Pfizer

لیپیٹور

LIPITOR®
(atorvastatin)

NAME OF THE MEDICINAL PRODUCT
LIPITOR®

QUALITATIVE AND QUANTITATIVE COMPOSITION
Active Ingredient: atorvastatin
The tablets for oral administration contain atorvastatin calcium equivalent to 10 mg, 20 mg & 40 mg atorvastatin.

PHARMACEUTICAL FORM
Tablets: 10 mg, 20 mg & 40 mg

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS
LIPITOR® is indicated as an adjunct to diet for the treatment of patients with elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides and to increase HDL-cholesterol in patients with primary hypercholesterolemia (heterozygous familial and non-familial hypercholesterolemia), combined (mixed) hyperlipidemia (*Fredrickson* Types IIa and IIb), elevated serum triglyceride levels (*Fredrickson* Type IV), and for patients with dysbetalipoproteinemia (*Fredrickson* Type III) who do not respond adequately to diet.

LIPITOR® is also indicated for the reduction of total cholesterol and LDL-cholesterol in patients with homozygous familial hypercholesterolemia when response to diet and other non-pharmacological measures are inadequate.

Prevention of Cardiovascular Complications
In patients without clinically evident cardiovascular disease, and with or without dyslipidemia, but with multiple risk factors for coronary heart disease such as smoking, hypertension, diabetes, low HDL-C, or a family history of early coronary heart disease, LIPITOR® is indicated to:
- reduce the risk of fatal coronary heart disease and non-fatal myocardial infarction,
- reduce the risk of stroke,
- reduce the risk of revascularization procedures and angina pectoris.

In patients with clinically evident coronary heart disease, LIPITOR® (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.

Pediatric Patients (10–17 years of age)
LIPITOR® is indicated as an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:
a. LDL-C remains ≥ 190 mg/dL or
b. LDL-C remains ≥ 160 mg/dL and:
- there is a positive family history of premature cardiovascular disease or
- two or more other CVD risk factors are present in the pediatric patient

POSOLOGY AND METHOD OF ADMINISTRATION
General – Before instituting therapy with LIPITOR®, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise and weight reduction in obese patients, and to treat underlying medical problems. The patient should continue on a standard cholesterol-lowering diet during treatment with LIPITOR®. The dosage range is 10 to 80 mg once daily. Doses may be given any time of the day, with or without food. Starting and maintenance dosage should be individualized according to baseline LDL-C levels, the goal of therapy, and patient response. After initiation and/or upon titration of LIPITOR®, lipid levels should be analyzed within 2 to 4 weeks, and dosage adjusted accordingly.

Primary Hypercholesterolemia and Combined (Mixed) Hyperlipidemia – The majority of patients are controlled with 10 mg LIPITOR® (atorvastatin) once a day. A therapeutic response is evident within two weeks, and the maximum response is usually achieved within four weeks. The response is maintained during chronic therapy.

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

Severe Dyslipidemias in Pediatric Patients – Experience in pediatrics is limited to a small number of patients (age 4–17 years) with severe dyslipidemias, such as familial hypercholesterolemia. The recommended starting dose in this population is 10mg of atorvastatin per day. The dose may be increased to 80mg daily, according to the response and tolerability. Doses should be individualized according to the recommended goal of therapy (see section **Therapeutic indications** and section **Pharmacodynamic properties**). Adjustments should be made at intervals of 4 weeks or more.

Use in Patients with Hepatic Insufficiency – (See ***section*** **Contraindications** and ***section*** **Special warnings and precautions for use**).

Use in Patients with Renal Insufficiency – Renal disease has no influence on the plasma concentrations or on the LDL-C reduction with LIPITOR®. Thus, no adjustment of the dose is required.

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

Use in Combination with Other Medicinal Compounds – In cases where co-administration of atorvastatin with cyclosporine, telepravir, or the combination tipranavir/ritonavir is necessary, the dose of atorvastatin should not exceed 10 mg (see section **Special warnings and precautions for use – Skeletal Muscle Effects** and section **Interaction with other medicinal products and other forms of**

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

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

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

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

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

Inducers of cytochrome P450 3A: Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (eg efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, (cytochrome P450 3A4 induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

Antacids: Co-administration of atorvastatin with an oral antacid suspension containing magnesium and aluminum hydroxides, decreased atorvastatin plasma concentrations approximately 35%; however, LDL-C reduction was not altered.

