**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use LIPITOR safely and effectively. See full prescribing information for LIPITOR.**

**LIPITOR® (atorvastatin calcium) film-coated tablets, for oral use**

**----------RECENT MAJOR CHANGES----------**

| | |
|---|---|
| Contraindications, Pregnancy and Lactation (4) | Removed 12/2022 |
| Warnings and Precautions, CNS Toxicity (5.5) | Removed 12/2022 |

**----------INDICATIONS AND USAGE----------**

LIPITOR is an HMG-CoA reductase inhibitor (statin) indicated (1):

- To reduce the risk of:
  - Myocardial infarction (MI), stroke, revascularization procedures, and angina in adults with multiple risk factors for coronary heart disease (CHD) but without clinically evident CHD.
  - MI and stroke in adults with type 2 diabetes mellitus with multiple risk factors for CHD but without clinically evident CHD.
  - Non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for congestive heart failure, and angina in adults with clinically evident CHD.
- As an adjunct to diet to reduce low-density lipoprotein (LDL-C) in:
  - Adults with primary hyperlipidemia.
  - Adults and pediatric patients aged 10 years and older with heterozygous familial hypercholesterolemia (HeFH).
- As an adjunct to other LDL-C-lowering therapies to reduce LDL-C in adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia.
- As an adjunct to diet for the treatment of adults with:
  - Primary dysbetaliproteinemia.
  - Hypertriglyceridemia.

**----------DOSAGE AND ADMINISTRATION----------**

- Take orally once daily with or without food (2.1).
- Assess LDL-C when clinically appropriate, as early as 4 weeks after initiating LIPITOR, and adjust dosage if necessary (2.1).
- *Adults* (2.2):
  - Recommended starting dosage is 10 or 20 mg once daily; dosage range is 10 mg to 80 mg once daily.
  - Patients requiring LDL-C reduction >45% may start at 40 mg once daily.
- *Pediatric Patients Aged 10 Years of Age and Older with HeFH*: Recommended starting dosage is 10 mg once daily; dosage range is 10 to 20 mg once daily (2.3).
- *Pediatric Patients Aged 10 Years of Age and Older with HoFH*: Recommended starting dosage is 10 to 20 mg once daily; dosage range is 10 to 80 mg once daily (2.4).
- See full prescribing information for LIPITOR dosage modifications due to drug interactions (2.5).

**----------DOSAGE FORMS AND STRENGTHS----------**

Film-Coated Tablets: 10; 20; 40; 80 mg of atorvastatin (3).

**----------CONTRAINDICATIONS----------**

- Acute liver failure or decompensated cirrhosis (4).
- Hypersensitivity to atorvastatin or any excipient in LIPITOR (4).

**----------WARNINGS AND PRECAUTIONS----------**

- *Myopathy and Rhabdomyolysis*: Risk factors include age 65 years or greater, uncontrolled hypothyroidism, renal impairment, concomitant use with certain other drugs, and higher LIPITOR dosage. Discontinue LIPITOR if markedly elevated CK levels occur or myopathy is diagnosed or suspected. Temporarily discontinue LIPITOR in patients experiencing an acute or serious condition at high risk of developing renal failure secondary to rhabdomyolysis. Inform patients of the risk of myopathy and rhabdomyolysis when starting or increasing LIPITOR dosage. Instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever (2.5, 5.1, 7.1, 8.5, 8.6).
- *Immune-Mediated Necrotizing Myopathy (IMNM):* Rare reports of IMNM, an autoimmune myopathy, have been reported with statin use. Discontinue LIPITOR if IMNM is suspected (5.2).
- *Hepatic Dysfunction:* Increases in serum transaminases have occurred, some persistent. Rare reports of fatal and non-fatal hepatic failure have occurred. Consider testing liver enzymes before initiating therapy and as clinically indicated thereafter. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue LIPITOR (5.3).

**----------ADVERSE REACTIONS----------**

Most common adverse reactions (incidence ≥5%) are nasopharyngitis, arthralgia, diarrhea, pain in extremity, and urinary tract infection (6.1).

**----------DRUG INTERACTIONS----------**

- See full prescribing information for details regarding concomitant use of LIPITOR with other drugs or grapefruit juice that increase the risk of myopathy and rhabdomyolysis (2.5, 7.1).
- *Rifampin*: May reduce atorvastatin plasma concentrations. Administer simultaneously with LIPITOR (7.2).
- *Oral Contraceptives:* May increase plasma levels of norethindrone and ethinyl estradiol; consider this effect when selecting an oral contraceptive (7.3).
- *Digoxin:* May increase digoxin plasma levels; monitor patients appropriately (7.3).

**----------USE IN SPECIFIC POPULATIONS----------**

- *Pregnancy:* May cause fetal harm. (8.1).
- *Lactation:* Breastfeeding not recommended during treatment with LIPITOR (8.2).

**See 17 for PATIENT COUNSELING INFORMATION and approved patient labeling.**

**Revised: 4/2024**

**FULL PRESCRIBING INFORMATION: CONTENTS***



*Sections or subsections omitted from the full prescribing information are not listed.

