SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lipitor 10 mg
Lipitor 20 mg
Lipitor 40 mg
Lipitor 80 mg

2 THERAPEUTIC INDICATION

Hypercholesterolaemia

LIPITOR is indicated as an adjunct to diet for reduction 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 (corresponding to types IIa and IIb of the Fredrickson classification) 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)

LIPITOR is indicated as an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:

a. LDL-C remains ≥ 190 mg/dL or
b. LDL-C remains ≥ 160 mg/dL and:
   - there is a positive family history of premature cardiovascular disease or
   - two or more other CVD risk factors are present in the pediatric patient

Prevention of cardiovascular disease

Prevention of cardiovascular and/or cerebrovascular events such as MI or stroke: as an adjunct to correction of other risk factors such as hypertension in patients with three or more additional risk factors or diabetes with one additional risk factor.

In patients with clinically evident coronary heart disease, LIPITOR is indicated to:
Reduce the risk of non-fatal myocardial infarction
Reduce the risk of fatal and non-fatal stroke
Reduce the risk for revascularization procedures
Reduce the risk of hospitalization for CHF
Reduce the risk of angina

3 DOSAGE AND ADMINISTRATION

General - Before instituting therapy with LIPITOR, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise and weight reduction in obese patients, and to treat underlying medical problems. The patient should continue on a standard cholesterol lowering diet during treatment with LIPITOR. (see National Cholesterol Education Program (NCEP) Guidelines, summarized in Table 1).
The usual starting dose is 10 mg or 20 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.

TABLE 1. NCEP Treatment Guidelines: LDL-C Goals and Cutpoints 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 (e.g., 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 (<4.5 mmol/L), 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 (<4.5 mmol/L) this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation.

LIPITOR has not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons (Fredrickson Types I and V).

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. A therapeutic response is evident within two weeks, and the maximum response is usually achieved within four weeks. The response is maintained during chronic therapy.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 treatments 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%).

Severe dyslipidemias in Pediatric Patients -
Experience in pediatrics is limited to a small number of patients (age 4-17 years) with severe dyslipidemias, such as familial hypercholesterolemia. The recommended starting dose in this population is 10 mg of LIPITOR per day. The dose may be increased to 80 mg daily, according to the response and tolerability. Doses should be individualized according to the recommended goal of therapy (see **section 2 Therapeutic indications, and section 9.4 Pediatric Use**).
Adjustments should be made at intervals of 4 weeks or more.

Prevention of cardiovascular or cerebrovascular events
In the primary prevention trials the dose was 10 mg/day. Higher dosages may be necessary in order to attain (LDL-) cholesterol levels according to current guidelines.

Use in Patients with Hepatic Insufficiency
(See sections 5 Contraindications and 6 Warnings and Precautions)

Dosage in Patients with Renal Insufficiency
Renal disease has no influence on the plasma concentrations or on the LDL-C reduction with LIPITOR ; thus, no adjustment of dose is required. (see **section 6 Warnings and Precautions**).

Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors
In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the hepatitis C protease inhibitor (telaprevir), therapy with LIPITOR should be avoided. In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing LIPITOR and the lowest dose necessary employed. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, therapy with LIPITOR should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of LIPITOR is employed.In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, therapy with LIPITOR should be limited to 40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of LIPITOR is employed (see section **6.1 Warnings and Precaution -Myopathy and Rhabdomyolysis and section 8 Drug Interactions).**

Use in Elderly
Efficacy and safety in patients older than 70 using recommended doses is similar to that seen in the general population. (see section**9.5 Use in Specific Populations- Geriatric Use).**

4 DOSAGE FORMS AND STRENGTHS

LIPITOR tablets are white round, film-coated, and are available in four strengths (see Table 1).

Table 1: LIPITOR Tablet Strengths and Identifying Features

Tablet Strength	Identifying Features
10 mg of atorvastatin	"10" on one side and "ATV" on the other
20 mg of atorvastatin	"20" on one side and "ATV" on the other.
40 mg of atorvastatin	"40" on one side and "ATV" on the other
80 mg of atorvastatin	"80" on one side and "ATV" on the other

5 CONTRAINDICATIONS

- Acute liver failure or decompensated cirrhosis *[see Warnings and Precautions (6.3)]*
- Hypersensitivity to atorvastatin or any excipients in LIPITOR. Hypersensitivity reactions, including anaphylaxis, angioneurotic edema, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported *[see Adverse Reactions (7)]*.
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6 WARNINGS AND PRECAUTIONS

6.1 Myopathy and Rhabdomyolysis

LIPITOR may cause myopathy (muscle pain, tenderness, or weakness associated with elevated creatine kinase [CK] and rhabdomyolysis . Acute kidney injury secondary to myoglobinuria and rare fatalities have occurred as a result of rhabdomyolysis in patients treated with statins, including LIPITOR.

