

and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

7 DRUG INTERACTIONS

The risk of myopathy during treatment with statins is increased with concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin, cyclosporine, or strong CYP 3A4 inhibitors (e.g., clarithromycin, HIV and HCV protease inhibitors, and itraconazole) [see *Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)*].

7.1 Strong Inhibitors of CYP 3A4

LIPITOR is metabolized by cytochrome P450 3A4. Concomitant administration of LIPITOR with strong inhibitors of CYP 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depend on the variability of effect on CYP 3A4.

Clarithromycin

Atorvastatin AUC was significantly increased with concomitant administration of LIPITOR 80 mg with clarithromycin (500 mg twice daily) compared to that of LIPITOR alone [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking clarithromycin, caution should be used when the LIPITOR dose exceeds 20 mg [see *Dosage and Administration (2.6) and Warnings and Precautions (5.1)*].

Combination of Protease Inhibitors

Atorvastatin AUC was significantly increased with concomitant administration of LIPITOR with several combinations of protease inhibitors [see *Clinical Pharmacology (12.3)*]. In patients taking tipranavir plus ritonavir or glecaprevir plus pibrentasvir, concomitant use of LIPITOR should be avoided. In patients taking lopinavir plus ritonavir, or simeprevir, use the lowest necessary LIPITOR dose. In patients taking saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, or elbasvir plus grazoprevir, the dose of LIPITOR should not exceed 20 mg. In patients taking nelfinavir the dose of LIPITOR should not exceed 40 mg and close clinical monitoring is recommended [see *Dosage and Administration (2.6) and Warnings and Precautions (5.1)*].

Itraconazole

Atorvastatin AUC was significantly increased with concomitant administration of LIPITOR 40 mg and itraconazole 200 mg [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking itraconazole, caution should be used when the LIPITOR dose exceeds 20 mg [see *Dosage and Administration (2.6) and Warnings and Precautions (5.1)*].

7.2 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).

7.3 Cyclosporine

Atorvastatin is a substrate of the hepatic transporters. Atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g., cyclosporine) can increase the bioavailability of atorvastatin. Atorvastatin AUC was significantly increased with concomitant administration of LIPITOR 10 mg and cyclosporine 5.2 mg/kg/day compared to that of LIPITOR alone [see *Clinical Pharmacology (12.3)*].

The co-administration of LIPITOR with cyclosporine should be avoided [see *Warnings and Precautions (5.1)*].

7.4 Letemovir

Concomitant administration of atorvastatin 20 mg and letemovir 480 mg daily resulted in an increase in exposure to atorvastatin (ratio of AUC: 3.29) [see *Clinical Pharmacology (12.3)*]. Letemovir inhibits efflux transporters P-gp, BCRP, MRP2, OAT2 and hepatic transporter OATP1B1/1B3, thus it increases exposure to atorvastatin. Do not exceed 20 mg LIPITOR daily [see *Dosage and Administration (2.6)*].

The magnitude of CYP3A- and OATP1B1/1B3-mediated drug interactions on co-administered drugs may be different when letemovir is co-administered with cyclosporine. Use of LIPITOR is not recommended in patients taking letemovir co-administered with cyclosporine.

7.5 Glecaprevir and Pibrentasvir; Elbasvir and Grazoprevir

Concomitant administration of glecaprevir and pibrentasvir or elbasvir and grazoprevir may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy.

Coadministration of glecaprevir and pibrentasvir with atorvastatin increase plasma concentrations of atorvastatin by 8.3-fold due in part to BCRP, OATP1B1/1B3, and CYP3A inhibition; therefore, coadministration of LIPITOR in patients receiving concomitant medications with products containing glecaprevir and pibrentasvir is not recommended.

Coadministration of elbasvir and grazoprevir with atorvastatin increase plasma concentrations of atorvastatin by 1.9-fold due in part to BCRP, OATP1B1/1B3, and CYP3A inhibition; therefore, the dose of LIPITOR should not exceed 20 mg daily in patients receiving concomitant medications with products containing elbasvir and grazoprevir [see *Dosage and Administration (2.6)*, *Warnings and Precautions (5.1)*, and *Clinical Pharmacology (12.3)*].

7.6 Gemfibrozil

Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are co-administered with gemfibrozil, concomitant administration of LIPITOR with gemfibrozil should be avoided [see *Warnings and Precautions (5.1)*].

7.7 Other Fibrates

Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of other fibrates, LIPITOR should be administered with caution when used concomitantly with other fibrates [see *Warnings and Precautions (5.1)*].

7.8 Niacin

The risk of skeletal muscle effects may be enhanced when LIPITOR is used in combination with niacin; a reduction in LIPITOR dosage should be considered in this setting [see *Warnings and Precautions (5.1)*].

7.9 Rifampin or other Inducers of Cytochrome P450 3A4

Concomitant administration of LIPITOR with inducers of cytochrome P450 3A4 (e.g., efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, simultaneous co-administration of LIPITOR with rifampin is recommended, as delayed administration of LIPITOR after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

7.10 Digoxin

When multiple doses of LIPITOR and digoxin were co-administered, steady state plasma digoxin concentrations increased [see *Clinical Pharmacology (12.3)*]. Patients taking digoxin should be monitored appropriately.

7.11 Oral Contraceptives

Co-administration of LIPITOR and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol [see *Clinical Pharmacology (12.3)*]. These increases should be considered when selecting an oral contraceptive for a woman taking LIPITOR.

7.12 Warfarin

LIPITOR had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

7.13 Colchicine

Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

LIPITOR is contraindicated for use in pregnant women since safety in pregnant women has not been established and there is no apparent benefit of lipid lowering drugs during pregnancy. Because HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, LIPITOR may cause fetal harm when administered to a pregnant woman. LIPITOR should be discontinued as soon as pregnancy is recognized [see *Contraindications (4)*]. Limited published data on the use of atorvastatin are insufficient to determine a drug-associated risk of major congenital malformations or miscarriage. In animal reproduction studies in rats and rabbits there was no evidence of embryo-fetal toxicity or congenital malformations at doses up to 30 and 20 times, respectively, the human exposure at the maximum recommended human dose (MRHD) of 80 mg, based on body surface area (mg/m²). In rats administered atorvastatin during gestation and lactation, decreased postnatal growth and development was observed at doses \geq 6 times the MRHD (see *Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

Limited published data on atorvastatin calcium from observational studies, meta-analyses and case reports have not shown an increased risk of major congenital malformations or miscarriage. Rare reports of congenital anomalies have been received following intrauterine exposure to other HMG-CoA reductase inhibitors. In a review of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or lovastatin, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate to exclude a \geq 3 to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified.