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**FULL PRESCRIBING INFORMATION**

## 1 INDICATIONS AND USAGE

LIPITOR is indicated:

- To reduce the risk of:
  - Myocardial infarction (MI), stroke, revascularization procedures, and angina in adults with multiple risk factors for coronary heart disease (CHD) but without clinically evident CHD
  - MI and stroke in adults with type 2 diabetes mellitus with multiple risk factors for CHD but without clinically evident CHD
  - Non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for congestive heart failure, and angina in adults with clinically evident CHD
- As an adjunct to diet to reduce low-density lipoprotein cholesterol (LDL-C) in:
  - Adults with primary hyperlipidemia.
  - Adults and pediatric patients aged 10 years and older with heterozygous familial hypercholesterolemia (HeFH).
- As an adjunct to other LDL-C-lowering therapies, or alone if such treatments are unavailable, to reduce LDL-C in adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia (HoFH).
- As an adjunct to diet for the treatment of adults with:
  - Primary dysbetalipoproteinemia
  - Hypertriglyceridemia

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Important Dosage Information

- Take Lipitor orally once daily at any time of the day, with or without food.
- Assess LDL-C when clinically appropriate, as early as 4 weeks after initiating LIPITOR, and adjust the dosage if necessary.
- If a dose is missed, advise patients not to take the missed dose and resume with the next scheduled dose.

### 2.2 Recommended Dosage in Adult Patients

The recommended starting dosage of LIPITOR is 10 mg to 20 mg once daily. The dosage range is 10 mg to 80 mg once daily. Patients who require reduction in LDL-C greater than 45% may be started at 40 mg once daily.

### 2.3 Recommended Dosage in Pediatric Patients 10 Years of Age and Older with HeFH

The recommended starting dosage of LIPITOR is 10 mg once daily. The dosage range is 10 mg to 20 mg once daily.

### 2.4 Recommended Dosage in Pediatric Patients 10 Years of Age and Older with HoFH

The recommended starting dosage of LIPITOR is 10 mg to 20 mg once daily. The dosage range is 10 mg to 80 mg once daily.

### 2.5 Dosage Modifications Due to Drug Interactions

Concomitant use of LIPITOR with the following drugs requires dosage modification of LIPITOR *[see Warnings and Precautions (5.1) and Drug Interactions (7.1)]*.

Anti-Viral Medications

- In patients taking saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, elbasvir plus grazoprevir or letermovir, do not exceed LIPITOR 20 mg once daily.
- In patients taking nelfinavir, do not exceed LIPITOR 40 mg once daily.

Select Azole Antifungals or Macrolide Antibiotics

- In patients taking clarithromycin or itraconazole, do not exceed LIPITOR 20 mg once daily.

For additional recommendations regarding concomitant use of LIPITOR with other anti-viral medications, azole antifungals or macrolide antibiotics, *see Drug Interactions (7.1).*

## 3 DOSAGE FORMS AND STRENGTHS

LIPITOR film-coated tablets:

**10 mg of atorvastatin**: white, elliptical, film-coated tablets with “VLE 155” on one side and “10” on the other

**20 mg of atorvastatin:** white, elliptical, film-coated tablets with "VLE 156" on one side and "20" on the other
**40 mg of atorvastatin:** white, elliptical, film-coated tablets with "VLE 157" on one side and "40" on the other
**80 mg of atorvastatin:** white, elliptical, film-coated tablets with "VLE 158" on one side and "80" on the other

## 4 CONTRAINDICATIONS

- Acute liver failure or decompensated cirrhosis *[see Warnings and Precautions (5.3)]*
- 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 (6.2)]*.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 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 (7.1) and Use in Specific Populations (8.5, 8.6)]*.

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 (2.5)]*. 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[see Adverse Reactions (6.1)]. Consider if the benefit of use of these products outweighs the increased risk of myopathy and rhabdomyolysis *[see Drug Interactions (7.1)]*.

Concomitant intake of large quantities, more than 1.2 liters daily, of grapefruit juice is not recommended in patients taking LIPITOR *[see Drug Interactions (7.1)]*.

Discontinue LIPITOR if markedly elevated CK levels occur or if myopathy is 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.

### 5.2 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.

### 5.3 Hepatic Dysfunction

Increases in serum transaminases have been reported with use of LIPITOR *[see Adverse Reactions (6.1)]*. 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 (8.7)]*.

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 (4)]*. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue LIPITOR.

### 5.4 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.

### 5.5 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 patients, 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 (6.1)]*. Consider the risk/benefit of use of LIPITOR 80 mg in patients with recent hemorrhagic stroke.

### 5.6 Excipients

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

## 6 ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Myopathy and Rhabdomyolysis *[see Warnings and Precautions (5.1)]*
- Immune-Mediated Necrotizing Myopathy [see Warnings and Precautions (5.2)]
- Hepatic Dysfunction *[see Warnings and Precautions (5.3)]*
- Increases in HbA1c and Fasting Serum Glucose Levels *[see Warnings and Precautions (5.4)]*

### 6.1 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% female, 91% White, 3% Black or African American, 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 1 summarizes adverse reactions reported in ≥ 2% and at a rate greater than placebo in patients treated with LIPITOR (n=8,755), from seventeen placebo-controlled trials.