Risk Factors for Myopathy
Risk factors for myopathy include age 65 years or greater, uncontrolled hypothyroidism, renal impairment, concomitant use with certain other drugs (including other lipid-lowering therapies), and higher LIPITOR dosage *[see Drug Interactions (8) and Use in Specific Populations (9.5, 9.6)]*.

Steps to Prevent or Reduce the Risk of Myopathy and Rhabdomyolysis

LIPITOR exposure may be increased by drug interactions due to inhibition of cytochrome P450 enzyme 3A4 (CYP3A4) and/or transporters (e.g., breast cancer resistant protein [BCRP], organic anion-transporting polypeptide [OATP1B1/OATP1B3] and P-glycoprotein [P-gp]), resulting in an increased risk of myopathy and rhabdomyolysis. Concomitant use of cyclosporine, gemfibrozil, tipranavir plus ritonavir, or glecaprevir plus pibrentasvir with LIPITOR is not recommended. LIPITOR dosage modifications are recommended for patients taking certain anti-viral, azole antifungals, or macrolide antibiotic medications *[see Dosage and Administration (3)]*. Cases of myopathy/rhabdomyolysis have been reported with atorvastatin co administered with lipid modifying doses (>1 gram/day) of niacin, fibrates, colchicine, and ledipasvir plus sofosbuvir. Consider if the benefit of use of these products outweighs the increased risk of myopathy and rhabdomyolysis *[see Drug Interactions (8.1)]*.

Concomitant intake of large quantities, more than 1.2 liters daily, of grapefruit juice is not recommended in patients taking LIPITOR *[see Drug Interactions (8.1)]*.

Discontinue LIPITOR if markedly elevated CK levels occur or if myopathy is either diagnosed or suspected. Muscle symptoms and CK elevations may resolve if LIPITOR is discontinued. Temporarily discontinue LIPITOR in patients experiencing an acute or serious condition at high risk of developing renal failure secondary to rhabdomyolysis (e.g., sepsis; shock; severe hypovolemia; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy).

Inform patients of the risk of myopathy and rhabdomyolysis when starting or increasing the LIPITOR dosage. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

6.2 Immune-Mediated Necrotizing Myopathy

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use, including reports of recurrence when the same or a different statin was administered.. IMNM is characterized by proximal muscle weakness and elevated serum creatine kinase, that persists despite discontinuation of statin treatment; positive anti-HMG CoA reductase antibody; muscle biopsy showing necrotizing myopathy; and improvement with immunosuppressive agents. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required. Discontinue LIPITOR if IMNM is suspected

6.3 Hepatic Dysfunction

Increases in serum transaminases have been reported with use of Lipitor *[see Adverse Reactions (7.1)]*. In most cases, these changes appeared soon after initiation, were transient, were not accompanied by symptoms, and resolved or improved on continued therapy or after a brief interruption in therapy. Persistent increases to more than three times the ULN in serum transaminases have occurred in approximately 0.7% of patients receiving LIPITOR in clinical trials.

There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including LIPITOR.

Patients who consume substantial quantities of alcohol and/or have a history of liver disease may be at increased risk for hepatic injury *[see Use in Specific Populations (9.7)]*.

Consider liver enzyme testing before LIPITOR initiation and when clinically indicated thereafter. LIPITOR is contraindicated in patients with acute liver failure or decompensated cirrhosis *[see Contraindications (5)]*. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue LIPITOR.

6.4 Increases in HbA1c and Fasting Serum Glucose Levels

Increases in HbA1c and fasting serum glucose levels have been reported with statins, including LIPITOR. Optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices.

6.5 Myasthenia Gravis and Ocular Myasthenia

In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia (see section 7). Atorvastatin should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

6.6 Increased Risk of Hemorrhagic Stroke in Patients on LIPITOR 80 mg with Recent Hemorrhagic Stroke

In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial where 2365 adult patiens without CHD who had a stroke or TIA within the preceding 6 months, were treated with LIPITOR 80 mg, a higher incidence of hemorrhagic stroke was seen in the LIPITOR 80 mg group compared to placebo (55, 2.3% Lipitor vs. 33, 1.4% placebo; HR: 1.68, 95% CI: 1.09, 2.59; p=0.0168). The incidence of fatal hemorrhagic stroke was similar across treatment groups (17 vs. 18 for the atorvastatin and placebo groups, respectively). The incidence of non-fatal hemorrhagic stroke was significantly higher in the Lipitor group (38, 1.6%) as compared to the placebo group (16, 0.7%). Some baseline characteristics, including hemorrhagic and lacunar stroke on study entry, were associated with a higher incidence of hemorrhagic stroke in the Lipitor group *[see Adverse Reactions (7.1)]*. Consider the risk/benefit of use of LIPITOR 80 mg in patients with recent hemorrhagic stroke.