Animal Data

Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was administered to pregnant rats and rabbits during organogenesis at oral doses up to 300 mg/kg/day and 100 mg/kg/day, respectively. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure at the MRHD based on surface area (mg/m²). In rats, the maternally toxic dose of 300 mg/kg resulted in increased post-implantation loss and decreased fetal body weight. At the maternally toxic doses of 50 and 100 mg/kg/day in rabbits, there was increased post-implantation loss, and at 100 mg/kg/day fetal body weights were decreased.

In a study in pregnant rats administered 20, 100, or 225 mg/kg/day from gestation day 7 through to lactation day 20 (weaning), there was decreased survival at birth, postnatal day 4, weaning, and post-weaning in pups of mothers dosed with 225 mg/kg/day, a dose at which maternal toxicity was observed. Pup body weight was decreased through postnatal day 21 at 100 mg/kg/day, and through postnatal day 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye-opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human exposure at the MRHD, based on AUC.

8.2 Lactation

Risk Summary

LIPITOR use is contraindicated during breastfeeding [see *Contraindications (4)*]. There is no available information on the effects of the drug on the breastfed infant or the effects of the drug on milk production. It is not known whether atorvastatin is present in human milk, but it has been shown that another drug in this class passes into human milk and atorvastatin is present in rat milk. Because of the potential for serious adverse reactions in a breastfed infant, advise women that breastfeeding is not recommended during treatment with LIPITOR.

8.3 Females and Males of Reproductive Potential

Contraception

LIPITOR may cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with LIPITOR [see *Use in Specific Populations (8.1)*].

8.4 Pediatric Use

Heterozygous Familial Hypercholesterolemia (HeFH)

The safety and effectiveness of LIPITOR have been established in pediatric patients, 10 years to 17 years of age, with HeFH as an adjunct to diet to reduce total cholesterol, LDL-C, and apo B levels when, after an adequate trial of diet therapy, the following are present:

- LDL-C \geq 190 mg/dL, or
- LDL-C \geq 160 mg/dL and
 - a positive family history of FH, or premature CVD in a first, or second-degree relative, or
 - two or more other CVD risk factors are present.

Use of LIPITOR for this indication is supported by evidence from [see *Dosage and Administration (2.2)*, *Adverse Reactions (6.1)*, *Clinical Pharmacology (12.3)*, and *Clinical Studies (14.6)*]:

- A placebo-controlled clinical trial of 6 months duration in 187 boys and postmenarchal girls, 10 years to 17 years of age. Patients treated with 10 mg or 20 mg daily LIPITOR had an adverse reaction profile generally similar to that of patients treated with placebo. In this limited controlled study, there was no significant effect on growth or sexual maturation in boys or on menstrual cycle length in girls.
- A three year open-label uncontrolled trial that included 163 pediatric patients 10 to 15 years of age with HeFH who were titrated to achieve a target LDL-C < 130 mg/dL. The safety and efficacy of LIPITOR in lowering LDL-C appeared generally consistent with that observed for adult patients, despite limitations of the uncontrolled study design

Advise postmenarchal girls of contraception recommendations, if appropriate for the patient [see *Use in Specific Populations (8.1)*, (8.3)].

The long-term efficacy of LIPITOR therapy initiated in childhood to reduce morbidity and mortality in adulthood has not been established.

The safety and efficacy of LIPITOR have not been established in pediatric patients younger than 10 years of age with HeFH.

Homozygous Familial Hypercholesterolemia (HoFH)

Clinical efficacy of LIPITOR with dosages up to 80 mg/day for 1 year was evaluated in an uncontrolled study of patients with HoFH including 8 pediatric patients [see *Clinical Studies (14.5)*].

8.5 Geriatric Use

Of the 39,828 patients who received LIPITOR in clinical studies, 15,813 (40%) were \geq 65 years old and 2,800 (7%) were \geq 75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older adults cannot be ruled out. Since advanced age (\geq 65 years) is a predisposing factor for myopathy, LIPITOR should be prescribed with caution in the elderly.

8.6 Hepatic Impairment

Lipitor is contraindicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels [see *Contraindications (4)* and *Clinical Pharmacology (12.3)*].

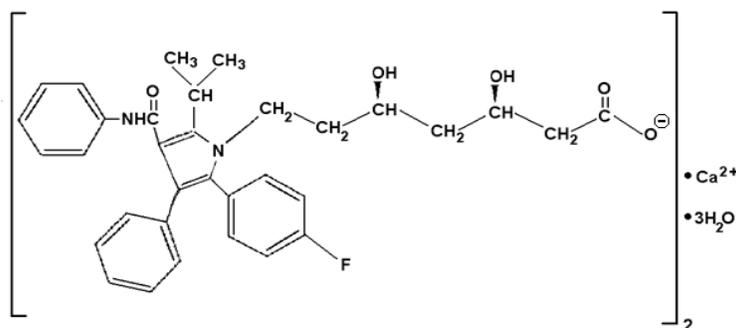
10 OVERDOSAGE

There is no specific treatment for LIPITOR overdose. In the event of an overdose, 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.

11 DESCRIPTION

LIPITOR is a synthetic lipid-lowering agent. Atorvastatin 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.

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is (C₃₃H₃₄FN₂O₅)₂Ca•3H₂O and its molecular weight is 1209.42. Its structural formula is:



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

LIPITOR Tablets for oral administration contain 10, 20, 40, or 80 mg of atorvastatin and the following inactive ingredients: calcium carbonate, USP; candelilla wax, FCC; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1-7040 (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80, NF; simethicone emulsion.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

LIPITOR 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. In animal models, LIPITOR 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 to enhance uptake and catabolism of LDL; LIPITOR also reduces LDL production and the number of LDL particles.

12.2 Pharmacodynamics

LIPITOR, as well as some of its metabolites, are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage, rather than systemic drug concentration, correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response [see *Dosage and Administration* (2)].

12.3 Pharmacokinetics

Absorption: LIPITOR is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to LIPITOR dose. The absolute bioavailability of atorvastatin (parent drug) 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 C_{max} and AUC, LDL-C reduction is similar whether LIPITOR is given with or without food. Plasma LIPITOR concentrations are lower (approximately 30% for C_{max} 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 [see *Dosage and Administration* (2)].