**Table 1: Adverse Reactions Occurring in ≥ 2% in Patients LIPITOR-Treated with any Dose and Greater than Placebo**

| Adverse Reaction | %Placebo N=7,311 | %10 mg N=3,908 | %20 mg N=188 | %40 mg N=604 | %80 mg N=4,055 | % Any dose N=8,755 |
|---|---|---|---|---|---|---|
| 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
*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% female; 94% White, 3% Black or African American, 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 (9.9%) 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% of 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% female; 93% White, 3% Black or African American, 1% Asian, 3% other) without clinically evident CHD but with a stroke or transient ischemic attack (TIA) within the previous 6 months 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 group.

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% Black or African American, 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 Special Populations (8.4) and Clinical Studies (14.6)]*.

### 6.2 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.
*Nervous system disorders:* dizziness, peripheral neuropathy.
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)

## 7 DRUG INTERACTIONS

### 7.1 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 2 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 2: 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.<br>• In patients taking lopinavir plus ritonavir, or simeprevir, consider the risk/benefit of concomitant use with atorvastatin.<br>• In patients taking saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, elbasvir plus grazoprevir or letermovir, do not exceed LIPITOR 20 mg.<br>• In patients taking nelfinavir, do not exceed LIPITOR 40 mg *[see Dosage and Administration (2.5)]*.<br>• Consider the risk/benefit of concomitant use of ledipasvir plus sofosbuvir with LIPITOR.<br>• 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 (2.5)]*. 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 ($\geq$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. |

### 7.2 Drug Interactions that may Decrease Exposure to LIPITOR

Table 3 presents drug interactions that may decrease exposure to LIPITOR and instructions for preventing or managing them.

**Table 3: 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. |

### 7.3 LIPITOR Effects on Other Drugs

Table 4 presents LIPITOR's effect on other drugs and instructions for preventing or managing them.

**Table 4: 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. |

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 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 of 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.

**8.2 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 (8.1), 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).

**8.4 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 males or females, or on menstrual cycle length in females.

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)]*.

The safety and efficacy 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).

### 8.5 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-associated 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 (5.1) and Clinical Pharmacology (12.3)]*.

### 8.6 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 (5.1) and Clinical Pharmacology (12.3)]*.

### 8.7 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 (4)]*.

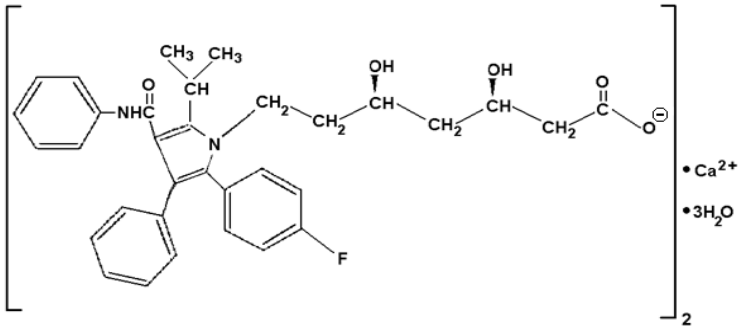
## 10 OVERDOSAGE

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 $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$ 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 Film-coated Tablets for oral administration contain 10, 20, 40, or 80 mg of atorvastatin
Lipitor 10 mg :Atorvastatin calcium trihydrate 10.85 mg equivalent to 10 mg atorvastatin
Lipitor 20 mg :Atorvastatin calcium trihydrate 21.69 mg equivalent to 20 mg atorvastatin
Lipitor 40 mg :Atorvastatin calcium trihydrate 43.38 mg equivalent to 40 mg atorvastatin
Lipitor 80 mg :Atorvastatin calcium trihydrate 86.76 mg equivalent to 80 mg atorvastatin

and the following inactive ingredients:
Calcium Carbonate, Microcrystalline cellulose, Lactose Monohydrate, Croscarmellose sodium, Polysorbate 80, Hydroxypropyl cellulose, Magnesium Stearate, Opadry White YS-1-7040, 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 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 (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 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 females differ from those in males (approximately 20% higher for Cmax and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with LIPITOR between males and females.

*Renal Impairment*
Renal disease has no influence on the plasma concentrations or LDL-C reduction of LIPITOR *[see Use in Specific Populations (8.6)]*.

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 (8.7)]*.

Drug Interactions

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 5: Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin**

| Co-administered drug and Dosage regimen | Atorvastatin | | |
|---|---|---|---|
| | dosage (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 dosage

[d] Three times daily

[e] Four times daily

[f] Every 8 hours

**TABLE 6: Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs**

| Atorvastatin | Co-administered drug and dosage regimen | | |
|---|---|---|---|
| | **Drug/dosage (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<br>- norethindrone 1 mg<br>- ethinyl estradiol 35□g | <br>1.28<br>1.19 | <br>1.23<br>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 dosage

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 2 years.