7 ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:
Myopathy and Rhabdomyolysis *[see Warnings and Precautions (6.1)]*
Immune-Mediated Necrotizing Myopathy *[see Warnings and Precautions (6.2)]*
Hepatic Dysfunction *[see Warnings and Precautions (6.3)]*
Increases in HbA1c and Fasting Serum Glucose Levels *[see Warnings and Precautions (6.4*)]

7.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the LIPITOR placebo-controlled clinical trial database of 16,066 patients (8755 LIPITOR vs. 7311 placebo; age range 10-93 years, 39% women, 91% White, 3% Black, 2% Asian, 4% other) with a median treatment duration of 53 weeks, the most common adverse reactions in patients treated with LIPITOR that led to treatment discontinuation and occurred at a rate greater than placebo were: myalgia (0.7%), diarrhea (0.5%), nausea (0.4%), alanine aminotransferase increase (0.4%), and hepatic enzyme increase (0.4%).

Table 2 summarizes adverse reactions reported in ≥ 2% and at a rate greater than placebo in patients treated with LIPITOR (n=8755), from seventeen placebo-controlled trials.

Table 2. Adverse Reactions Occurring in ≥ 2% in Patients LIPITOR-Treated with any Dose and Greater than Placebo

Adverse Reaction	**% Placebo N=7311**	**% 10 mg N=3908**	**% 20 mg N=188**	**% 40 mg N=604**	**% 80 mg N=4055**	**% Any dose N=8755**
Nasopharyngitis	8.2	12.9	5.3	7.0	4.2	8.3
Arthralgia	6.5	8.9	11.7	10.6	4.3	6.9
Diarrhea	6.3	7.3	6.4	14.1	5.2	6.8
Pain in extremity	5.9	8.5	3.7	9.3	3.1	6.0
Urinary tract infection	5.6	6.9	6.4	8.0	4.1	5.7
Dyspepsia	4.3	5.9	3.2	6.0	3.3	4.7
Nausea	3.5	3.7	3.7	7.1	3.8	4.0
Musculoskeletal pain	3.6	5.2	3.2	5.1	2.3	3.8
Muscle Spasms	3.0	4.6	4.8	5.1	2.4	3.6
Myalgia	3.1	3.6	5.9	8.4	2.7	3.5
Insomnia	2.9	2.8	1.1	5.3	2.8	3.0
Pharyngolaryngeal pain	2.1	3.9	1.6	2.8	0.7	2.3

Other adverse reactions reported in placebo-controlled trials include:
Body as a whole: malaise, pyrexia
Digestive system: abdominal discomfort, eructation, flatulence, hepatitis, cholestasis; *Musculoskeletal system*: musculoskeletal pain, muscle fatigue, neck pain, joint swelling, lupus like syndrom
Metabolic and nutritional system: transaminases increase, liver function test abnormal, blood alkaline phosphatase increase, creatine phosphokinase increase, hyperglycemia;

Nervous system: nightmare
Respiratory system: epistaxis;
Skin and appendages: urticaria;
Special senses: vision blurred, tinnitus,;
Urogenital system: white blood cells urine positive.

Elevations in Liver Enzyme Tests
Persistent elevations in serum transaminases, defined as more than 3 times the ULN and occurring on 2 or more occasions, occurred in 0.7% of patients who received LIPITOR in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.

One patient in clinical trials developed jaundice. Increases in liver enzyme tests in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent liver enzyme elevations continued treatment with a reduced dose of LIPITOR.

*Treating to New Targets Study (TNT)*In TNT *[see Clinical Studies (14.1)]* 10,001 patients (age range 29-78 years, 19% women; 94 % White, 3% Black,1%, Asian 2% other) with clinically evident CHD were treated with LIPITOR 10 mg daily (n=5006) or LIPITOR 80 mg daily (n=4995). In the high- dose LIPITOR group, there were more patients with serious adverse reactions (1.8%) and discontinuations due to adverse reactions i9.9%) as compared to the low-dose group (1.4%; 8.1%, respectively) during a median follow-up of 4.9 years. Persistent transaminase elevations (≥3 x ULN twice within 4-10 days) occurred in 1.3 individuals with Lipitor 80 mg and in (0.2% of individuals with Lipitor 10 mg. Elevations of CK (≥ 10 x ULN) were higher in the high-dose Lipitor group (0.3%) compared to the low-dose Lipitor group (0.1%).

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)
In SPARCL,4731 patients (age range 21–92 years, 40% women; 93% White, 3% Black, 1% Asian, 3% other) without clinically evident CHD but with a stroke or transient ischemic attack (TIA) within the previous 6 months were treated with LIPITOR 80 mg (n=2365) or placebo (n=2366) for a median follow-up of 4.9 years.,There was a higher incidence of persistent hepatic transaminase elevations (≥ 3 x ULN twice within 4-10 days) in the Lipitor group (0.9%) compared to placebo (0.1%). Elevations of CK (>10 x ULN) were rare, but were higher in the Lipitor group (0.1%) compared to placebo (0.0%). Diabetes was reported as an adverse reaction in 6.1% of subjects in the Lipitor group and 3.8% of subjects in the placebo.