Distribution: Mean volume of distribution of LIPITOR is approximately 381 liters. LIPITOR is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, LIPITOR is likely to be secreted in human milk [see *Contraindications* (4) and *Use in Specific Populations* (8.2)].

Metabolism: LIPITOR 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 LIPITOR. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of LIPITOR metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of LIPITOR in humans following co-administration with erythromycin, a known inhibitor of this isozyme [see *Drug Interactions* (7.1)]. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion: LIPITOR and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of LIPITOR 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 LIPITOR is recovered in urine following oral administration.

Specific Populations

Geriatric: Plasma concentrations of LIPITOR are higher (approximately 40% for C_{max} and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults [see *Use in Specific Populations (8.5)*].

Pediatric: Apparent oral clearance of atorvastatin in pediatric subjects appeared similar to that of adults when scaled allometrically by body weight as the body weight was the only significant covariate in atorvastatin population PK model with data including pediatric HeFH patients (ages 10 years to 17 years of age, n=29) in an open-label, 8-week study.

Gender: Plasma concentrations of LIPITOR in women differ from those in men (approximately 20% higher for C_{max} and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with LIPITOR between men and women.

Renal Impairment: Renal disease has no influence on the plasma concentrations or LDL-C reduction of LIPITOR; thus, dose adjustment in patients with renal dysfunction is not necessary [see *Dosage and Administration (2.5) and Warnings and Precautions (5.1)*].

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

Hepatic Impairment: In patients with chronic alcoholic liver disease, plasma concentrations of LIPITOR are markedly increased. C_{max} and AUC are each 4-fold greater in patients with Childs-Pugh A disease. C_{max} and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease [see *Contraindications (4)*].

Drug Interaction Studies

Atorvastatin is a substrate of the hepatic transporters, OATP1B1 and OATP1B3 transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporter BCRP, which may limit the intestinal absorption and biliary clearance of atorvastatin.

TABLE 4. Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Ratio of AUC ^{&}	Ratio of C _{max} ^{&}
#Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QD ^a for 28 days	8.69	10.66
#Tipranavir 500 mg BID ^b /ritonavir 200 mg BID ^b , 7 days	10 mg, SD ^c	9.36	8.58
#Glecaprevir 400 mg QD ^a /pibrentasvir 120 mg QD ^a , 7 days	10 mg QD ^a for 7 days	8.28	22.00
#Telaprevir 750 mg q8h ^f , 10 days	20 mg, SD ^c	7.88	10.60
#, ‡Saquinavir 400 mg BID ^b / ritonavir 400 mg BID ^b , 15 days	40 mg QD ^a for 4 days	3.93	4.31
#Elbasvir 50 mg QD ^a /grazoprevir 200 mg QD ^a , 13 days	10 mg SD ^c	1.94	4.34
#Simeprevir 150 mg QD ^a , 10 days	40 mg SD ^c	2.12	1.70
#Clarithromycin 500 mg BID ^b , 9 days	80 mg QD ^a for 8 days	4.54	5.38
#Darunavir 300 mg BID ^b /ritonavir 100 mg BID ^b , 9 days	10 mg QD ^a for 4 days	3.45	2.25
#Itraconazole 200 mg QD ^a , 4 days	40 mg SD ^c	3.32	1.20
#Letemovir 480 mg QD ^a , 10 days	20 mg SD ^c	3.29	2.17
#Fosamprenavir 700 mg BID ^b /ritonavir 100 mg BID ^b , 14 days	10 mg QD ^a for 4 days	2.53	2.84
#Fosamprenavir 1400 mg BID ^b , 14 days	10 mg QD ^a for 4 days	2.30	4.04
#Nelfinavir 1250 mg BID ^b , 14 days	10 mg QD ^a for 28 days	1.74	2.22
#Grapefruit Juice, 240 mL QD ^{a,*}	40 mg, SD ^c	1.37	1.16
Diltiazem 240 mg QD ^a , 28 days	40 mg, SD ^c	1.51	1.00
Erythromycin 500 mg QID ^e , 7 days	10 mg, SD ^c	1.33	1.38
Amlodipine 10 mg, single dose	80 mg, SD ^c	1.18	0.91
Cimetidine 300 mg QID ^e , 2 weeks	10 mg QD ^a for 2 weeks	1.00	0.89
Colestipol 10 g BID ^b , 24 weeks	40 mg QD ^a for 8 weeks	NA	0.74**
Maalox TC [®] 30 mL QID ^e , 17 days	10 mg QD ^a for 15 days	0.66	0.67
Efavirenz 600 mg QD ^a , 14 days	10 mg for 3 days	0.59	1.01
#Rifampin 600 mg QD ^a , 7 days (co-administered) †	40 mg SD ^c	1.12	2.90
#Rifampin 600 mg QD ^a , 5 days (doses separated) †	40 mg SD ^c	0.20	0.60
#Gemfibrozil 600 mg BID ^b , 7 days	40 mg SD ^c	1.35	1.00
#Fenofibrate 160 mg QD ^a , 7 days	40 mg SD ^c	1.03	1.02
Boceprevir 800 mg TID ^d , 7 days	40 mg SD ^c	2.32	2.66

[&] Represents ratio of treatments (co-administered drug plus atorvastatin vs. atorvastatin alone).

[#] See Sections 5.1 and 7 for clinical significance.

^{*} Greater increases in AUC (ratio of AUC up to 2.5) and/or C_{max} (ratio of C_{max} up to 1.71) have been reported with excessive grapefruit consumption (≥ 750 mL - 1.2 liters per day).

^{**} Ratio based on a 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.

^a Once daily

^b Twice daily

^c Single dose

^d Three times daily

^e Four times daily

^f Every 8 hours

TABLE 5. Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs

Atorvastatin	Co-administered drug and dosing regimen		
	Drug/Dose (mg)	Ratio of AUC	Ratio of Cmax
80 mg QD ^a for 15 days	Antipyrine, 600 mg SD ^c	1.03	0.89
80 mg QD ^a for 10 days	# Digoxin 0.25 mg QD ^a , 20 days	1.15	1.20
40 mg QD ^a for 22 days	Oral contraceptive QD ^a , 2 months		
	- norethindrone 1 mg - ethinyl estradiol 35µg	1.28 1.19	1.23 1.30
10 mg, SD ^c	Tipranavir 500 mg BID ^b /ritonavir 200 mg BID ^b , 7 days	1.08	0.96
10 mg QD ^a for 4 days	Fosamprenavir 1400 mg BID ^b , 14 days	0.73	0.82
10 mg QD ^a for 4 days	Fosamprenavir 700 mg BID ^b /ritonavir 100 mg BID ^b , 14 days	0.99	0.94

See Section 7 for clinical significance.