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

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

Digoxin: When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steady- state plasma digoxin concentrations were unaffected. However, digoxin concentrations increased approximately 20% following administration of digoxin with 80 mg atorvastatin daily. Patients taking digoxin should be monitored appropriately.

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

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

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

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

Amlodipine: In a drug-drug interaction study in healthy subjects, co-adminstration of atorvastatin 80 mg and amlodipine 10 mg resulted in an 18% increase in exposure to atorvastatin which was not clinically meaningful.

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

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

Fertility, pregnancy and lactation
LIPITOR® (atorvastatin) is contraindicated in pregnancy. Women of childbearing potential should use adequate contraceptive measures. LIPITOR® should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards to the fetus.

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

Effects on ability to drive and use machines: None known.

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

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

Infections and infestations: nasopharyngitis
Metabolism and nutrition disorders: hyperglycemia
Respiratory, thoracic and mediastinal disorders: pharyngolaryngeal pain, epistaxis
Gastrointestinal disorders: diarrhoea, dyspepsia, nausea, flatulence
Musculoskeletal and connective tissue disorders: arthralgia, pain in extremity, musculoskeletal pain, muscle spasms, myalgia, joint swelling
Investigations: liver function test abnormal, blood creatine phosphokinase increased
Additional adverse effects reported in atorvastatin placebo-controlled clinical trials include:

Psychiatric disorders: nightmare
Eye disorders: vision blurred
Ear and labyrinth disorders: tinnitus
Gastrointestinal disorders: abdominal discomfort, eructation
Hepatobiliary disorders: hepatitis, cholestasis
Skin and subcutaneous tissue disorders: urticaria
Musculoskeletal and connective tissue disorders: muscle fatigue, neck pain
General disorders and administration site conditions: malaise, pyrexia
Investigations: white blood cells urine positive
Not all effects listed above have been causally associated with atorvastatin therapy.

Pediatric Patients (ages 10–17 years)

LIPITOR® (atorvastatin) is contraindicated in patients who have:

- Hypersensitivity to any component of this medication,
- Active liver disease or unexplained persistent elevations of serum transaminases exceeding three times the upper limit of normal,

or who are:

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

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Persistent increases in serum transaminases (>3 x ULN on two or more occasions) occurred in 0.7% of patients who received atorvastatin in these clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40 and 80 mg respectively. Increases were generally not associated with jaundice or other clinical signs or symptoms. When the dosage of atorvastatin was reduced, or drug treatment interrupted or discontinued, transaminase levels returned to pre-treatment levels. Most patients continued treatment on a reduced dose of atorvastatin without sequelae.

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

Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin (see **section Contraindications**).

Skeletal Muscle Effects – Myalgia has been reported in atorvastatin-treated patients (see ***section*** **Undesirable effects**). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 x ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, azole antifungals, colchicine, telaprevir, or the combination of tipranavir/ritonavir. Many of these drugs inhibit cytochrome P450 3A4 metabolism and/or drug-transport. CYP 3A4 is the primary hepatic isozymes known to be involved in the biotransformation of atorvastatin. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Therefore, lower starting and maintenance doses of atorvastatin should also be considered when taken concomitantly with the aforementioned drugs. (See *section* **Interaction with other medicinal products and other forms of interaction**). Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. Atorvastatin may cause an elevation of creatine phosphokinase (see ***section*** **Undesirable effects**).

As with other drugs in this class, rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria, have been reported. Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

Hemorrhagic Stroke – A post-hoc analysis of a clinical study in 4,731 patients without CHD who had a stroke or TIA within the preceding 6 months and were initiated on atorvastatin 80 mg, revealed a higher incidence of hemorrhagic stroke in the atorvastatin 80 mg group compared to placebo (55 atorvastatin vs 33 placebo). Patients with hemorrhagic stroke on entry appeared to be at increased risk for recurrent hemorrhagic stroke (7 atorvastatin vs 2 placebo). However, in patients treated with atorvastatin 80 mg there were fewer strokes of any type (265 vs 311) and fewer CHD events (123 vs 204). (***See section*** **Pharmacodynamic properties – Recurrent Stroke**)

Endocrine Function – Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporine, fibric acid derivatives, lipid-modifying doses of niacin or cytochrome P450 3A4 inhibitors (eg erythromycin, and azole antifungals) (See below and also ***section*** **Posology and method of administration: Use in Combination with Other Medicinal Compounds and *section* Special warnings and precautions for use: Skeletal Muscle Effects**).