In a post-hoc analysis, LIPITOR 80 mg reduced the incidence of ischemic stroke (9.2% vs. 11.6%) and increased the incidence of hemorrhagic stroke (2.3% vs. 1.4%) compared to placebo. The incidence of fatal hemorrhagic stroke was similar between groups (17 LIPITOR vs. 18 placebo). The incidence of non-fatal hemorrhagic strokes was significantly greater in the Lipitor group (38 non- fatal hemorrhagic strokes) as compared to the placebo group (16 non-fatal hemorrhagic strokes). Patients who entered the trial with a hemorrhagic stroke appeared to be at increased risk for hemorrhagic stroke (16% LIPITOR vs. 4% placebo)..

Adverse Reactions from Clinical Studies of LIPITOR in Pediatric Patients with HeFH
In a 26-week controlled study in pediatric patients with HeFH (ages 10 years to 17 years) (n=140, 31% female; 92% White, 1.6% Blacks, 1.6% Asians, 4.8% other), the safety and tolerability profile of LIPITOR 10 to 20 mg daily, as an adjunct to diet to reduce total cholesterol, LDL-C, and apo B levels, was generally similar to that of placebo *[see Use in Specific Populations (9.4) and Clinical Studies (14.6)]*.

7.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of LIPITOR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal disorders: pancreatitis
General disorders: fatigue

Hepatobiliary Disorders: fatal and non-fatal hepatic failure
Immune system disorders: anaphylaxis
Injury: tendon rupture
Musculoskeletal and connective tissue disorders: rhabdomyolysis, myositis.
There have been rare reports of immune-mediated necrotizing myopathy associated with statin use
Eye disorders: ocular myasthenia
Nervous System Disorders: dizziness, peripheral neuropathy, myasthenia gravis
There have been rare reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with the use. of all statins. Cognitive impairment was generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).
There have been rare reports of new onset or exacerbation of myasthenia gravis, including ocular myasthenia, and reports of recurrence when the same or a different statin was administered
Psychiatric disorders: depression
Respiratory disorders: interstitial lung disease
Skin and subcutaneous tissue disorders: angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

8 DRUG INTERACTIONS

8.1 Drug Interactions that may Increase the Risk of Myopathy and Rhabdomyolysis with LIPITOR

LIPITOR is a substrate of CYP3A4 and transporters (e.g., OATP1B1/1B3, P-gp, or BCRP). LIPITOR plasma levels can be significantly increased with concomitant administration of inhibitors of CYP3A4 and transporters. Table 3 includes a list of drugs that may increase exposure to Lipitor and may increase the risk of myopathy and rhabdomyolysis when used concomitantly and instructions for preventing or managing them *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

Table 3: Drug Interactions that may Increase the Risk of Myopathy and Rhabdomyolysis with LIPITOR

Cyclosporine or Gemfibrozil	
Clinical Impact:	Atorvastatin plasma levels were significantly increased with concomitant administration of LIPITOR and cyclosporine, an inhibitor of CYP3A4 and OATP1B1 *[see Clinical Pharmacology (12.3)]*. Gemfibrozil may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of cyclosporine or gemfibrozil with LIPITOR.
Intervention:	Concomitant use of cyclosporine or gemfibrozil with LIPITOR is not recommended.
Anti-Viral Medications	
Clinical Impact:	Atorvastatin plasma levels were significantly increased with concomitant administration of LIPITOR with many anti-viral medications, which are inhibitors of CYP3A4 and/or transporters (e.g., BCRP, OATP1B1/1B3, P-gp, MRP2, and/or OAT2) *[see Clinical Pharmacology (12.3)]*. Cases of myopathy and rhabdomyolysis have been reported with concomitant use of ledipasvir plus sofosbuvir with LIPITOR.
Intervention:	• Concomitant use of tipranavir plus ritonavir or glecaprevir plus pibrentasvir with LIPITOR is not recommended. • In patients taking lopinavir plus ritonavir, or simeprevir, consider the risk/benefit of concomitant use with atorvastatin.