^a Once daily

^b Twice daily

^c Single dose

13 NONCLINICAL TOXICOLOGY

13.1 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.

In female rats, atorvastatin at doses up to 225 mg/kg (56 times the human exposure) did not cause adverse effects on fertility. Studies in male 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.

14 CLINICAL STUDIES

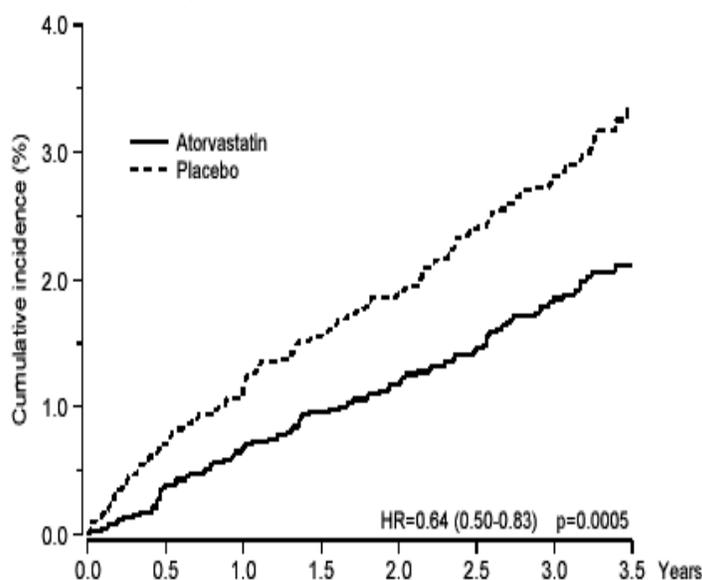
14.1 Prevention of Cardiovascular Disease

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of LIPITOR 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 ≤251 mg/dL (6.5 mmol/L). Additionally, all patients had at least 3 of the following cardiovascular risk factors: male gender (81.1%), age >55 years (84.5%), smoking (33.2%), diabetes (24.3%), history of CHD in a first-degree relative (26%), TC:HDL >6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypertrophy (14.4%), prior cerebrovascular event (9.8%), specific ECG abnormality (14.3%), proteinuria/albuminuria (62.4%). 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 LIPITOR 10 mg daily (n=5168) or placebo (n=5137), using a covariate adaptive method which took into account the distribution of nine baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients were followed for a median duration of 3.3 years.

The effect of 10 mg/day of LIPITOR on lipid levels was similar to that seen in previous clinical trials.

LIPITOR significantly reduced the rate of coronary events [either fatal coronary heart disease (46 events in the placebo group vs. 40 events in the LIPITOR group) or non-fatal MI (108 events in the placebo group vs. 60 events in the LIPITOR group)] with a relative risk reduction of 36% [(based on incidences of 1.9% for LIPITOR vs. 3.0% for placebo), $p=0.0005$ (see Figure 1)]. The risk reduction was consistent regardless of age, smoking status, obesity, or presence of renal dysfunction. The effect of LIPITOR was seen regardless of baseline LDL levels. Due to the small number of events, results for women were inconclusive.

Figure 1: Effect of LIPITOR 10 mg/day on Cumulative Incidence of Non-Fatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT-LLA)



LIPITOR also significantly decreased the relative risk for revascularization procedures by 42% (incidences of 1.4% for LIPITOR and 2.5% for placebo). 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 (incidences of 1.7% for LIPITOR and 2.3% for placebo). There was no significant difference between the treatment groups for death due to cardiovascular causes ($p=0.51$) or noncardiovascular causes ($p=0.17$).

In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of LIPITOR on cardiovascular disease (CVD) endpoints was assessed in 2838 subjects (94% white, 68% male), ages 40–75 with type 2 diabetes based on WHO criteria, without prior history of cardiovascular disease and with LDL ≤ 160 mg/dL and TG ≤ 600 mg/dL. In addition to diabetes, subjects had 1 or more of the following risk factors: current smoking (23%), hypertension (80%), retinopathy (30%), or microalbuminuria (9%) or macroalbuminuria (3%). No subjects on hemodialysis were enrolled in the study. In this multicenter, placebo-controlled, double-blind clinical trial, subjects were randomly allocated to either LIPITOR 10 mg daily (1429) or placebo (1411) in a 1:1 ratio and were followed for a median duration of 3.9 years. The primary endpoint was the occurrence of any of the major cardiovascular events: myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke. The primary analysis was the time to first occurrence of the primary endpoint.

Baseline characteristics of subjects were: mean age of 62 years, mean HbA_{1c} 7.7%; median LDL-C 120 mg/dL; median TC 207 mg/dL; median TG 151 mg/dL; median HDL-C 52 mg/dL.

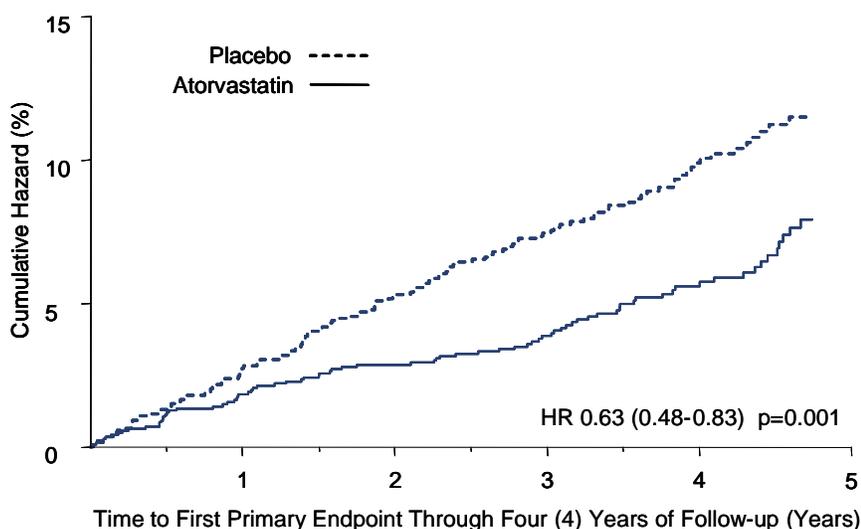
The effect of LIPITOR 10 mg/day on lipid levels was similar to that seen in previous clinical trials.

