibitors (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.) should be avoided if possible. In cases where co-administration of these medicinal products with atorvastatin cannot be avoided, lower starting and maximum doses of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended. In patients taking telaprevir, concomitant use of atorvastatin should be avoided. The dose of atorvastatin should not exceed 40 mg daily when taking with boceprevir and close clinical monitoring 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 *(see Section Interactions)*.

Paediatric use

Developmental safety in the paediatric population has not been established *(see Section Adverse Reactions)*.

Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (*see Section Adverse Reactions*). 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.

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/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Lactose

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

Others

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 HMG-CoA reductase inhibitors.

Interactions

Effect of coadministered medicinal products on atorvastatin

Atorvastatin is metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate to transport proteins e.g. the hepatic uptake transporter OATP1B1. Concomitant administration of medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivates and ezetimibe *(see Section Warnings and Precautions*).

CYP3A4 Inhibitors

Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin (see Table 1 and specific information below). Coadministration of potent CYP3A4 inhibitors (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.) should be avoided if possible. In cases where coadministration of these medicinal products with atorvastatin cannot be avoided lower starting and maximum doses of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended (see Table 1).

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

CYP3A4 Inducers

Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (e.g. efavirenz, rifampin, St. John's Wort) 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. The effect of rifampin on atorvastatin concentrations in hepatocytes is, however, unknown and if concomitant administration cannot be avoided, patients should be carefully monitored for efficacy.

Transporter Protein Inhibitors

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

Ezetimibe

The use of ezetimibe alone is associated with muscle related events, including rhabdomyolysis. The risk of these events may therefore be increased with concomitant use of ezetimibe and atorvastatin. Appropiate clinical monitoring of these patients is recommended.

Fusidic acid

Interaction studies with atorvastatin and fusidic acid have not been conducted. As with other statins, muscle related events, including rhabdomyolysis, have been reported in post-marketing experience with atorvastatin and fusidic acid given concurrently. The mechanism of this interaction is not known. Patients should be closely monitored and temporary suspension of atorvastatin treatment may be appropriate *(see Section Warnings and Precautions*).

Colestipol

Plasma concentrations of atorvastatin and its active metabolites were lower (by approximately 25%) when colestipol was co-administered with atorvastatin. However, lipid effects were greater when atorvastatin and colestipol were co-administered than when either drug was given alone.

Gemfibrozil/fibric acid derivatives

The use of fibrates alone is occasionally associated with muscle related events, including rhabdomyolysis. . The risk of these events may be increased with the concomitant use of fibric acid derivatives and atorvastatin If concomitant administration cannot be avoided, the lowest dose of atorvastatin to achieve the therapeutic objective should be used and the patients should be appropriately monitored *(see Section Warnings and Precautions)*.

Effect of atorvastatin on co-administered medicinal products

Digoxin

When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steady- state digoxin concentrations increased slightly Patients taking digoxin should be monitored appropriately.

Oral contraceptives

Co-administration of atorvastatin with an oral contraceptive produced increases in plasma concentrations of norethisterone and ethinyl oestradiol. These increased concentrations should be considered when selecting oral contraceptive doses.

Warfarin

In a clinical study in patients receiving chronic warfarin therapy, co-administration of atorvastatin 80 mg daily with warfarin caused a small decrease of about 1.7 seconds in prothrombin time during the first 4 days of dosing which returned to normal within 15 days of atorvastatin treatment. Although only very rare cases of clinically significant anticoagulant interactions have been reported, prothrombin time should be determined before starting atorvastatin in patients taking coumarin anticoagulants and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of atorvastatin is changed or discontinued, the same procedure should be repeated. Atorvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Paediatric population

Drug-drug interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known. The above mentioned interactions for adults and the warnings in section Warnings and Precautions should be taken into account for the paediatric population.