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

Transporter Inhibitors: Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g. cyclosporine) can increase the bioavailability of atorvastatin. Concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day resulted in a 7.7 fold increase in exposure to atorvastatin. (See also *section* **Posology and method of administration – Use in Combination with Other Medicinal Compounds**)

Erythromycin/Clarithromycin: Co-administration of atorvastatin and erythromycin (500 mg four times daily), or clarithromycin (500 mg twice daily) known inhibitors of cytochrome P450 3A4, was associated with higher plasma concentrations of atorvastatin (see ***section*** **Special warnings and precautions for use: Skeletal Muscle Effects**).

In post-marketing experience, the following additional undesirable effects have been reported: **Blood and Lymphatic System Disorders:** thrombocytopenia, **Immune System Disorders:** allergic reactions (including anaphylaxis), **Injury, poisoning and procedural complications:** tendon rupture, **Metabolism and Nutrition Disorders:** weight gain, **Nervous System Disorders:** hypoesthesia, amnesia, dizziness, dysgeusia, **Gastrointestinal disorders:** Pancreatitis, **Skin and Subcutaneous Tissue Disorders:** Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, bullous rashes, **Musculoskeletal and Connective Tissue Disorders:** rhabdomyolysis, back pain, **General Disorders and Administration Site Conditions:** chest pain, peripheral edema, fatigue.

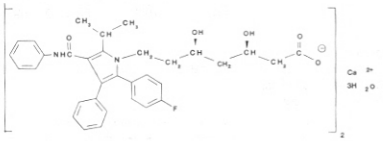
OVERDOSAGE

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

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES

Atorvastatin calcium is a synthetic lipid-lowering agent, which is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.
The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$ and its molecular weight is 1209.42. Its structural formula is:



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

Mechanism of Action – Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol.[1,2] In patients with homozygous and heterozygous familial hypercholesterolemia (FH), nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia, atorvastatin reduces total-C (total cholesterol), LDL-C (low-density lipoprotein cholesterol), and apo B (apolipoprotein B). Atorvastatin also reduces VLDL-C (very-low-density lipoprotein cholesterol) and TG (triglycerides) and produces variable increases in HDL-C (high-density lipoprotein cholesterol).

Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL.

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

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

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

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

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

The effects of atorvastatin on ischemic events and total mortality were studied in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering study (MIRACL). This multicenter, randomized, double-blind, placebo-controlled study followed 3086 patients with acute coronary syndromes; unstable angina or non-Q wave myocardial infarction. Patients were treated with standard care, including diet, and either atorvastatin 80 mg daily or placebo for a median duration of 16 weeks. The final LDL-C, total-C, HDL-C and TG levels were 72, 147, 48, 139 mg/dL in the atorvastatin group, respectively, and 135, 217, 46, and 187 mg/dL, respectively, in the placebo group. Atorvastatin significantly reduced the risk of ischemic events and death by 16%. The risk of experiencing rehospitalization for angina pectoris with documented evidence of myocardial ischemia was significantly reduced by 26%. Atorvastatin reduced the risk of ischemic events and death to a similar extent across the range of baseline LDL-C. In addition, atorvastatin reduced the risk of ischemic events and death to similar extents in patients with non-Q wave MI and unstable angina, as well as in males and females and in patients ≤65 years of age and >65 years of age.

