

Lipitor

(Atorvastatin)

PRESENTATION

Active Ingredient: atorvastatin.

The tablets for oral administration contain atorvastatin calcium equivalent to 10, 20, 40 or 80 mg atorvastatin.

PHARMACEUTICAL FORM

Film coated tablets

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS

Lipitor is indicated as an adjunct to diet for the treatment of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides and to increase HDL-cholesterol in patients with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (Fredrickson Types IIa and IIb) when response to diet and other nonpharmacological measures is inadequate.

Lipitor is also indicated 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.

Pediatric Patients (10-17 years of age)

Atorvastatin 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 \geq 190 mg/dL or
- b. LDL-C remains \geq 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

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving Lipitor and should continue on this diet during treatment with Lipitor. The usual starting dose is 10 mg or 20 mg once daily. Patients who require a large reduction in LDL –(more than 45%) may be started at 40 mg once daily. The dosage range of Lipitor is 10 to 80 mg once daily. Starting and maintenance doses should be individualized according to baseline LDL-C levels, the goal of therapy, and patient response. Adjustment of dosage should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once a day.

Doses may be given at any time of day with or without food. After initiation and/or upon titration of Lipitor, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

Therapy with lipid-altering agents should be a component of multiple-risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. 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 nonpharmacological measures has been inadequate (see National Cholesterol Education Program (NCEP) Guidelines, summarized in Table 1).

TABLE 1. NCEP Treatment Guidelines: LDL-C Goals and Cut points for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD ^a or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional) ^b
2+ Risk Factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥160
0-1 Risk factor ^c	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

^a CHD, coronary heart disease

^b Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of < 100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.

^c Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dL, non HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

Prior to initiating therapy with Lipitor, secondary causes for hypercholesterolemia (eg, poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C, HDL-C, and TG. For patients with TG <400 mg/dL, LDL-C can be estimated using the following equation: LDL-C = total-C - (0.20 x [TG] + HDL-C). For TG levels >400 mg/dL, this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation.

NCEP (National Cholesterol Education Program) Pediatric Panel Guidelines
Classification of cholesterol levels in pediatric patients with a familial history of hypercholesterolemia or premature cardiovascular disease is summarized below:

Category	Total-C (mg/dL)	LDL-C (mg/dL)
Acceptable	<170	<110
Borderline	170-199	110-129
High	≥200	≥130

Primary Hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (Fredrickson Types IIa and IIb)

Patients should be started with Lipitor 10 mg daily or 20 mg once daily. Patients who require a large reduction in LDL- (more than 45%) may be started at 40 mg once daily. The dosage range of Lipitor is 10 to 80 mg once daily. Doses should be individualized and adjusted every 4 weeks to 40 mg daily. Thereafter, either the dose may be increased to a maximum of 80 mg daily or a bile acid sequestrant may be combined with 40 mg Lipitor.

Homozygous Familial Hypercholesterolaemia

The dosage of Lipitor in patients with homozygous FH is 10 to 80 mg daily. Lipitor should be used as an adjunct to other lipid-lowering treatment (e.g. LDL apheresis) in these patients or if such treatment are unavailable.

In a compassionate-use study of patients with homozygous familial hyper-cholesterolaemia, most patients responded to 80mg of atorvastatin with a greater than 15% reduction in LDL-C (18%-45%).

Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age) -

The recommended starting dose of atorvastatin is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy (see **NCEP Pediatric Panel Guidelines, Therapeutic Indications**, and **section Pharmacodynamic Properties**). Adjustments should be made at intervals of 4 weeks or more.

Use in Patients with Hepatic Insufficiency

See sections "Contraindications" and "Special Warnings and Special Precautions for Use".

Dosage in Patients with Renal Insufficiency

Renal disease has no influence on the plasma concentrations nor lipid effects of Lipitor; thus, no adjustment of dose is required.

Use in children

Lipitor has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age

Use in Elderly

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

CONTRAINDICATIONS

Lipitor is contraindicated in patients with hypersensitivity to any component of this medication, active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal, myopathy, during pregnancy, while breastfeeding, and in women of child-bearing potential not using appropriate contraceptive measures.

Atorvastatin 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.

If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

Liver Effects

Liver function tests should be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation in dose, and periodically (e.g. semi-annually) thereafter. Patients who develop any signs or symptoms suggestive of liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies) is (are) resolved. Should an increase in transaminases of greater than 3 times the upper limit of normal persist, reduction of dose or withdrawal of Lipitor is recommended.

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 80mg.

Atorvastatin can cause an elevation in transaminases (see section "Adverse Effects").

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 80mg 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 pretreatment levels. Most patients continued treatment on a reduced dose of atorvastatin without sequelae.

Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin (see "Contraindications").

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

Skeletal Muscle Effects

Rhabdomyolysis with acute renal failure secondary to myoglobinuria has been reported with Atorvastatin and with other drugs in this class.