LIPITOR significantly reduced the rate of major cardiovascular events (primary endpoint events) (83 events in the LIPITOR group vs. 127 events in the placebo group) with a relative risk reduction of 37%, HR 0.63, 95% CI (0.48, 0.83) ($p=0.001$) (see Figure 2). An effect of LIPITOR was seen regardless of age, sex, or baseline lipid levels.

LIPITOR significantly reduced the risk of stroke by 48% (21 events in the LIPITOR group vs. 39 events in the placebo group), HR 0.52, 95% CI (0.31, 0.89) ($p=0.016$) and reduced the risk of MI by 42% (38 events in the LIPITOR group vs. 64 events in the placebo group), HR 0.58, 95.1% CI (0.39, 0.86) ($p=0.007$). There was no significant difference between the treatment groups for angina, revascularization procedures, and acute CHD death.

There were 61 deaths in the LIPITOR group vs. 82 deaths in the placebo group (HR 0.73, $p=0.059$).

Figure 2: Effect of LIPITOR 10 mg/day on Time to Occurrence of Major Cardiovascular Event (myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke) in CARDS



In the Treating to New Targets Study (TNT), the effect of LIPITOR 80 mg/day vs. LIPITOR 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 LIPITOR 10 mg/day. Subjects were randomly assigned to either 10 mg/day or 80 mg/day of LIPITOR and followed for a median duration of 4.9 years. The primary endpoint was the time-to-first occurrence of any of the following major cardiovascular events (MCVE): death due to CHD, non-fatal myocardial infarction, resuscitated cardiac arrest, and fatal and non-fatal stroke. 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 LIPITOR and 99, 177, 152, 129, and 48 mg/dL during treatment with 10 mg of LIPITOR.

Treatment with LIPITOR 80 mg/day significantly reduced the rate of MCVE (434 events in the 80 mg/day group vs. 548 events in the 10 mg/day group) with a relative risk reduction of 22%, HR 0.78, 95% CI (0.69, 0.89), $p=0.0002$ (see Figure 3 and Table 6). The overall risk reduction was consistent regardless of age (< 65 , ≥ 65) or gender.

Figure 3: Effect of LIPITOR 80 mg/day vs. 10 mg/day on Time to Occurrence of Major Cardiovascular Events (TNT)

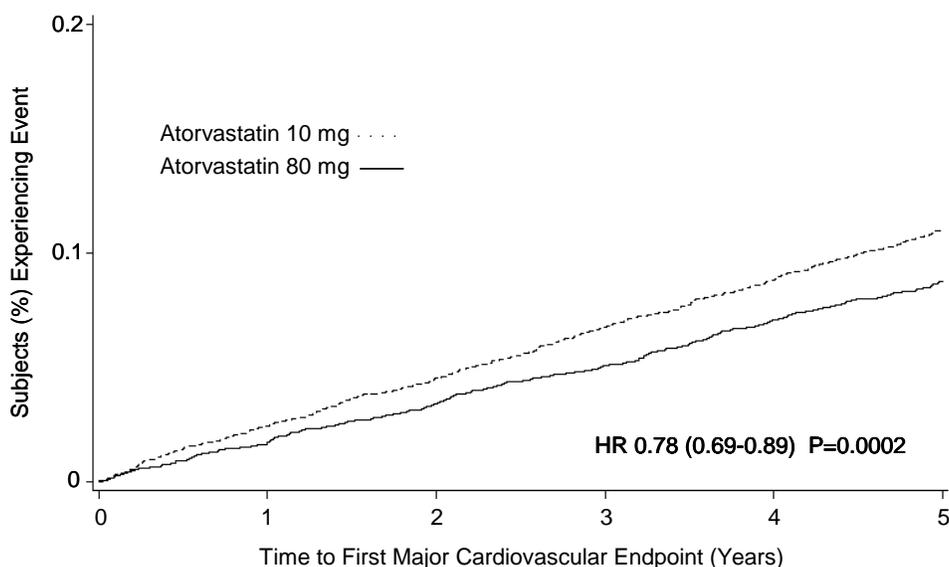


TABLE 6. Overview of Efficacy Results in TNT

Endpoint	Atorvastatin 10 mg (N=5006)		Atorvastatin 80 mg (N=4995)		HR ^a (95%CI)
	n	(%)	n	(%)	
PRIMARY ENDPOINT					
First major cardiovascular endpoint	548	(10.9)	434	(8.7)	0.78 (0.69, 0.89)
Components of the Primary Endpoint					
CHD death	127	(2.5)	101	(2.0)	0.80 (0.61, 1.03)
Non-fatal, non-procedure related MI	308	(6.2)	243	(4.9)	0.78 (0.66, 0.93)
Resuscitated cardiac arrest	26	(0.5)	25	(0.5)	0.96 (0.56, 1.67)
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 PVD endpoint	282	(5.6)	275	(5.5)	0.97 (0.83, 1.15)
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)
All-cause mortality	282	(5.6)	284	(5.7)	1.01 (0.85, 1.19)
Components of All-Cause Mortality					
Cardiovascular death	155	(3.1)	126	(2.5)	0.81 (0.64, 1.03)
Noncardiovascular death	127	(2.5)	158	(3.2)	1.25 (0.99, 1.57)
Cancer death	75	(1.5)	85	(1.7)	1.13 (0.83, 1.55)
Other non-CV death	43	(0.9)	58	(1.2)	1.35 (0.91, 2.00)
Suicide, homicide, and othertraumatic non-CV death	9	(0.2)	15	(0.3)	1.67 (0.73, 3.82)

^a Atorvastatin 80 mg: atorvastatin 10 mg

^b Component of other secondary endpoints

* Secondary endpoints not included in primary endpoint

HR=hazard ratio; CHD=coronary heart disease; CI=confidence interval; MI=myocardial infarction; CHF=congestive heart failure; CV=cardiovascular; PVD=peripheral vascular disease; CABG=coronary artery bypass graft
Confidence intervals for the Secondary Endpoints were not adjusted for multiple comparisons

Of the events that comprised the primary efficacy endpoint, treatment with LIPITOR 80 mg/day significantly reduced the rate of non-fatal, non-procedure related MI and fatal and non-fatal stroke, but not CHD death or resuscitated cardiac arrest (Table 6). Of the predefined secondary endpoints, treatment with LIPITOR 80 mg/day significantly reduced the rate of coronary revascularization, angina, and hospitalization for heart failure, but not peripheral vascular disease. The reduction in the rate of CHF with hospitalization was only observed in the 8% of patients with a prior history of CHF.