Prevention of Cardiovascular Complications

In the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA), the effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40–80 years of age (mean of 63 years), without a previous myocardial infarction and with TC levels <6.5 mmol/l (251 mg/dl). Additionally all patients had at least 3 of the following cardiovascular risk factors: male gender, age >55 years, smoking, diabetes, history of CHD in a first-degree relative, TC:HDL >6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria. In this double-blind,

placebo-controlled study patients were treated with anti-hypertensive therapy (Goal BP <140/90 mm Hg for non-diabetic patients, <130/80 mm Hg for diabetic patients) and allocated to either atorvastatin 10 mg daily (n=5168) or placebo (n=5137). As the effect of atorvastatin treatment compared to placebo exceeded the significance threshold during an interim analysis, the ASCOT-LLA was terminated early at 3.3 years instead of 5 years. Additionally, blood pressure was well controlled and similar in patients assigned atorvastatin and placebo. These changes persisted throughout the treatment period.

Atorvastatin reduced the rate of the following events:

Event	Risk decrease (%)	No. of events (atorvastatin vs placebo)	p-value
Coronary events (fatal CHD plus non-fatal MI)	36 %	100 vs 154	0.0005
Total cardiovascular events and revascularization procedures	20 %	389 vs. 483	0.0008
Total coronary events	29 %	178 vs. 247	0.0006
Fatal and non-fatal stroke*	26 %	89 vs. 119	0.0332

* Although the reduction of fatal and non-fatal strokes did not reach a pre-defined significance level (p=0.01), a favorable trend was observed with a 26% relative risk reduction.

The total mortality and cardiovascular mortality have not been significantly reduced although a favorable trend was observed.

In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of atorvastatin on fatal and nonfatal cardiovascular disease was assessed in 2838 patients with type 2 diabetes 40–75 years of age, without prior history of cardiovascular disease and with LDL ≤ 4.14 mmol/l (160 mg/dl) and TG ≤ 6.78mmol/l (600 mg/dl). Additionally, all patients had at least 1 of the following risk factors: hypertension, current smoking, retinopathy, microalbuminuria or macroalbuminuria.

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

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

Event	Relative Risk Reduction (%)	No of Events (atorvastatin vs placebo)	p-value
Major cardiovascular events [fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularization, stroke]	37 %	83 vs. 127	0.0010
MI (fatal and non-fatal AMI, silent MI)	42 %	38 vs. 64	0.0070
Stroke (Fatal and non-fatal)	48 %	21 vs. 39	0.0163

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

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

A relative risk reduction in death of 27% (82 deaths in the placebo group compared to 61 deaths in the treatment arm) has been observed with a borderline statistical significance (p=0.0592). The overall incidence of adverse events or serious adverse events was similar between the treatment groups.

Atherosclerosis

In the Reversing Atherosclerosis with Aggressive Lipid-Lowering Study (REVERSAL), the effect of atorvastatin 80 mg and 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), the median percent change, from baseline, in total atheroma volume (the primary study criteria) was -0.4% (p=0.98) in the atorvastatin group and +2.7% (p=0.001) in the pravastatin group (n=249). When compared to pravastatin, the effects of atorvastatin were statistically significant (p=0.02).

In the atorvastatin group, LDL-C was reduced to a mean of 2.04 mmol/L ± 0.8 (78.9 mg/dL ± 30) from baseline 3.89 mmol/L ± 0.7 (150 mg/dL ± 28) and in the pravastatin group, LDL-C was reduced to a mean of 2.85 mmol/L ± 0.7 (110 mg/dL ± 26) from baseline 3.89 mmol/L ± 0.7 (150 mg/dL ± 26) (p<0.0001). Atorvastatin also significantly reduced mean 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-C by 2.9% (pravastatin: +5.6%, p=*NS*). There was a 36.4% mean reduction in CRP in the atorvastatin group compared to a 5.2% reduction in the pravastatin group (p<0.0001).

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

Recurrent Stroke

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

Atorvastatin 80 mg reduced the risk of the primary endpoint of fatal or non-fatal stroke by 15% (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 for baseline factors) compared to placebo. Atorvastatin 80 mg significantly reduced the risk of major coronary events (HR 0.67; 95% CI, 0.51–0.89; p=0.006), any CHD event (HR 0.60; 95% CI, 0.48–0.74; p<0.001), and revascularization procedures (HR 0.57; 95% CI, 0.44–0.74; p<0.001).