	• In patients taking saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, elbasvir plus grazoprevir or letermovir, do not exceed LIPITOR 20 mg. • In patients taking nelfinavir, do not exceed LIPITOR 40 mg *[see Dosage and Administration (3)]*. • Consider the risk/benefit of concomitant use of ledipasvir plus sofosbuvir with LIPITOR. • Monitor all patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Examples:	Tipranavir plus ritonavir, glecaprevir plus pibrentasvir, lopinavir plus ritonavir, simeprevir, saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, elbasvir plus grazoprevir, letermovir, nelfinavir, and ledipasvir plus sofosbuvir.
Select Azole Antifungals or Macrolide Antibiotics	
Clinical Impact:	Atorvastatin plasma levels were significantly increased with concomitant administration of LIPITOR with select azole antifungals or macrolide antibiotics, due to inhibition of CYP3A4 and/or transporters *[see Clinical Pharmacology (12.3)]*.
Intervention:	In patients taking clarithromycin or itraconazole, do not exceed LIPITOR 20 mg *[see Dosage and Administration (3)]*. Consider the risk/benefit of concomitant use of other azole antifungals or macrolide antibiotics with LIPITOR. Monitor all patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Examples:	Erythromycin, clarithromycin, itraconazole, ketoconazole, posaconazole, and voriconazole.
Niacin	
Clinical Impact:	Cases of myopathy and rhabdomyolysis have been observed with concomitant use of lipid modifying dosages of niacin (≥1 gram/day niacin) with LIPITOR.
Intervention:	Consider if the benefit of using lipid modifying dosages of niacin concomitantly with LIPITOR outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Fibrates (other than Gemfibrozil)	
Clinical Impact:	Fibrates may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of fibrates with LIPITOR.
Intervention:	Consider if the benefit of using fibrates concomitantly with LIPITOR outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Colchicine	
Clinical Impact:	Cases of myopathy and rhabdomyolysis have been reported with concomitant use of colchicine with LIPITOR.
Intervention:	Consider the risk/benefit of concomitant use of colchicine with LIPITOR. If concomitant use is decided, monitor patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Grapefruit Juice	
Clinical Impact:	Grapefruit juice consumption, especially excessive consumption, more than 1.2 liters/daily, can raise the plasma levels of atorvastatin and may increase the risk of myopathy and rhabdomyolysis.
Intervention:	Avoid intake of large quantities of grapefruit juice, more than 1.2 liters daily, when taking LIPITOR.

8.2 Drug Interactions that may Decrease Exposure to LIPITOR

Table 4 presents drug interactions that may decrease exposure to LIPITOR and instructions for preventing or managing them.

Table 4: Drug Interactions that may Decrease Exposure to LIPITOR

Rifampin	
Clinical Impact:	Concomitant administration of LIPITOR with rifampin, an inducer of cytochrome P450 3A4 and inhibitor of OATP1B1, can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, delayed administration of LIPITOR after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

Intervention:	Administer LIPITOR and rifampin simultaneously.

8.3 LIPITOR Effects on Other Drugs

Table 5 presents LIPITOR's effect on other drugs and instructions for preventing or managing them.

Table 5: LIPITOR Effects on Other Drugs

Oral Contraceptives	
Clinical Impact:	Co-administration of LIPITOR and an oral contraceptive increased plasma concentrations of norethindrone and ethinyl estradiol *[see Clinical Pharmacology (12.3)]*.
Intervention:	Consider this when selecting an oral contraceptive for patients taking LIPITOR.
Digoxin	
Clinical Impact:	When multiple doses of LIPITOR and digoxin were co-administered, steady state plasma digoxin concentrations increased *[see Clinical Pharmacology (12.3)]*.
Intervention:	Monitor patients taking digoxin appropriately.

9 USE IN SPECIFIC POPULATIONS

9.1 Pregnancy

Risk Summary
Discontinue LIPITOR when pregnancy is recognized. Alternatively, consider the ongoing therapeutic needs of the individual patient. LIPITOR decreases synthesis of cholesterol and possibly other biologically active substances derived from cholesterol ; therefore, LIPITOR may cause fetal harm when administered to pregnant patients based on the mechanism of action *[see Clinical Pharmacology (12.1)]*. In addition, treatment of hyperlipidemia is not generally necessary during pregnancy. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hyperlipidemia for most patients.

Available data from case series and prospective and retrospective observational cohort studies over decades of use with statins in pregnant women have not identified a drug-associated risk of major congenital malformations . Published data from prospective and retrospective observational cohort studies with LIPITOR use in pregnant women are insufficient to determine if there is a drug- associated risk of miscarriage (see Data). In animal reproduction studies , no adverse developmental effects were observed in pregnant rats or rabbits orally administered atorvastatin at doses that resulted in 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/m^2). In rats administered atorvastatin during gestation and lactation, decreased postnatal growth and development delay were observed at doses ≥ 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
A Medicaid cohort linkage study of 1152 statin-exposed pregnant women compared to 886,996 controls did not find a significant teratogenic effect from maternal use of statins in the first trimester of pregnancy, after adjusting for potential confounders – including maternal age, diabetes mellitus, hypertension, obesity, and alcohol and tobacco use – using propensity score-based methods. The relative risk of congenital malformations between the group with statin use and the group with no statin use in the first trimester was
1.07 (95% confidence interval 0.85 to 1.37) after controlling for confounders, particularly pre-existing diabetes mellitus. There were also no statistically significant increases in any of the organ-specific malformations assessed after accounting for confounders. In the majority pregnancies, statin treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. Study limitations include reliance on physician coding to define the presence

of a malformation, lack of control for certain confounders such as body mass index, use of prescription dispensing as verification for the use of a statin, and lack of information on non-live births.

Animal Data
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/m^2). 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.
Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma.