## 14 CLINICAL STUDIES

Prevention of Cardiovascular Disease

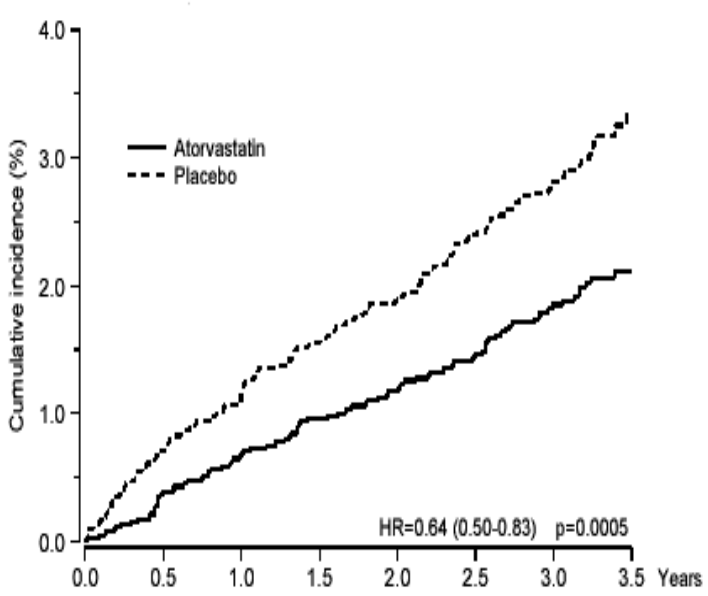
In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of LIPITOR on fatal and non-fatal coronary heart disease was assessed in 10,305 patients with hypertension, 40-80 years of age (mean of 63 years ; 19% female; 95% White, 3% Black or African American, 1% South Asian, 1% other), without 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 or African American, 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 HbA1c 7.7%; median LDL-C 120 mg/dL; median TC 207 mg/dL; median TG 151 mg/dL; median HDL-C 52 mg/dL.

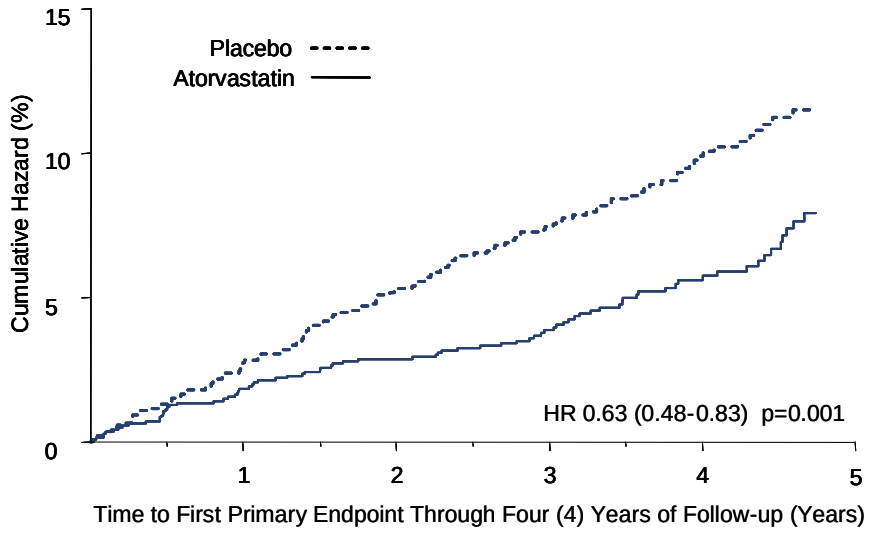
The effect of LIPITOR 10 mg/day on lipid levels was similar to that seen in previous clinical trials.

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 7). 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)**

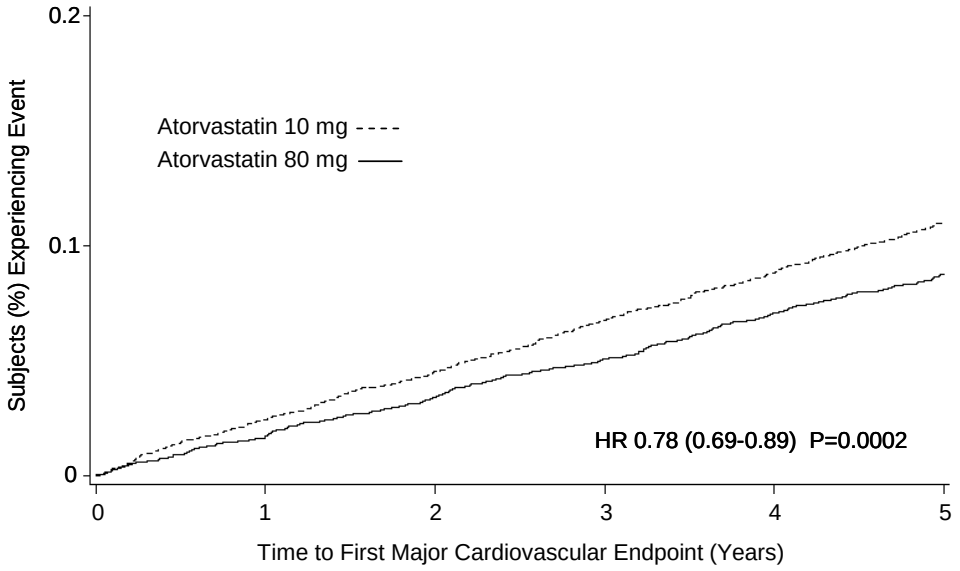



**TABLE 7: Overview of Efficacy Results in TNT**

| **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 othertraumatic non-CV death | 9 | (0.2) | 15 | (0.3) | 1.67 (0.73, 3.82) |

* 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
[a] Atorvastatin 80 mg: atorvastatin 10 mg
[b] Component of other secondary endpoints

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 7). 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 7). 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.