In a post-hoc analysis, atorvastatin 80 mg reduced the incidence of ischemic stroke (218/2365, 9.2% vs. 274/2366, 11.6%, p=0.01) and increased the incidence of hemorrhagic stroke (55/2365, 2.3% vs. 33/2366, 1.4%, p=0.02) compared to placebo. The incidence of fatal hemorrhagic stroke was similar between groups (17 atorvastatin vs. 18 placebo). Reduction in the risk of cardiovascular events with atorvastatin 80 mg was demonstrated in all patient groups except in patients who entered the study with a hemorrhagic stroke and had a recurrent hemorrhagic stroke (7 atorvastatin vs 2 placebo).

In patients treated with atorvastatin 80 mg there were fewer strokes of any type (265 atorvastatin vs 311 placebo) and fewer CHD events (123 atorvastatin vs 204 placebo). Overall mortality was similar across treatment groups (216 atorvastatin vs 211 placebo). The overall incidence of adverse events and serious adverse events was similar between treatment groups.

Reduction of Cardiovascular Events

PHARMACOKINETIC PROPERTIES

Absorption – Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within one to two hours. Extent of absorption and plasma atorvastatin concentrations increase in proportion to atorvastatin dose. Atorvastatin tablets are 95% to 99% bioavailable compared with solutions. The absolute bioavailability of atorvastatin is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9% respectively, as assessed by Cmax and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration[a] (see ***section* Posology and method of administration**).

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

Metabolism – Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *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. *In vitro* studies suggest the importance of atorvastatin metabolism by hepatic cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this isozyme. *In vitro* studies also indicate that atorvastatin is a weak inhibitor of cytochrome P450 3A4. Atorvastatin coadministration did not produce a clinically significant effect in plasma concentrations of terfenadine, a compound predominantly metabolized by cytochrome P450 3A4; therefore, it is unlikely that atorvastatin will significantly alter the pharmacokinetics of other cytochrome P450 3A4 substrates (see ***section* Interaction with other medicinal products and other forms of interaction**). In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion – Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extrahepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Special Populations

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

Children – Pharmacokinetic studies have not been conducted in the pediatric population.

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

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

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

Hepatic Insufficiency – Plasma concentrations of atorvastatin are markedly increased (approximately 16-fold in Cmax and 11-fold in AUC) in patients with chronic alcoholic liver disease (Childs-Pugh B) (see section **Contraindications**).

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

Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC[b]	Change in Cmax[b]
[f] Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QD for 28 days	↑ 7.7 fold	↑ 9.7 fold
[c] Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	10 mg, SD	↑ 8.4 fold	↑ 7.6 fold
[f] Telaprevir 750 mg q8h, 10 days	20 mg, SD	↑ 6.9 fold	↑ 9.6 fold
[f, i] Saquinavir 400 mg BID/ ritonavir 400 mg BID, 15 days	40 mg QD for 4 days	↑ 2.9 fold	↑ 3.3 fold
[f] Clarithromycin 500 mg BID, 9 days	80 mg QD for 8 days	↑ 3.4 fold	↑ 4.4 fold
[f] Darunavir 300 mg BID/ritonavir 100 mg BID, 9 days	10 mg QD for 4 days	↑ 2.4 fold	↑ 1.3 fold
[f] Itraconazole 200 mg QD, 4 days	40 mg SD	↑ 2.3 fold	↑ 0.2 fold
[f] Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	10 mg QD for 4 days	↑ 1.5 fold	↑ 1.8 fold
[f] Fosamprenavir 1400 mg BID, 14 days	10 mg QD for 4 days	↑ 1.3 fold	↑ 3.0 fold
[f] Nelfinavir 1250 mg BID, 14 days	10 mg QD for 28 days	↑ 0.74 fold	↑ 1.2 fold
[f] Grapefruit Juice, 240 mL QD *	40 mg, SD	↑ 0.37 fold	↑ 0.16 fold
Diltiazem 240 mg QD, 28 days	40 mg, SD	↑ 0.51 fold	0 fold
Erythromycin 500 mg QID, 7 days	10 mg, SD	↑ 0.33 fold	↑ 0.38 fold
Amlodipine 10 mg, single dose	80 mg, SD	↑ 0.15 fold	↓ 0.12 fold
Cimetidine 300 mg QD, 4 weeks	10 mg QD for 2 weeks	↓ 0.001 fold	↓ 0.11 fold
Colestipol 10 mg BID, 28 weeks	40 mg QD for 28 weeks	Not determined	↓ 0.26 fold**
Maalox TC® 30 mL QD, 17 days	10 mg QD for 15 days	↓ 0.33 fold	↓ 0.34 fold
Efavirenz 600 mg QD, 14 days	10 mg for 3 days	↓ 0.41 fold	↓ 0.01 fold
[f] Rifampin 600 mg QD, 7 days	40 mg SD	↑ 0.30 fold	↑ 1.72 fold