There was no significant difference between the treatment groups for all-cause mortality (Table 6). The proportions of subjects who experienced cardiovascular death, including the components of CHD death and fatal stroke, were numerically smaller in the LIPITOR 80 mg group than in the LIPITOR 10 mg treatment group. The proportions of subjects who experienced noncardiovascular death were numerically larger in the LIPITOR 80 mg group than in the LIPITOR 10 mg treatment group.

In the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study (IDEAL), treatment with LIPITOR 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 LIPITOR 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, non-fatal MI, and resuscitated cardiac arrest): 411 (9.3%) in the LIPITOR 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 LIPITOR 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 LIPITOR 80 mg group and the simvastatin 20–40 mg group.

14.2 Hyperlipidemia and Mixed Dyslipidemia

LIPITOR reduces total-C, LDL-C, VLDL-C, apo B, and TG, and increases HDL-C in patients with hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (*Fredrickson* Types IIa and IIb). Therapeutic response is seen within 2 weeks, and maximum response is usually achieved within 4 weeks and maintained during chronic therapy.

LIPITOR is effective in a wide variety of patient populations with hyperlipidemia, with and without hypertriglyceridemia, in men and women, and in the elderly.

In two multicenter, placebo-controlled, dose-response studies in patients with hyperlipidemia, LIPITOR given as a single dose over 6 weeks, significantly reduced total-C, LDL-C, apo B, and TG. (Pooled results are provided in Table 7.)

TABLE 7. Dose Response in Patients With Primary Hyperlipidemia (Adjusted Mean % Change From Baseline)^a

Dose	N	TC	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Placebo	21	4	4	3	10	-3	7
10	22	-29	-39	-32	-19	6	-34
20	20	-33	-43	-35	-26	9	-41
40	21	-37	-50	-42	-29	6	-45
80	23	-45	-60	-50	-37	5	-53

^a Results are pooled from 2 dose-response studies.

In patients with *Fredrickson* Types IIa and IIb hyperlipoproteinemia pooled from 24 controlled trials, the median (25th and 75th percentile) percent changes from baseline in HDL-C for LIPITOR 10, 20, 40, and 80 mg were 6.4 (-1.4, 14), 8.7 (0, 17), 7.8 (0, 16), and 5.1 (-2.7, 15), respectively. Additionally, analysis of the pooled data demonstrated consistent and significant decreases in total-C, LDL-C, TG, total-C/HDL-C, and LDL-C/HDL-C.

In three multicenter, double-blind studies in patients with hyperlipidemia, LIPITOR was compared to other statins. After randomization, patients were treated for 16 weeks with either LIPITOR 10 mg per day or a fixed dose of the comparative agent (Table 8).

TABLE 8. Mean Percentage Change From Baseline at Endpoint (Double-Blind, Randomized, Active-Controlled Trials)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
<i>Study 1</i>							
LIPITOR 10 mg	707	-27 ^a	-36 ^a	-28 ^a	-17 ^a	+7	-37 ^a
Lovastatin 20 mg	191	-19	-27	-20	-6	+7	-28
95% CI for Diff ¹		-9.2, -6.5	-10.7, -7.1	-10.0, -6.5	-15.2, -7.1	-1.7, 2.0	-11.1, -7.1
<i>Study 2</i>							
LIPITOR 10 mg	222	-25 ^b	-35 ^b	-27 ^b	-17 ^b	+6	-36 ^b
Pravastatin 20 mg	77	-17	-23	-17	-9	+8	-28
95% CI for Diff ¹		-10.8, -6.1	-14.5, -8.2	-13.4, -7.4	-14.1, -0.7	-4.9, 1.6	-11.5, -4.1
<i>Study 3</i>							
LIPITOR 10 mg	132	-29 ^c	-37 ^c	-34 ^c	-23 ^c	+7	-39 ^c
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff ¹		-8.7, -2.7	-10.1, -2.6	-8.0, -1.1	-15.1, -0.7	-4.3, 3.9	-9.6, -1.9

¹ A negative value for the 95% CI for the difference between treatments favors LIPITOR for all except HDL-C, for which a positive value favors LIPITOR. If the range does not include 0, this indicates a statistically significant difference.

^a Significantly different from lovastatin, ANCOVA, $p \leq 0.05$

^b Significantly different from pravastatin, ANCOVA, $p \leq 0.05$

^c Significantly different from simvastatin, ANCOVA, $p \leq 0.05$

The impact on clinical outcomes of the differences in lipid-altering effects between treatments shown in Table 8 is not known. Table 8 does not contain data comparing the effects of LIPITOR 10 mg and higher doses of lovastatin, pravastatin, and simvastatin. The drugs compared in the studies summarized in the table are not necessarily interchangeable.

14.3 Hypertriglyceridemia

The response to LIPITOR in 64 patients with isolated hypertriglyceridemia (*Fredrickson* Type IV) treated across several clinical trials is shown in the table below (Table 9). For the LIPITOR-treated patients, median (min, max) baseline TG level was 565 (267–1502).

TABLE 9. Combined Patients With Isolated Elevated TG: Median (min, max) Percentage Change From Baseline

	Placebo (N=12)	LIPITOR 10 mg (N=37)	LIPITOR 20 mg (N=13)	LIPITOR 80 mg (N=14)
Triglycerides	-12.4 (-36.6, 82.7)	-41.0 (-76.2, 49.4)	-38.7 (-62.7, 29.5)	-51.8 (-82.8, 41.3)
Total-C	-2.3 (-15.5, 24.4)	-28.2 (-44.9, -6.8)	-34.9 (-49.6, -15.2)	-44.4 (-63.5, -3.8)
LDL-C	3.6 (-31.3, 31.6)	-26.5 (-57.7, 9.8)	-30.4 (-53.9, 0.3)	-40.5 (-60.6, -13.8)
HDL-C	3.8 (-18.6, 13.4)	13.8 (-9.7, 61.5)	11.0 (-3.2, 25.2)	7.5 (-10.8, 37.2)
VLDL-C	-1.0 (-31.9, 53.2)	-48.8 (-85.8, 57.3)	-44.6 (-62.2, -10.8)	-62.0 (-88.2, 37.6)
non-HDL-C	-2.8 (-17.6, 30.0)	-33.0 (-52.1, -13.3)	-42.7 (-53.7, -17.4)	-51.5 (-72.9, -4.3)

14.4 Dysbetalipoproteinemia

The results of an open-label crossover study of 16 patients (genotypes: 14 apo E2/E2 and 2 apo E3/E2) with dysbetalipoproteinemia (*Fredrickson* Type III) are shown in the table below (Table 10).