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 8.)

**TABLE 8: 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 trials.

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 9).

**TABLE 9: Mean Percentage Change From Baseline at Endpoint (Double-Blind, Randomized, Active-Controlled Trials)**

| Treatment (Daily Dosage) | 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[1] | | -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[1] | | -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[1] | | -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 9 does not contain data comparing the effects of LIPITOR 10 mg and higher dosages of lovastatin, pravastatin, and simvastatin. The drugs compared in the trials summarized in the table are not necessarily exchangeable.

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 10). For the LIPITOR-treated patients, median (min, max) baseline TG level was 565 (267-1502).

**TABLE 10: 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) |
|---|---|---|---|---|
| TG | -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) |

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 11).

**TABLE 11: Open-Label Crossover Trial of 16 Patients With Dysbetalipoproteinemia**

| | | 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) |
| TG | 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 trial without a concurrent control group, 29 patients (mean age of 22 years, median age of 24 years, 31% <18 years) with HoFH received maximum daily doses of 20 to 80 mg of LIPITOR. The mean LDL-C reduction in this trial 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%.

HeFH in Pediatric Patients

In a double-blind, placebo-controlled trial followed by an open-label phase, 187 males and post-menarchal females 10 years to 17 years of age (mean age 14.1 years; 31% female; 92% White, 1.6% Black or African American, 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, TG, and apolipoprotein B during the 26-week double-blind phase (see Table 12).

**TABLE 12: Lipid-altering Effects of LIPITOR in Adolescent Males and Females 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 males and 81 females). 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 , African American 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, 20 mg and 40 mg film coated tablets: Carton box contains 1, 2, 3 or 4 (Opaque aluminum PVC / aluminum foil ) blisters each of 7 film coated tablets with insert leaflet.
80 mg film coated tablets: Carton box contains 1, 2 [Al/(OPA-Film/PVC)] blisters each of 7 film coated tablets with insert leaflet.

**Storage**

Store at a temperature not exceeding 30°C, in a dry place.

Do not use Lipitor after the expiry date which is stated on Blister label after EXP:. The expiry date refers to the last day of the month.

## 17 PATIENT COUNSELING INFORMATION

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

*Myopathy and Rhabdomyolysis*
Advise patients that LIPITOR may cause myopathy and rhabdomyolysis. Inform patients that the risk is also increased when taking certain types of medication or consuming large quantities of grapefruit juice and they should discuss all medication, both prescription and over the counter, with their healthcare provider. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness particularly if accompanied by malaise or fever *[see Warnings and Precautions (5.1), Drug Interactions (7.1)]*.

*Hepatic Dysfunction*
Inform patients that LIPITOR may cause liver enzyme elevations and possibly liver failure. Advise patients to promptly report fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice *[see Warnings and Precautions (5.3)]*.

*Increases in HbA1c and Fasting Serum Glucose Levels*
Inform patients that increases in HbA1c and fasting serum glucose levels may occur with LIPITOR. Encourage patients to optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices *[see Warnings and Precautions (5.4)]*.

*Pregnancy*
Advise pregnant patients and patients who can become pregnant of the potential risk to a fetus. Advise patients to inform their healthcare provider of a known or suspected pregnancy to discuss if LIPITOR should be discontinued *[see Use in Specific Populations (8.1)]*.

*Lactation*

Advise patients that breastfeeding is not recommended during treatment with LIPITOR *[see Use in Specific Populations (8.2)]*.

*Missed Doses*
If a dose is missed, advise patients not to take the missed dose and resume with the next scheduled dose

Manufacturer :

Manufactured by Viatris Egypt under license of Viatris Pharma GmbH- Switzerland.

**Revision Date: April 2024**

**To report any side effect:**

**THIS IS A MEDICAMENT**

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the Pharmacist who sold the medicament.
- The doctor and the Pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

**Keep all medicaments out of reach and sight of children**

**Council of Arab Health Ministers**
**Union of Arabic Pharmacists**

**Egypt:**
Pharmacovigilance center, Viatris Egypt Company: pv.egypt@viatris.com
Egyptian Pharmacovigilance center (EPVC),EDA: pv.followup@edaegypt.gov.eg

معلومات المريض

**ليبيتور** (LIPITOR)
أقراص أتورفاستاتين الكالسيوم،
للاستخدام عن طريق الفم

**ما ليبيتور؟**
ليبيتور عبارة عن دواء يُصرف بوصفة طبية يحتوي على دواء مخفض للكوليسترول (ستاتين) يُدعى أتورفاستاتين. يُستخدم ليبيتور:

- للحد من المخاطر التالية:
  - النوبة القلبية، والسكتة الدماغية، وأنواع محددة من جراحات القلب وآلام الصدر لدى البالغين غير المصابين بأمراض القلب ولكن لديهم عوامل خطر أخرى متعددة متعلقة بأمراض القلب.
  - النوبة القلبية والسكتة الدماغية لدى البالغين المصابين بمرض السكري من النوع الثاني وغير المصابين بأمراض القلب ولكن لديهم عوامل خطر أخرى متعددة.
  - النوبة القلبية التي لا تسبب الوفاة، والسكتة الدماغية، وأنواع محددة من جراحات القلب، والاستشفاء في حالة قصور القلب الاحتقاني، وآلام الصدر لدى البالغين المصابين بأمراض القلب.
- بالإضافة إلى نظام غذائي لخفض كوليسترول البروتين الدهني المنخفض الكثافة (LDL-C) أو الكوليسترول الضار:
  - لدى البالغين المصابين بفرط شحوم الدم الأولي.
  - لدى البالغين والأطفال الذين يبلغون من العمر 10 سنوات فأكثر المصابين بفرط كوليسترول الدم العائلي المتخالف الجينات (HeFH). وهذه حالة وراثية تسبب المستويات العالية للكوليسترول الضار.
- بالإضافة إلى علاجات خفض الكوليسترول الأخرى أو بمفرده في حال عدم توفر هذه العلاجات مع البالغين والأطفال الذين يبلغون
من العمر 10 سنوات فأكثر المصابين بفرط الكوليسترول العائلي المتماثل الجينات (HoFH). وهذه حالة وراثية تسبب المستويات العالية للكوليسترول الضار.
- بالإضافة إلى نظام غذائي لعلاج البالغين المصابين بالمشكلات التالية:
  - شذوذ البروتين الشحمي البيتا في الدم الأولي (وهي حالة وراثية تسبب ارتفاع مستويات الكوليسترول والدهون).
  - فرط ثلاثي غليسيريد الدم.

لا يُعرف إذا كان ليبيتور آمنًا وفعالاً للأطفال الذين تقل أعمارهم عن 10 أعوام المصابين بفرط كوليسترول الدم العائلي المتخالف الجينات (HeFH) أو فرط الكوليسترول العائلي المتماثل الجينات (HoFH) أو للأطفال المصابين بأنواع أخرى من فرط شحوم الدم (بخلاف فرط كوليسترول الدم العائلي المتخالف الجينات (HeFH) أو فرط الكوليسترول العائلي المتماثل الجينات (HoFH)).

**لا تتناول ليبيتور في الحالات التالية:**

- إذا كنت تعاني من مشكلات في الكبد (قصور الكبد الحاد أو تشمع الكبد اللاتعويضي)
- إذا كنت تعاني من حساسية تجاه الأتروفاستاتين أو أيٍّ من المكونات الأخرى التي يحتوي عليها ليبيتور. توقف عن استخدام ليبيتور واطلب المساعدة الطبية في الحال إذا كنت تعاني من أعراض تفاعل حساسية خطير، بما في ذلك:
  - تورم الوجه أو الشفتَين أو اللسان أو الحلق

- مشكلات في التنفس أو البلع
- الإغماء أو الشعور بالدوار
- تسارع ضربات القلب
- الطفح الجلدي الحاد أو الحكة
- أعراض تشبه الإنفلونزا، بما في ذلك الحمى والتهاب الحلق والسعال والتعب وآلام المفاصل

راجع نهاية هذه النشرة للاطلاع على قائمة كاملة بالمكونات الموجودة في ليبيتور.

- قبل تناول ليبيتور، أخبر مقدم الرعاية الصحية عن كل الحالات الطبية التي تعاني منها، بما في ذلك إذا:
- كنت تعاني من آلام أو ضعف لا يمكن تفسيره في العضلات
- كنت تشرب أكثر من كوبَين من الكحول يوميًا
- كنت مصابًا بالسكري
- كنت تعاني من مشكلات في الغدة الدرقية
- كنت تعاني من مشكلات في الكلى
- كنت قد أصبت بسكتة دماغية
- كنتِ حاملاً أو تعتزمين الحمل. إذ قد يلحق ليبيتور الأذى بالجنين. إذا حملتِ، فتوقفي عن تناول ليبيتور واتصلي بمقدم الرعاية الصحية على الفور.
- كنتِ ترضعين أو تعتزمين الإرضاع. يجب أن تقرري مع مقدم الرعاية الصحية إذا ما كنتِ ستتناولين ليبيتور أو سترضعين. ويجب ألا تقومي بكلا الأمرين. تحدثي مع مقدم الرعاية الصحية عن أفضل طريقة لتغذية طفلك إذا كنتِ تتناولين ليبيتور.

**أخبر مقدم الرعاية الصحية بكل الأدوية التي تتناولها،** بما في ذلك الأدوية التي تُصرف بوصفة طبية والأدوية التي تُصرف من دون وصفة طبية والفيتامينات والمكملات العشبية. يمكن أن يتسبب ليبيتور وبعض الأدوية الأخرى في زيادة خطر التعرض لمشكلات العضلات أو الآثار الجانبية الأخرى. وعلى وجه الخصوص، أخبر مقدم الرعاية الصحية إذا كنت تتناول أدوية لعلاج:

- الجهاز المناعي (سيكلوسبورين)
- الكوليسترول (جمفبروزيل)
- الالتهابات (إريثروميسين، وكلاريثروميسين، وإيتراكونازول، وكيتوكونازول، وبوساكونازول، وفوريكونازول)
- حبوب منع الحمل
- قصور القلب (ديجوكسين)
- النِقرس (كولشيسين)
- نياسين
- أدوية الفايبرات
- معالجة نقص المناعة البشري (HIV) أو الإيدز أو التهاب الكبد C (مضادات للفيروسات)
  - تيبرانافير مع ريتونافير
  - جليكابريفير مع بيبرنتاسفير