Table 1: Effect of coadministered medicinal products on the pharmacokinetics of atorvastatin

Co-administered medicinal product and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC[&]	Clinical Recommendation[#]
Tipranavir 500 mg BID/ Ritonavir 200 mg BID, 8 days (days 14 to 21)	40 mg on day 1, 10 mg on day 20	↑ 9.4 fold	In cases where coadministration with atorvastatin is necessary, do not exceed 10 mg atorvastatin daily. Clinical monitoring of these patients is recommended
Ciclosporin 5.2 mg/kg/day, stable dose	10 mg OD for 28 days	↑ 8.7 fold	
Lopinavir 400 mg BID/ Ritonavir 100 mg BID, 14 days	20 mg OD for 4 days	↑ 5.9 fold	In cases where coadministration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 20 mg, clinical monitoring of these patients is recommended.
–Clarithromycin 500 mg BID, 9 days	80 mg OD for 8 days	↑ 4.4 fold	
Saquinavir 400 mg BID/ Ritonavir (300 mg BID from days 5-7, increased to 400 mg BID on day 8), days 5-18, 30 min after atorvastatin dosing	40 mg OD for 4 days	↑ 3.9 fold	In cases where coadministration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 40 mg, clinical monitoring of these patients is recommended.
Darunavir 300 mg BID/Ritonavir 100 mg BID, 9 days	10 mg OD for 4 days	↑ 3.3 fold	
Itraconazole 200 mg OD, 4 days	40 mg SD	↑ 3.3 fold	

Fosamprenavir 700 mg BID/ Ritonavir 100 mg BID, 14 days	10 mg OD for 4 days	↑ 2.5 fold	
Fosamprenavir 1400 mg BID, 14 days	10 mg OD for 4 days	↑ 2.3 fold	
Nelfinavir 1250 mg BID, 14 days	10 mg OD for 28 days	↑ 1.7 fold^	No specific recommendation
Grapefruit Juice, 240 mL OD *	40 mg, SD	↑ 37%	Concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended.
Diltiazem 240 mg OD, 28 days	40 mg, SD	↑ 51%	After initiation or following dose adjustments of diltiazem, appropriate clinical monitoring of these patients is recommended.
Erythromycin 500 mg QID, 7 days	10 mg, SD	↑ 33%^	Lower maximum dose and clinical monitoring of these patients is recommended.
Amlodipine 10 mg, single dose	80 mg, SD	↑ 18%	No specific recommendation
Cimetidine 300 mg QID, 2 weeks	10 mg OD for 4 weeks	↓ less than 1%^	No specific recommendation
Antacid suspension of magnesium and aluminium hydroxides, 30 mL QID, 2 weeks	10 mg OD for 4 weeks	↓ 35%^	No specific recommendation
Efavirenz 600 mg OD, 14 days	10 mg for 3 days	↓ 41%	No specific recommendation
Rifampin 600 mg OD, 7 days (co-administered)	40 mg SD	↑ 30%	If coadministration cannot be avoided, simultaneous coadministration of atorvastatin with rifampin is recommended, with clinical monitoring.
Rifampin 600 mg OD, 5 days (doses separated)	40 mg SD	↓ 80%	
Gemfibrozil 600 mg BID, 7 days	40 mg SD	↑ 35%	Lower starting dose and clinical monitoring of these patients is recommended.
Fenofibrate 160 mg OD, 7 days	40 mg SD	↑ 3%	Lower starting dose and clinical monitoring of these patients is recommended.

[&] Data given as x-fold change represent a simple ratio between co-administration and atorvastatin alone (i.e., 1-fold = no change). Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change).

See sections Warnings and Precautions and Interactions for clinical significance.

* Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of medicinal products metabolised by CYP3A4. Intake of one 240 ml glass of grapefruit juice also resulted in a decreased AUC of 20.4% for the active orthohydroxy metabolite. Large quantities of grapefruit juice (over 1.2 l daily for 5 days) increased AUC of atorvastatin 2.5 fold and AUC of active (atorvastatin and metabolites).