9.2 Lactation

Risk Summary

There is no information about the presence of atorvastatin in human milk, the effects of the drug on the breastfed infant or the effects of the drug on milk production. However, it has been shown that another drug in this class passes into human milk . Studies in rats have shown that atorvastatin and/or its metabolites are present in the breast milk of lactating rats. When a drug is present in. animal milk, it is likely that the drug will be present in human milk *(see Data)*. Statins, including LIPITOR, decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol and may cause harm to the breastfed infant. Because of the potential for serious adverse reactions in a breastfed infant, based on the mechanism of action,advise patients that breastfeeding is not recommended during treatment with LIPITOR. *[see Use in Specific Populations (9.1), Clinical Pharmacology (12.1)]*.

Data
Following a single oral administration of 10 mg/kg of radioactive atorvastatin to lactating rats, the concentration of total radioactivity was determined. Atorvastatin and/or its metabolites were measured in the breast milk and pup plasma at a 2:1 ratio (milk:plasma).

9.4 Pediatric Use

The safety and effectiveness of LIPITOR as an adjunct to diet to reduce LDL-C

have been established pediatric patients 10 years of age and older with HeFH. Use of LIPITOR for this indication is based on a double-blind,

placebo-controlled clinical trial in 187 pediatric patients 10 years of age and older with HeFH. In this limited controlled trial, there was no significant effect on growth or sexual maturation in the boys or girls, or on menstrual cycle length in girls.
The safety and effectiveness of LIPITOR as an adjunct to other LDL-C-lowering

therapies to reduce LDL-C have been established pediatric patients 10 years of age and older with HoFH. Use of LIPITOR for this indication is based on a trial without a concurrent control group in 8 pediatric patients 10 years of age and older with HoFH *[see Clinical Studies (14)]*.

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The safety and effectiveness of LIPITOR have not been established in pediatric patients younger than 10 years of age with HeFH or HoFH, or in pediatric patients with other types of hyperlipidemia (other than HeFH or HoFH).
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9.5 Geriatric Use

Of the total number of LIPITOR-treated patients in clinical trials, 15,813 (40%) were ≥65 years old and 2,800 (7%) were ≥75 years old.
No overall differences in safety or effectiveness were observed between these patients and younger patients.
Advanced age (≥65 years) is a risk factor for Lipitor-assocoayed myopathy and rhabdomyolysis. Dose selection for an elderly patient should be cautious, recognizing the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of myopathy. Monitor geriatric patients receiving LIPITOR for the increased risk of myopathy *[see Warnings and Precautions (6.1) and Clinical Pharmacology (12.3)]*.

9.6 Renal Impairment

Renal impairment is a risk factor for myopathy and rhabdomyolysis. Monitor all patients with renal impairment for development of myopathy. Renal impairment does not affect the plasma concentrations of LIPITOR, therefore there is no dosage adjustment in patients with renal impairment *[see Warnings and Precautions (6.1) and Clinical Pharmacology (12.3)].*

9.7 Hepatic Impairment

In patients with chronic alcoholic liver disease, plasma concentrations of LIPITOR are markedly increased. Cmax and AUC are each 4-fold greater in patients with Childs-Pugh A disease. Cmax and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease. Lipitor is contraindicated in patients with acute liver failure or decompensated cirrhosis *[see Contraindications (5)]*.

10 OVERDOSAGE

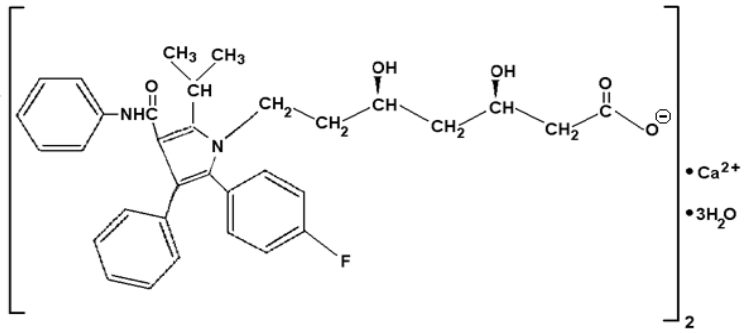
No specific antidotes for LIPITOR are known. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance LIPITOR clearance.

11 DESCRIPTION

LIPITOR (atorvastatin) is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase.

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, 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 $(C_{33}H_{34}FN_2O_5)_2Ca•3H_2O$ 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 use contain 10 mg, 20 mg , 40 mg, or 80 mg of atorvastatin and the following inactive ingredients: calcium carbonate, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, polysorbate 80Opadry White YS-1-7040 (hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, talc);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 (3)]*.

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 Cmax and AUC, LDL-C reduction is similar whether LIPITOR is given with or without food. Plasma LIPITOR concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration .

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.

Elimination

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 (8.1)]*. 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 Cmax and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults.

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 Cmax 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 *[see Use in Specific Populations (9.6)]*.

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. Cmax and AUC are each 4-fold greater in patients with Childs-Pugh A disease. Cmax and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease *[see Use in Specific Populations (9.7)]*.