TABLE 10. Open-Label Crossover Study of 16 Patients With Dysbetalipoproteinemia (*Fredrickson* Type III)

	Median (min, max) at Baseline (mg/dL)	Median % Change (min, max)	
		LIPITOR 10 mg	LIPITOR 80 mg
Total-C	442 (225, 1320)	-37 (-85, 17)	-58 (-90, -31)
Triglycerides	678 (273, 5990)	-39 (-92, -8)	-53 (-95, -30)
IDL-C + VLDL-C	215 (111, 613)	-32 (-76, 9)	-63 (-90, -8)
non-HDL-C	411 (218, 1272)	-43 (-87, -19)	-64 (-92, -36)

14.5 Homozygous Familial Hypercholesterolemia

In a study without a concurrent control group, 29 patients ages 6 years to 37 years with HoFH received maximum daily doses of 20 to 80 mg of LIPITOR. The mean LDL-C reduction in this study was 18%. Twenty-five patients with a reduction in LDL-C had a mean response of 20% (range of 7% to 53%, median of 24%); the remaining 4 patients had 7% to 24% increases in LDL-C. Five of the 29 patients had absent LDL-receptor function. Of these, 2 patients also had a portacaval shunt and had no significant reduction in LDL-C. The remaining 3 receptor-negative patients had a mean LDL-C reduction of 22%.

14.6 Heterozygous Familial Hypercholesterolemia in Pediatric Patients

In a double-blind, placebo-controlled study followed by an open-label phase, 187 boys and post-menarchal girls 10 years to 17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (HeFH) or severe hypercholesterolemia, were randomized to LIPITOR (n=140) or placebo (n=47) for 26 weeks and then all received LIPITOR for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level \geq 190 mg/dL or 2) a baseline LDL-C level \geq 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 LIPITOR group compared to 230.0 mg/dL (range: 160.0–324.5 mg/dL) in the placebo group. The dosage of LIPITOR (once daily) was 10 mg for the first 4 weeks and uptitrated to 20 mg if the LDL-C level was $>$ 130 mg/dL. The number of LIPITOR-treated patients who required uptitration to 20 mg after Week 4 during the double-blind phase was 78 (55.7%).

LIPITOR significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26-week double-blind phase (see Table 11).

TABLE 11. Lipid-altering Effects of LIPITOR in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia (Mean Percentage 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
LIPITOR	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 LIPITOR 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.

Atorvastatin was also studied in a three year open-label, uncontrolled trial that included 163 patients with HeFH who were 10 years to 15 years old (82 boys and 81 girls). All patients had a clinical diagnosis of HeFH confirmed by genetic analysis (if not already confirmed by family history). Approximately 98% were Caucasian, and less than 1% were Black or Asian. Mean LDL-C at baseline was 232 mg/dL. The starting atorvastatin dosage was 10 mg once daily and doses were adjusted to achieve a target of < 130 mg/dL LDL-C. The reductions in LDL-C from baseline were generally consistent across age groups within the trial as well as with previous clinical studies in both adult and pediatric placebo-controlled trials.

The long-term efficacy of LIPITOR therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

16 HOW SUPPLIED/STORAGE AND HANDLING

10 mg tablets (10 mg of atorvastatin): coded “PD 155” on one side and “10” on the other.

NDC 0071-0155-23 bottles of 90

NDC 0071-0155-34 bottles of 5000

NDC 0071-0155-40 10 x 10 unit dose blisters

NDC 0071-0155-10 bottles of 1000

20 mg tablets (20 mg of atorvastatin): coded “PD 156” on one side and “20” on the other.

NDC 0071-0156-23 bottles of 90

NDC 0071-0156-40 10 x 10 unit dose blisters

NDC 0071-0156-94 bottles of 5000

NDC 0071-0156-10 bottles of 1000

40 mg tablets (40 mg of atorvastatin): coded “PD 157” on one side and “40” on the other.

NDC 0071-0157-23 bottles of 90

NDC 0071-0157-73 bottles of 500

NDC 0071-0157-88 bottles of 2500

NDC 0071-0157-40 10 x 10 unit dose blisters

80 mg tablets (80 mg of atorvastatin): coded “PD 158” on one side and “80” on the other.

NDC 0071-0158-23 bottles of 90

NDC 0071-0158-73 bottles of 500

NDC 0071-0158-88 bottles of 2500

NDC 0071-0158-92 8 x 8 unit dose blisters

Storage

Store at controlled room temperature 20 - 25°C (68 - 77°F) [see USP].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Patients taking LIPITOR should be advised that cholesterol is a chronic condition and they should adhere to their medication along with their National Cholesterol Education Program (NCEP)-recommended diet, a regular exercise program as appropriate, and periodic testing of a fasting lipid panel to determine goal attainment.

Patients should be advised about substances they should not take concomitantly with atorvastatin [see Warnings and Precautions (5.1)]. Patients should also be advised to inform other healthcare professionals prescribing a new medication that they are taking LIPITOR.

17.1 Muscle Pain

All patients starting therapy with LIPITOR should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness, or weakness particularly if accompanied by malaise or fever or if these muscle signs or symptoms persist after discontinuing LIPITOR. The risk of this occurring is increased when taking certain types of medication or consuming larger quantities (>1 liter) of grapefruit juice. They should discuss all medication, both prescription and over the counter, with their healthcare professional.

17.2 Liver Enzymes

It is recommended that liver enzyme tests be performed before the initiation of LIPITOR and if signs or symptoms of liver injury occur. All patients treated with LIPITOR should be advised to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice.

17.3 Embryofetal Toxicity

Advise females of reproductive potential of the risk to a fetus, to use effective contraception during treatment and to inform their healthcare provider of a known or suspected pregnancy [see *Contraindications (4) and Use in Specific Populations (8.1, 8.3)*].

17.4 Lactation

Advise women not to breastfeed during treatment with LIPITOR [see *Contraindications (4) and Use in Specific Populations (8.2)*].