Uncomplicated myalgia has been reported in Lipitor-treated patients. Lipitor therapy should be discontinued if markedly elevated creatine phosphokinase (CPK) levels occur or myopathy is diagnosed or suspected. Patients who develop any signs or symptoms suggestive of myopathy should have CPK levels measured periodically, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy (see "Interaction with other Medicaments and Other Forms of Interactions"). Should significant increases in CPK (greater than ten times the

upper limit of normal) persist, reduction of dose or withdrawal of Lipitor is recommended. (See *Interaction With Other Medicaments and Other Forms of Interaction*).

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

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).

Adolescent females and women of childbearing potential should be counseled on appropriate contraceptive methods while on atorvastatin therapy (see **section Pregnancy and Lactation**).

INTERACTIONS WITH OTHER MEDICAMENTS AND OTHER FORMS OF INDICATION

The risk of myopathy during treatment with other drugs in this class is increased with concurrent administration of cyclosporin, fibric acid derivatives, erythromycin, macrolide antibiotics, azole antifungals or niacin (see "Special Warnings and Special Precautions for Use").

Atorvastatin is metabolized by cytochrome P450 3A4.

Based on experience with other HMG-CoA reductase inhibitors caution should be exercised when Lipitor is administered with inhibitors of cytochrome P450 3A4 (e.g. cyclosporin, macrolide antibiotics including erythromycin and azole antifungals including itraconazole). The effect of inducers of cytochrome P450 3A4 (e.g. rifampicin or phenytoin) on Lipitor is unknown. The possible interaction with other substrates of this isoenzyme is unknown but should be considered for other drugs with a narrow therapeutic index, for example, antiarrhythmic agents Class III including amiodarone. In clinical studies in which Lipitor was administered with antihypertensives or hypoglycaemic agents no clinically significant interactions were seen.

Clarithromycin/Erythromycin

In healthy individuals, coadministration of Lipitor with erythromycin (500 mg QID), a known inhibitor of cytochrome P450 3A4, was associated with higher plasma concentrations of atorvastatin.

Digoxin

Coadministration of multiple doses of Lipitor and digoxin increased steady-state plasma digoxin concentrations by approximately 20%. Patients taking digoxin should be monitored appropriately.

Oral contraceptives

Coadministration of Lipitor with an oral contraceptive produced increases in concentrations of norethindrone and ethinyl oestradiol by approximately 30% and 20%. These increased concentrations should be considered when selecting oral contraceptive doses.

Colestipol

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

Antacid

Coadministration of Lipitor with an oral antacid suspension containing magnesium and aluminium hydroxides decreased plasma concentrations of atorvastatin and its active metabolites by approximately 35%; however, LDL-C reduction was not altered.

Warfarin, cimetidine

Atorvastatin interaction studies with warfarin and with cimetidine were conducted, and no clinically significant interactions were seen.

Phenazone

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

Amlodipine

Atorvastatin pharmacokinetics were not altered by the coadministration of atorvastatin 80 mg and amlodipine 10 mg at steady state.

Protease inhibitors

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC(0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the in vivo mouse micronucleus test.

Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

PREGNANCY AND LACTATION

Lipitor is contraindicated in pregnancy and while breast feeding. Women of childbearing potential should use appropriate contraceptive measures. The safety of atorvastatin in pregnancy and lactation has not yet been proven.

There is evidence from animal studies that HMG-CoA reductase inhibitors may influence the development of embryos or fetuses. The development of rat offspring was delayed and post-natal survival reduced during exposure of the dams to atorvastatin at doses above 20 mg/kg/day (the clinical systemic exposure).

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy.

Atorvastatin 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. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.*

It is not known whether this drug is excreted in human milk. Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking Lipitor should not breast-feed.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There is no pattern of reported adverse events suggesting that patients taking Lipitor will have any impairment of ability to drive and use hazardous machinery.

ADVERSE EFFECTS

Lipitor is generally well-tolerated. Adverse reactions have usually been mild and transient. Less than 2% of patients were discontinued from clinical trials due to side effects attributed to Lipitor.

The most frequent (1% or more) adverse effects associated with Lipitor therapy, in patients participating in controlled clinical studies are constipation, flatulence, dyspepsia, abdominal pain, headache, nausea, myalgia, asthenia, diarrhoea, insomnia.

As with other HMG-CoA reductase inhibitors elevated serum transaminases have been reported in patients receiving Lipitor. 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% of patients on Lipitor. These elevations were dose related and were reversible in all patients.

Elevated serum creatine phosphokinase (CPK) levels greater than 3 times upper limit of normal occurred in 2.5% of patients on Lipitor, similar to other HMG-CoA reductase inhibitors in clinical trials. Levels above 10 times the normal upper range occurred in 0.4% of Lipitor-treated patients. Of these patients, 0.1% had concurrent muscle pain, tenderness or weakness.