^ Total atorvastatin equivalent activity

Increase is indicated as "↑", decrease as "↓"

OD = once daily; SD = single dose; BID = twice daily; QID = four times daily

Table 2: Effect of atorvastatin on the pharmacokinetics of co-administered medicinal products

Atorvastatin and dosing regimen	Coadministered medicinal product		
	Medicinal product/Dose (mg)	Change in AUC[&]	Clinical Recommendation
80 mg OD for 10 days	Digoxin 0.25 mg OD, 20 days	↑ 15%	Patients taking digoxin should be monitored appropriately.
40 mg OD for 22 days	Oral contraceptive OD, 2 months norethindrone 1 mg ethinyl estradiol 35 µg	↑ 28% ↑ 19%	No specific recommendation
80 mg OD for 15 days	* Phenazone, 600 mg SD	↑ 3%	No specific recommendation

[&] Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change)

* Coadministration of multiple doses of atorvastatin and phenazone showed little or no detectable effect in the clearance of phenazone.

Increase is indicated as "↑", decrease as "↓"

OD = once daily; SD = single dose

Pregnancy and Lactation

Fertility

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

Pregnancy

Atorvastatin is contraindicated during pregnancy *(see Section Contraindications*).

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 foetal 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, atorvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with atorvastatin should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant *(see Section Contraindications)*

Women of childbearing potential

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

Lactation

Atorvastatin is contraindicated while breast-feeding *(see Section Contraindications)*. Because of the potential for serious adverse reactions, women taking atorvastatin should not breast-feed their infants. In rats, plasma concentrations of atorvastatin and its active metabolites are similar to those in milk. It is not known whether atorvastatin or its metabolites is excreted in human milk.

Ability to perform tasks that require judgement, motor or cognitive skills

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

Adverse Reactions

Adverse reactions are ranked under headings of frequency using the following convention:

Very common ≥1/10

Common ≥1/100 to <1/10

Uncommon ≥1/1000 to <1/100

Rare ≥1/10000 to <1/1000

Very rare <1/10000

Not known (cannot be estimated from the available data).

Clinical Trial Data and Post Marketing Data

In the atorvastatin placebo-controlled clinical trial database of 16,066 (8755 Atorvastatin vs. 7311 placebo) patients treated for a mean period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo.

The adverse reactions presented below are based on data from clinical studies and extensive post-marketing experience.

Infections and infestations

Common: nasopharyngitis

Blood and lymphatic system disorders

Rare: thrombocytopenia

Immune system disorders

Common: allergic reactions,

Very rare: anaphylaxis

Metabolism and nutrition disorders

Common: hyperglycaemia

Uncommon: hypoglycaemia, weight gain, anorexia

Respiratory, thoracic and mediastinal disorders

Common: pharyngolaryngeal pain, epistaxis

Psychiatric disorders

Uncommon: insomnia, nightmare

Nervous system disorders

Common: headache

Uncommon: dizziness, paraesthaesia, hypoesthesia, dysgeusia, amnesia.

Rare: peripheral neuropathy

Eye disorders

Uncommon: vision blurred

Rare: visual disturbance

Ear and labyrinth disorders

Uncommon: tinnitus

Very rare: hearing loss

Gastrointestinal disorders

Common: constipation, flatulence, dyspepsia, nausea, diarrhoea

Uncommon: vomiting, abdominal pain upper and lower, eructation, pancreatitis

Hepatobiliary disorders

Common: liver function test abnormal, blood creatine kinase increased

Uncommon: hepatitis,

Rare: cholestasis

Very rare: hepatic failure

Skin and subcutaneous tissue disorders

Uncommon: urticaria, alopecia, rash, pruritus

Rare: angioneurotic oedema, dermatitis bullous, erythema multiforme, Stevens-Johnson syndrome,toxic epidermal necrolysis

Renal and urinary disorders

Uncommon : white blood cells urine positive

Musculoskeletal and connective tissue disorders

Common: arthralgia, pain in extremity, muscle spasms, myalgia, joint swelling, back pain

Uncommon: neck pain, muscle fatigue,

Rare: myositis, rhabdomyolysis, myopathy, tendonopathy, rupture

Reproductive system and breast disorders

Very rare: gynecomastia

General disorders and administration site conditions

Uncommon: malaise, asthenia, chest pain, fatigue, peripheral oedema, pyrexia.