- ليديباسفير مع سوفوسبوفير
- سيميبريفير
- ساكوينافير مع ريتونافير
- دارونافير مع ريتونافير
- فوسامبرينافير
- فوسامبرينافير مع ريتونافير
- إلباسفير مع غرازوبريفير
- ليتيرموفير
- نيلفينافير

اطلب قائمة بالأدوية من مقدم الرعاية الصحية أو من الصيدلي إذا لم تكن متأكدًا. يجب أن تعرف كل الأدوية التي تتناولها. احتفظ بقائمة منها لتريها لمقدم الرعاية الصحية أو للصيدلي عند الحصول على دواء جديد.

**كيف يجب أن أتناول ليبيتور؟**

- تناول ليبيتور كما يخبرك مقدم الرعاية الصحية بتناوله تمامًا.
- لا تغير الجرعة أو تتوقف عن تناول ليبيتور من دون التحدث مع مقدم الرعاية الصحية .
- قد يجري مقدم الرعاية الصحية فحوصات الدم للتحقق من مستويات الكوليسترول لديك في أثناء خضوعك للعلاج باستخدام ليبيتور. قد يتم تغيير جرعتك من ليبيتور استنادًا إلى نتائج فحوصات الدم هذه.
- تناول ليبيتور يوميًا في أي وقت من اليوم. يمكن تناول ليبيتور مع الطعام أو من دونه.
- قد يطلب منك مقدم الرعاية الصحية البدء باتباع نظام غذائي لخفض الكوليسترول قبل إعطائك ليبيتور. التزم بهذا النظام الغذائي المنخفض الدهون في أثناء تناولك ليبيتور.
- إذا فاتتك إحدى جرعات ليبيتور، فانتظر وتناول الجرعة التالية في الوقت المعتاد. لا تتناول جرعتَين من ليبيتور في الوقت نفسه.
- إذ تناولت كمية كبيرة من ليبيتور. أو جرعة زائدة منه، فاتصل بمقدم الرعاية الصحية أو بمركز مكافحة السموم أو اقصد أقرب غرفة طوارئ على الفور.

**ما الذي يجب أن أتجنبه في أثناء تناول ليبيتور؟**

- تفادَ شرب أكثر من 1,2 لتر من عصير الجريب فروت يوميًا.

**ما الآثار الجانبية المحتملة لدواء ليبيتور؟**

**من الممكن أن يسبب ليبيتور آثارًا جانبية خطيرة، تتضمن:**

- **آلام العضلات وليونتها وضعفها (الاعتلال العضلي).** قد تكون مشكلات العضلات، بما في ذلك انهيار العضلات، خطيرة لدى بعض الأشخاص، وقد تسبب ضررًا في الكلى يمكن أن يؤدي إلى الوفاة في حالات نادرة.

**أخبر مقدم الرعاية الصحية في الحال إذا كنت تعاني من أيٍّ من الأعراض التالية:**

- الألم أو ليونة أو ضعف لا يمكن تفسيره في العضلات، لا سيما إذا كنت تعاني أيضًا من الحمى أو تشعر بتعب يفوق المعتاد في أثناء تناولك ليبيتور.
- مشكلات في العضلات لا تختفي بعد أن يطلب منك مقدم الرعاية الصحية التوقف عن تناول ليبيتور. قد يجري مقدم الرعاية الصحية المزيد من الفحوصات لتشخيص سبب مشكلات العضلات التي تعاني منها.

تزيد فرص تعرضك لمشكلات العضلات إذا:

- كنت تتناول بعض الأدوية الأخرى في أثناء تناولك ليبيتور
- كنت تشرب كميات كبيرة من عصير الجريب فروت
- كنت تبلغ من العمر 65 عامًا أو أكثر
- كنت مصابًا بمشكلات في الغدة الدرقية (قصور الدرقية) لا يمكن السيطرة عليها

- كنت تعاني من مشكلات في الكلى
- كنت تأخذ جرعات كبيرة من ليبيتور

- **مشكلات الكبد.** بجب أن يجري مقدم الرعاية الصحية فحوصات الدم للتحقق من حالة كبدك قبل أن تبدأ في تناول ليبيتور، وفي حال معاناتك من أعراض مرتبطة بمشكلات الكبد في أثناء تناولك ليبيتور. اتصل بمقدم الرعاية الصحية في الحال إذا كنت تعاني من الأعراض التالية المرتبطة بمشكلات الكبد:
  - الشعور بالتعب أو الضعف
  - الغثيان أو التقيؤ
  - فقدان الشهية
  - ألم في المنطقة العلوية من البطن
  - البول بلون كهرماني داكن
  - اصفرار البشرة أو بياض العينَين

- **ارتفاع مستوى السكر في الدم.** قد يرتفع مستوى السكر في الدم في أثناء تناولك ليبيتور.

احرص على ممارسة الرياضة بانتظام واختيار الأطعمة الصحية للحفاظ على وزن جسد صحي.