Drug Interaction

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 6. Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	**Ratio of AUC[&]**	**Ratio of Cmax[&]**
[#]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
[#]Letermovir 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 Cmax (ratio of Cmax 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 7. 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

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

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

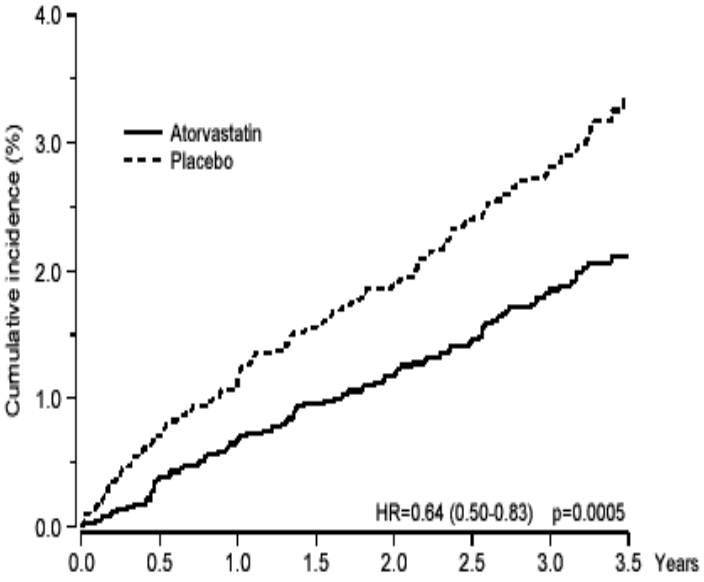
14.1 Prevention of Cardiovascular Disease

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 patients with hypertension, 40-80 years of age (mean of 63 years; 19% women; 95% White, 3% Black, 1% South Asian, 1% other), without a previous myocardial infarction and with total cholesterol (TC) levels ≤251 mg/dL. Additionally, all patients had at least 3 of the following cardiovascular risk factors: male gender (81.%), age >55 years (85%), smoking (33%), diabetes (24%), history of CHD in a first-degree relative (26%), TC:HDL >6 (14%), peripheral vascular disease (5%), left ventricular hypertrophy (14%), prior cerebrovascular event (10%), specific ECG abnormality (14%), proteinuria/albuminuria (62%). In this double-blind, placebo-controlled trial, patients were treated with anti-hypertensive therapy (goal BP <140/90 mm Hg for patients without diabetes; <130/80 mm Hg for patients with diabetes) 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.

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, 2% Black, 2% South Asian, 1% other;, 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 triglycerides (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 trial. 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.

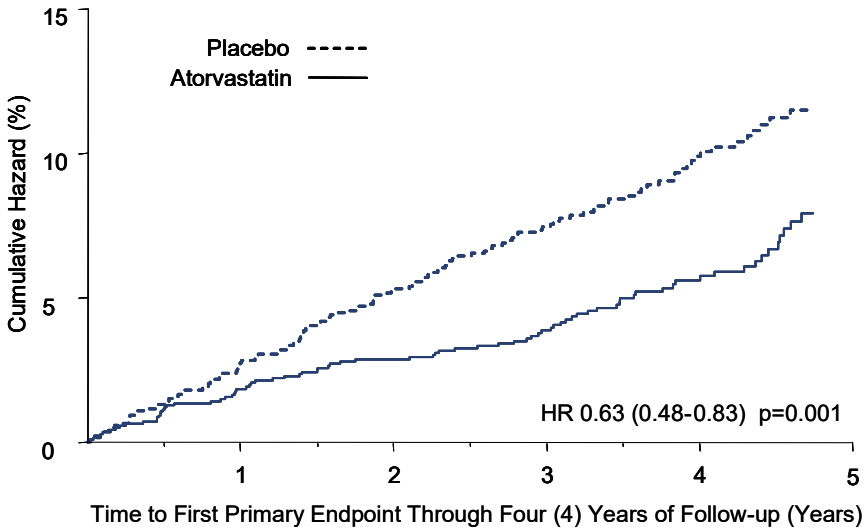
The effect of LIPITOR 10 mg/day on lipid levels was similar to that seen in previous clinical trials.

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 sex.