Investigations

Common: blood creatine kinase increased

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

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

Children & Adolescents

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

Nervous system disorders

Common: headache

Gastrointestinal disorders

Common: abdominal pain

Hepatobiliary disorders

Common: alanine aminotransferase increased, blood creatine phosphokinase increased

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

The following adverse events have been reported with some statins:

Metabolism and nutrition disorders

Not known: diabetes mellitus (frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI>30kg/m^2, raised triglycerides, history of hypertension)).

Psychiatric disorders

Not known: depression

Respiratory, thoracic and mediastinal disorders

Not known: interstitial lung disease, especially with long term therapy *(see Section Warnings and Precautions)*

Reproductive system and breast disorders

Not known: sexual dysfunction

Overdosage

Specific treatment is not available for atorvastatin overdosage. 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.

Clinical Pharmacology

Pharmacodynamics

Pharmacotherapeutic group

Lipid modifiying agents, HMG-CoA reductase inhibitors

ATC Code

C10AA05

Mechanism of Action; Pharmacodynamic effects

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 catabolised primarily through the high affinity 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 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.

Pharmacokinetics

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. 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 ≥ 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 products are further metabolised 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.

Elimination

Atorvastatin and atorvastatin metabolites are substrates of P-glycoprotein.

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.

Special patient populations

Children

In an open label, 8-week study, Tanner Stage 1 (N=15) and Tanner Stage ≥ 2 (N=24) paediatric patients (ages 6-17 years) with heterozygous familial hypercholesterolaemia and baseline LDL-C ≥ 4 mmol/L were treated with 5 or 10 mg of chewable or 10 or 20 mg of film coated atorvastatin tablets once daily, respectively. Body weight was the only significant covariate in atorvastatin population PK model. Apparent oral clearance of atorvastatin in 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.

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.

Renal impairment

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

Hepatic impairment

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

Other patient characteristics

Gender

Concentrations of atorvastatin and its active metabolites in women differ (approximately 20% higher for Cmax and 10% lower for AUC) from those in men. These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.

SLOC1B1 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.

Clinical Studies

Not relevant for this product.

NON-CLINICAL INFORMATION

Atorvastatin was negative for mutagenic and clastogenic potential in a battery of 4 *in vitro* tests and 1 *in vivo* assay. Atorvastatin was not found to be carcinogenic in rats, but high doses in mice (resulting in 6-11 fold the AUC0-24h reached in humans at the highest recommended dose) showed hepatocellular adenomas in males and hepatocellular carcinomas in females.

There is evidence from animal experimental studies that HMG-CoA reductase inhibitors may affect the development of embryos or foetuses. In rats, rabbits and dogs atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses foetal toxicity was observed in rats and rabbits. The development of the rat offspring was delayed and post-natal survival reduced during exposure of the dams to high doses of atorvastatin. In rats, there is evidence of placental transfer. In rats, plasma concentrations of atorvastatin are similar to those in milk. It is not known whether atorvastatin or its metabolites are excreted in human milk.

PHARMACEUTICAL INFORMATION

Shelf-Life

The expiry date is indicated on the packaging.

Storage

Store below 30°C

Nature and Contents of Container

Alu/Alu Blister

Incompatibilities

There are no relevant data available.

Use and Handling

There are no special requirements for use or handling of this product.

Pack size: 28's and 30's

Manufactured by:

Dr. Reddy's Laboratories Limited
Survey No.41, Bachupally Village,
Bachupally Mandal, Medchal
Malkajgiri District, Telangana, India

Product Registration Holder:

THE ZYFAS MEDICAL CO;
7 Jalan Molek 3/10, Taman Molek
81100 Johor Bahru. Malaysia

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