The following additional adverse effects have been reported in clinical trials of Lipitor. Not all effects listed have necessarily been associated with Lipitor therapy: angioneurotic edema, muscle cramps, myositis, myopathy, paraesthesia, peripheral neuropathy, pancreatitis,

hepatitis, cholestatic jaundice, anorexia, vomiting, alopecia, pruritus, impotence, hyperglycaemia and hypoglycaemia, dizziness, chest pain, angina and rash.

Post-Marketing Experience –

Rare adverse events that have been reported post-marketing which are not listed above and which may have no causal relationship to the drug include the following:

Body as a Whole: allergic reactions (including anaphylaxis and urticaria), back pain, chest pain, malaise.

Musculoskeletal System: arthralgia, rhabdomyolysis.

Skin and Appendages: bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis), urticaria.

Ear and Labyrinth Disorders: tinnitus.

Nervous System: hypoesthesia, dizziness, amnesia.

Metabolic and Nutritional Disorders: peripheral edema, weight gain.

Hemic and Lymphatic System: thrombocytopenia.

OVERDOSE

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

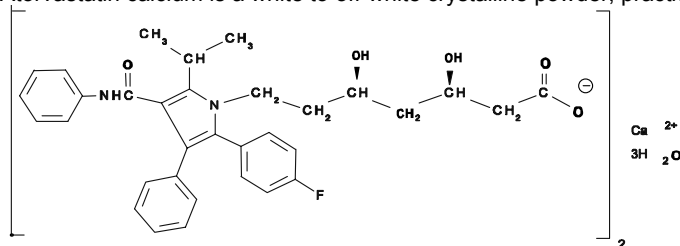
PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMICS

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 responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. In patients with heterozygous familial hypercholesterolemia (FH), nonfamilial forms of hypercholesterolemia, and mixed

dyslipidemia, atorvastatin reduces total-C (total cholesterol), LDL-C (low-density lipoprotein cholesterol), and apoB (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).

Triglycerides and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolized primarily through the high affinity LDL receptor. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis 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 medication.

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 A 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. Mortality and morbidity studies with atorvastatin have not yet been completed.

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.

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**).

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 \geq 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.¹

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.

Pharmacokinetic Properties

Pharmacokinetics and Drug Metabolism

Absorption: Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. Atorvastatin tablets are 95% to 99% bioavailable compared to 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.

Distribution: Mean volume of distribution of atorvastatin is approximately 381 L. Atorvastatin is ≥ 98% bound to plasma proteins.

Metabolism: Atorvastatin is metabolized by cytochrome P450 3A4 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 of HMG-CoA reductase is

attributed to active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Excretion: Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, the drug 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 of HMG-CoA reductase is approximately 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 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.

Children: Pharmacokinetic data in the paediatric population are not available.

Gender: Concentrations of atorvastatin and its active metabolites in women differ (approximately 20% higher for C_{max} 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.

Renal Insufficiency: Renal disease has no influence on the plasma concentrations of lipid effects of atorvastatin and its active metabolites. Thus, dose adjustment in patients with renal dysfunction is not necessary

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 and its active metabolites are markedly increased (approximately 16-fold in C_{max} and 11-fold in AUC) in patients with chronic alcohol liver disease (Childs-Pugh B).

Preclinical Safety Data

Atorvastatin was not carcinogenic in rats. The maximum dose used was 63-fold higher than the highest human dose (80 mg/day) on a mg/kg body-weight basis and 8- to 16-fold higher based on AUC (0-24) values as determined by total inhibitory activity. In a 2-year study in mice, incidences of hepatocellular adenoma in males and hepatocellular carcinomas in females were increased at the maximum dose used, which was 250-fold higher than the highest human dose on mg/kg body-weight basis. Systemic exposure was 6- to 11-fold higher based on AUC (0-24). Atorvastatin did not demonstrate mutagenic or clastogenic potential in 4 *in vitro* tests with and without metabolic activation and in 1 *in vivo* assay. In animal studies atorvastatin had no effect on male or female fertility at doses up to 175 and 225 mg/kg/day, respectively, and was not teratogenic.

PHARMACEUTICAL PARTICULARS

Incompatibilities

None

Special Precautions for Storage

In a dry place below 25°C.

Package

Lipitor is supplied in blister pack of 30 tablets (3x10's)

Instructions for Use/Handling

No special instructions needed.

Further information is available upon request.

Manufactured by

10, 20, 40mg tablets: Godecke AG, Germany for Parke-Davis GmbH, Germany.

80mg tablets: Heinrich Mack Nachf. GmbH & Co. KG, Illertissen, Germany.

Imported by

Neopharm Ltd.

POB 7063, Petach-Tiqva 49170

Tel: 03-9373777

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פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר על ידו