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

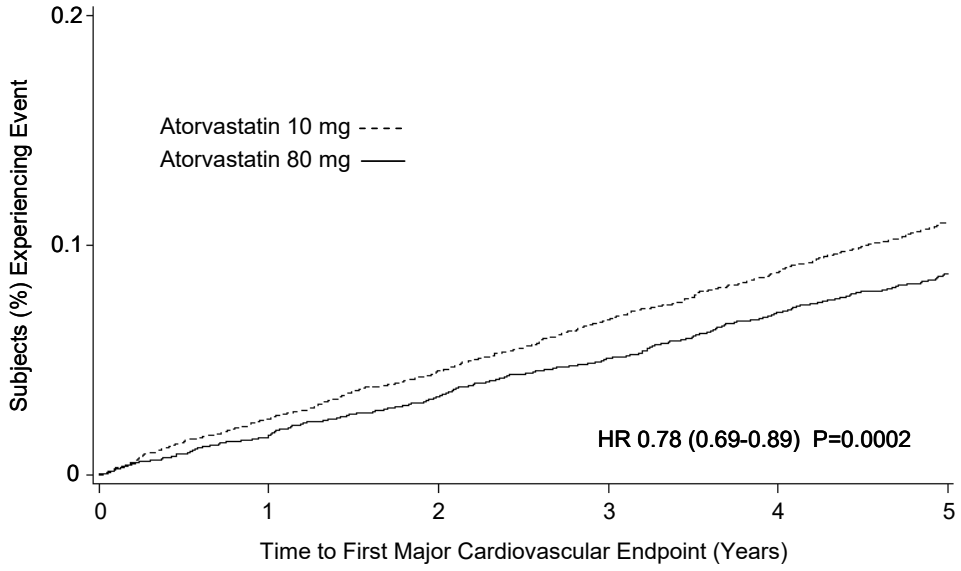


TABLE 8. Overview of Efficacy Results in TNT

Endpoint	Atorvastatin 10 mg (N=5006)		Atorvastatin 80 mg (N=4995)		HR[a] (95%CI)
PRIMARY ENDPOINT	n	(%)	n	(%)	
First major cardiovascular endpoint	548	(10.9)	434	(8.7)	0.78 (0.69, 0.89)
Components of the Primary Endpoint					
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 other traumatic 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 8). 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.

14.2 Primary Hyperlipidemia in Adults

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

In two multicenter, placebo-controlled, dose-response trials 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 9.)

TABLE 9. Dose Response in Patients with Primary Hyperlipidemia (Adjusted Mean % Change From Baseline)[a]

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

[a] Results are pooled from 2 dose-response

In three multicenter, double-blind trials 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 10).

TABLE 10. 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	
Trial 1							
LIPITOR 10 mg	707	-27[a]	-36[a]	-28[a]	-17[a]	+7	
Lovastatin 20 mg	191	-19	-27	-20	-6	+7	
95% CI for Diff[l]		-9.2, -6.5	-10.7, -7.1	-10.0, -6.5	-15.2, -7.1	-1.7, 2.0	
Trial 2							
LIPITOR 10 mg	222	-25[b]	-35[b]	-27[b]	-17[b]	+6	
Pravastatin 20 mg	77	-17	-23	-17	-9	+8	
95% CI for Diff[l]		-10.8, -6.1	-14.5, -8.2	-13.4, -7.4	-14.1, -0.7	-4.9, 1.6	
Trial 3							
LIPITOR 10 mg	132	-29[c]	-37[c]	-34[c]	-23[c]	+7	
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	
95% CI for Diff[l]		-8.7, -2.7	-10.1, -2.6	-8.0, -1.1	-15.1, -0.7	-4.3, 3.9	

[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, $p \leq 0.05$

Table 10 does not contain data comparing the effects of LIPITOR 10 mg and higher doses of lovastatin, pravastatin, and simvastatin. The drugs compared in the trials summarized in the table are not necessarily interchangeable.

14.3 Hypertriglyceridemia in Adults

The response to LIPITOR in 64 patients with isolated hypertriglyceridemia treated across several clinical trials is shown in the table below (Table 11). For the LIPITOR-treated patients, median (min, max) baseline TG level was 565 (267-1502).

TABLE 11. 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)
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 in Adults

The results of an open-label crossover trial of 16 patients (genotypes: 14 apo E2/E2 and 2 apo E3/E2) with dysbetalipoproteinemia are shown in the table below (Table 12).

TABLE 12. Open-Label Crossover Trial of 16 Patients with Dysbetalipoproteinemia (*Fredrickson* Type III)

		Median % Change (min, max)	
	Median (min, max) at Baseline (mg/dL)	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)

HoFH in Adults and Pediatric Patients

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 HePh in Pediatric Patients

In a double-blind, placebo-controlled trial followed by an open-label phase, 187 boys and post-menarchal girls 10 years to 17 years of age (mean age 14.1 yearss; 31% female; 92% White, 1.6% Blacks, 1.6% Asians, 4.8% other) 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 trial required 1) a baseline LDL-C level ≥ 190 mg/dL or 2) a baseline LDL-C level ≥ 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 219 mg/dL (range: 139–385 mg/dL) in the LIPITOR group compared to 230 mg/dL (range: 160–325 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 (56%).

LIPITOR significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26-week double-blind phase (see Table 13).

TABLE 13. 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 White, 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 trials in both adult and pediatric placebo-controlled trials.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

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

Blister packs containing 10, 30, 50, and 100 film-coated tablets.

Not all pack sizes may be marketed.

Storage
Store below 25°C
Shelf life
The expiry date of the product is indicated on the packaging materials

License Holder
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