Secondary Prevention of Cardiovascular Events

In the Treating to New Targets Study (TNT), the effect of atorvastatin 80 mg/day vs. atorvastatin 10 mg/day on the reduction in cardiovascular events was assessed in 10,001 subjects (94% white, 81% male, 38% ≥65 years) with clinically evident coronary heart disease who had achieved a target LDL-C level <130 mg/dL after completing an 8-week, open-label, run-in period with atorvastatin 10 mg/day. Subjects were randomly assigned to either 10 mg/day or 80 mg/day of atorvastatin and followed for a median duration of 4.9 years. The mean LDL-C, TC, TG, non-HDL and HDL cholesterol levels at 12 weeks were 73, 145, 128, 98 and 47 mg/dL during treatment with 80 mg of atorvastatin and 99, 177, 152, 129 and 48 mg/dL during treatment with 10 mg of atorvastatin.

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

Atorvastatin 80 mg significantly reduced the risk of the following:

Significant Endpoint	Atorvastatin 10 mg (N=5006)		Atorvastatin 80 mg (N=4995)		HR[a] (95%CI)
PRIMARY ENDPOINT*	N	(%)	n	(%)	
First major cardiovascular endpoint	548	(10.9)	434	(8.7)	0.78 (0.69, 0.89)
Components of the Primary Endpoint					
Nonfatal, non-procedure related MI	308	(6.2)	243	(4.9)	0.78 (0.66, 0.93)
Stroke (fatal and non-fatal)	155	(3.1)	117	(2.3)	0.75 (0.59, 0.96)
SECONDARY ENDPOINTS**					
First CHF with hospitalization	164	(3.3)	122	(2.4)	0.74 (0.59, 0.94)
First CABG or other coronary revascularization procedure[b]	904	(18.1)	667	(13.4)	0.72 (0.65, 0.80)
First documented angina endpoint[b]	615	(12.3)	545	(10.9)	0.88 (0.79, 0.99)

a Atorvastatin 80 mg: atorvastatin 10 mg
b component of other secondary endpoints
* major cardiovascular endpoint (MCVE) = death due to CHD, non-fatal myocardial infarction, resuscitated cardiac arrest, and fatal and non-fatal stroke
** secondary endpoints not included in primary endpoint

HR=hazard ratio; CI=confidence interval; MI=myocardial infarction; CHF=congestive heart failure; CABG=coronary artery bypass graft

Confidence intervals for the Secondary Endpoints were not adjusted for multiple comparisons

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

In the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study (IDEAL), treatment with atorvastatin 80 mg/day was compared to treatment with simvastatin 20–40 mg/day in 8,888 subjects up to 80 years of age with a history of CHD to assess whether reduction in CV risk could be achieved. Patients were mainly male (81%), white (99%) with an average age of 61.7 years, and an average LDL-C of 121.5 mg/dL at randomization; 76% were on statin therapy. In this prospective, randomized, open-label, blinded endpoint (PROBE) trial with no run-in period, subjects were followed for a median duration of 4.8 years. The mean LDL-C, TC, TG, HDL and non-HDL cholesterol levels at Week 12 were 78, 145, 115, 45 and 100 mg/dL during treatment with 80 mg of atorvastatin and 105, 179, 142, 47 and 132 mg/dL during treatment with 20–40 mg of simvastatin.