**تتضمن أكثر أعراض ليبيتور الجانبية شيوعًا ما يلي:**

- احتقان الأنف، التهاب الحلق، رشح الأنف
- الإسهال
- التهاب المسالك البولية
- الغثيان
- التشنجات العضلية
- ألم في الحلق
- آلام العضلات والمفاصل
- ألم في الأطراف
- اضطراب المعدة
- آلام العضلات والعظام
- صعوبة النوم

تحدث إلى مقدم الرعاية الصحية أو الصيدلي إذا كنت تعاني من أعراض جانبية تزعجك أو لا تختفي.
هذه ليست كل الآثار الجانبية لدواء ليبيتور. اتصل بمقدم الرعاية الصحية للحصول على المشورة الطبية بشأن الآثار الجانبية

**اذا واجهت أياً من الآثار او الاعراض الجانبية الخطيرة التالية، توقف عن تناول الدواء الخاص بك واخبر مقدم الرعاية الصحية على الفور او اذهب إلى اقرب مستشفي وقسم الطوارئ**

**الآثار الجانبية الخطيرة : تلون البول باللون الاحمر**

**يحتوي ليبيتور على اللاكتوز**
إذا أخبرك طبيبك أنك لا تستطيع تحمل بعض السكريات، فتواصل مع مقدم الرعاية الصحية قبل تناول هذا المنتج الدوائي.

**للإبلاغ عن الآثار الجانبية:**

**مصر:**
مركز اليقظة الدوائية، شركة فياترس مصر: pv.egypt@viatris.com

مركز اليقظة الدوائية المصري (EPVC)، هيئة الدواء المصرية (EDA): pv.followup@edaegypt.gov.eg

**كيف أقوم بتخزين ليبيتور؟**

- خزِّن ليبيتور في درجة حرارة غرفة لا تتعدي 30 درجة مئوية , في مكان جاف
- لا تحتفظ بالدواء المنتهي الصلاحية أو الذي لم تعد بحاجة إليه.

**حافظ على وجود ليبيتور وكل الأدوية بعيدًا عن متناول الأطفال.**

**معلومات عامة عن الاستخدام الآمن والفعال لعلاج ليبيتور.**
توصف الأدوية في بعض الأحيان لأغراض أخرى بخلاف تلك المذكورة في نشرة معلومات المريض. لا تستخدم ليبيتور في علاج حالة لم يتم وصفه لها. لا تعطِ ليبيتور لأشخاص آخرين، حتى إذا كانوا يعانون من الأعراض نفسها التي تعاني أنت منها. فقد يلحق بهم الضرر. إذا كنت ترغب في الحصول على مزيد من المعلومات عن ليبيتور، فتحدث إلى مقدم الرعاية الصحية . يمكنك أن تطلب من الصيدلي أو مقدم الرعاية الصحية معلومات عن ليبيتور توجَّه للأطباء المتخصصين.

**ما مكونات ليبيتور؟**
**المادة الفعالة:** أتورڤاستاتين الكالسيوم ثلاثي المائية 10.85 مجم و 21.69 مجم و43.38 مجم و86.76 مجم مكافئ ل أتورڤاستاتين 10مجم و 20 مجم و 40 مجم و 80 مجم على التوالي.
**المواد غير الفعالة :**
كربونات الكالسيوم، سليولوز دقيق التبلور، لاكتوز أحادي الهيدرات، كروس كارميلوز الصوديوم، بولي سوربات 80، سليولوز الهيدروكسي بروبيل، ستيارات المغنيسيوم، أوبادري أبيض YS-1-7040 ، مستحلب سيميثيكون.

**العبوة المعتمدة:**
أقراص مغلفة 10 مجم و20 مجم و40 مجم:
علبة كرتونية تحتوي على 1 أو 2 أو 3 أو 4 شرائط (Opaque aluminumPVC/ aluminum) ، يحتوي كل منها على 7 أقراص مغلفة و نشرة داخليه.
أقراص مغلفة 80 مجم:
علبة كرتونية تحتوي على 1 أو 2 شرائط [Al/(OPA-Film/PVC)]، يحتوي كل منها على 7 أقراص مغلفة و نشرة داخلية.
***الخواص الفيزيائية:***
10مجم من أتورڤاستاتين : أقراص بيضاء اللون، مغلّفة، بيضاوية الشكل، منقوش عبارة "VLE 155" على أحد جانبيها ورقم "10" على الجانب الآخر.
20 مجم من أتورڤاستاتين : أقراص بيضاء اللون، مغلّفة، بيضاوية الشكل، منقوش عبارة "VLE 156" على أحد جانبيها ورقم "20" على الجانب الآخر.
40 مجم من أتورڤاستاتين : أقراص بيضاء اللون، مغلّفة، بيضاوية الشكل، منقوش عبارة "VLE 157" على أحد جانبيها ورقم "40" على الجانب الآخر.
80 مجم من أتورڤاستاتين : أقراص بيضاء اللون، مغلّفة، بيضاوية الشكل، منقوش عبارة "VLE 158" على أحد جانبيها ورقم "80" على الجانب الآخر.

**الشركة المصنّعة:**
**تصنيع شركة فياترس مصر بترخيص من فياترس فارما GmbH سويسرا**
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