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.



LAB-0021-36.2a

PATIENT INFORMATION



(LIP-ih-tore))

Read the Patient Information that comes with LIPITOR before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your condition or treatment.

If you have any questions about LIPITOR, ask your doctor or pharmacist.

What is LIPITOR?

LIPITOR is a prescription medicine that lowers cholesterol in your blood. It lowers the LDL-C ("bad" cholesterol) and triglycerides in your blood. It can raise your HDL-C ("good" cholesterol) as well. LIPITOR is for adults and children over 10 whose cholesterol does not come down enough with exercise and a low-fat diet alone.

LIPITOR can lower the risk for heart attack, stroke, certain types of heart surgery, and chest pain in patients who have heart disease or risk factors for heart disease such as:

- age, smoking, high blood pressure, low HDL-C, heart disease in the family.

LIPITOR can lower the risk for heart attack or stroke in patients with diabetes and risk factors such as:

- eye problems, kidney problems, smoking, or high blood pressure.

LIPITOR starts to work in about 2 weeks.

What is Cholesterol?

Cholesterol and triglycerides are fats that are made in your body. They are also found in foods. You need some cholesterol for good health, but too much is not good for you. Cholesterol and triglycerides can clog your blood vessels. It is especially important to lower your cholesterol if you have heart disease, smoke, have diabetes or high blood pressure, are older, or if

heart disease starts early in your family.

Who Should Not Take LIPITOR?

Do not take LIPITOR if you:

- are pregnant or think you may be pregnant, or are planning to become pregnant. LIPITOR may harm your unborn baby. If you get pregnant, stop taking LIPITOR and call your doctor right away.
- are breast feeding. LIPITOR can pass into your breast milk and may harm your baby.
- have liver problems.
- are allergic to LIPITOR or any of its ingredients. The active ingredient is atorvastatin. See the end of this leaflet for a complete list of ingredients in LIPITOR.

LIPITOR dosing has not been established in children under 10 years of age.

Before You Start LIPITOR

Tell your doctor if you:

- have muscle aches or weakness
- drink more than 2 glasses of alcohol daily
- have diabetes
- have a thyroid problem
- have kidney problems

Some medicines should not be taken with LIPITOR. Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. LIPITOR and certain other medicines can interact causing serious side effects. Especially tell your doctor if you take medicines for:

- your immune system
- cholesterol
- infections
- birth control
- heart failure
- HIV or AIDS
- hepatitis C virus
- anti-virals

Know all the medicines you take. Keep a list of them with you to show your doctor and pharmacist.

How Should I Take LIPITOR?

- Take LIPITOR exactly as prescribed by your doctor. Do not change your dose or stop LIPITOR without talking to your doctor. Your doctor may do blood tests to check your cholesterol levels during your treatment with LIPITOR. Your dose of LIPITOR may be changed based on these blood test results.
- Take LIPITOR each day at any time of day at about the same time each day. LIPITOR can be taken with or without food.

Don't break LIPITOR tablets before taking.

- Your doctor should start you on a low-fat diet before giving you LIPITOR. Stay on this low-fat diet when you take LIPITOR.
- If you miss a dose of LIPITOR, take it as soon as you remember. Do not take LIPITOR if it has been more than 12 hours since you missed your last dose. Wait and take the next dose at your regular time. Do not take 2 doses of LIPITOR at the same time.
- If you take too much LIPITOR or overdose, call your doctor or Poison Control Center right away. Or go to the nearest emergency room.

What Should I Avoid While Taking LIPITOR?

- Talk to your doctor before you start any new medicines. This includes prescription and non-prescription medicines, vitamins, and herbal supplements. LIPITOR and certain other medicines can interact causing serious side effects.
- Do not get pregnant. If you get pregnant, stop taking LIPITOR right away and call your doctor.

What are the Possible Side Effects of LIPITOR?

LIPITOR can cause serious side effects. These side effects have happened only to a small number of people. Your doctor can monitor you for them. These side effects usually go away if your dose is lowered or LIPITOR is stopped. These serious side effects include:

- **Muscle problems.** LIPITOR can cause serious muscle problems that can lead to kidney problems, including kidney failure. You have a higher chance for muscle problems if you are taking certain other medicines with LIPITOR.
- **Liver problems.** Your doctor should do blood tests to check your liver before you start taking LIPITOR and if you have symptoms of liver problems while you take LIPITOR. Call your doctor right away if you have the following symptoms of liver problems:
 - feel tired or weak
 - loss of appetite
 - upper belly pain
 - dark amber colored urine
 - yellowing of your skin or the whites of your eyes

Call your doctor right away if you have:

- muscle problems like weakness, tenderness, or pain that happen without a good reason, especially if you also have a fever or feel more tired than usual. This may be an early sign of a rare muscle problem.
- muscle problems that do not go away even after your doctor has advised you to stop taking LIPITOR. Your doctor may do further tests to diagnose the cause of your muscle problems.
- allergic reactions including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing

or swallowing which may require treatment right away.

- nausea and vomiting.
- passing brown or dark-colored urine.
- you feel more tired than usual
- your skin and whites of your eyes get yellow.
- stomach pain.
- allergic skin reactions.

In clinical studies, patients reported the following common side effects while taking LIPITOR: diarrhea, upset stomach, muscle and joint pain, and alterations in some laboratory blood tests.

The following additional side effects have been reported with LIPITOR: tiredness, tendon problems, memory loss, and confusion.

Talk to your doctor or pharmacist if you have side effects that bother you or that will not go away.

These are not all the side effects of LIPITOR. Ask your doctor or pharmacist for a complete list.

How do I store LIPITOR

- Store LIPITOR at room temperature, 68 to 77°F (20 to 25°C).
- Do not keep medicine that is out of date or that you no longer need.
- **Keep LIPITOR and all medicines out of the reach of children.** Be sure that if you throw medicine away, it is out of the reach of children.

General Information About LIPITOR

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use LIPITOR for a condition for which it was not prescribed. Do not give LIPITOR to other people, even if they have the same problem you have. It may harm them.

This leaflet summarizes the most important information about LIPITOR. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about LIPITOR that is written for health professionals. Or you can go to the LIPITOR website at www.lipitor.com.

What are the Ingredients in LIPITOR?

Active Ingredient: atorvastatin calcium

Inactive Ingredients: calcium carbonate, USP; candelilla wax, FCC; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1-7040 (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80, NF; simethicone emulsion.



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