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

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

Heterozygous Familial Hypercholesterolemia in Pediatric 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 hypercholesterolemia (FH) or severe hypercholesterolemia were randomized to atorvastatin (n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level ≥ 190 mg/dL or 2) a baseline LDL-C ≥ 160 mg/dL and positive family history of FH or documented premature cardiovascular disease in a first- or second-degree relative. The mean baseline LDL-C value was 218.6 mg/dL (range: 138.5–385.0 mg/dL) in the atorvastatin group compared to 230.0 mg/dL (range: 160.0–324.5 mg/dL) in placebo group. The dosage of atorvastatin (once daily) was 10 mg for the first 4 weeks and up-titrated to 20 mg if the LDL-C level was > 130 mg/dL. The number of atorvastatin-treated patients who required up-titration to 20 mg after Week 4 during the double-blind phase was 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 5)

TABLE 5
Lipid-lowering Effects of Atorvastatin in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia
(Mean Percent Change from Baseline at Endpoint in Intention-to-Treat Population)

DOSAGE	N	Total-C	LDL-C	HDL-C	TG	Apolipoprotein 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 130.7 mg/dL (range: 70.0–242.0 mg/dL) in the Atorvastatin group compared to 228.5 mg/dL (range: 152.0–385.0 mg/dL) in the placebo group during the 26 week double-blind phase.

In this limited controlled study, there was no detectable effect on growth or sexual maturation in boys or on menstrual cycle 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.

(Co-administered) [†]			
[#] Rifampin 600 mg QD, 5 days (doses separated) [†]	40 mg SD	↓ 0.80 fold	↓ 0.40 fold
[#] Gemfibrozil 600 mg BID, 7 days	40 mg SD	↑ 0.35 fold	↓ 0.004 fold
[#] Fenofibrate 160 mg QD, 7 days	40 mg SD	↑ 0.03 fold	↑ 0.02 fold

[&] "fold" change = change ratio [(I-B)/B], where I = pharmacokinetic value during the Interaction phase, and B = pharmacokinetic value during the Baseline phase
[#] See Section 4.4 and 4.5 for clinical significance
* Greater increases in AUC (up to 1.5 fold) and/or Cmax (up to 0.71 fold) have been reported with excessive grapefruit consumption (≥ 750 mL – 1.2 liters per day).
** Single sample taken 8–16 h post dose
[†] Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.
[‡] The dose of saquinavir plus ritonavir in this study is not the clinically used dose. The increase in atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore caution should be applied and the lowest dose necessary should be used.

Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs

Atorvastatin	Co-administered drug and dosing regimen		
	Drug/Dose (mg)	Change in AUC[&]	Change in Cmax[&]
80 mg QD for 15 days	Antipyrine, 600 mg SD	↑ 0.03 fold	↓ 0.11 fold
80 mg QD for 14 days	[#] Digoxin 0.25 mg QD, 20 days	↑ 0.15 fold	↑ 0.20 fold
40 mg QD for 22 days	Oral contraceptive QD, 2 months – norethindrone 1 mg – ethinyl estradiol 35µg	 ↑ 0.28 fold ↑ 0.19 fold	 ↑ 0.23 fold ↑ 0.30 fold
10 mg, SD	Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	No change	No change
10 mg, QD for 4 days	Fosamprenavir, 1400 mg BID, 14 days	↓ 0.27 fold	↓ 0.18 fold
10 mg QD for 4 days	Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	No change	No change

[&] "fold" change = change ratio [(I-B)/B], where I = pharmacokinetic value during the Interactions phase, and B = pharmacokinetic value during the Baseline phase
[#] See Section Interactions for clinical significance

PRECLINICAL SAFETY DATA

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

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

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

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

PHARMACEUTICAL PARTICULARS

SHELF LIFE

LIPITOR® should not be used beyond the expiry date. 36 months

HOW SUPPLIED

LIPITOR® (atorvastatin) is available as 10 mg, 20 mg & 40 mg in blister card of 10's tablet each in a carton.

INSTRUCTIONS

Avoid exposure to heat & sunlight.
Store in a dry place at 20 – 25°C.
Keep out of the reach of children.

CAUTION

To be sold on the prescription of a registered medical practitioner only.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات: دوا کو گرمی اور سورج کی روشنی سے بچائیں۔
دوا کو خشک جگہ پر ۲۰ سے ۲۵ ڈگری سینٹی گریڈ درجہ حرارت پر رکھیں۔ بچوں کی پہنچ سے دور رکھیں۔
تاکید: صرف رجسٹرڈ میڈیکل پریکٹشنر کے نسخہ پر فروخت کریں۔

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