Keep the Cholesterol Conversation Going

Make the most of your treatment with LIPITOR by filling out and taking this Doctor Discussion Guide to your next appointment. That way, you can get your questions answered and understand how your treatment is working for you. It’s easy to forget what you wanted to ask in the middle of an appointment. Review the below questions beforehand to see which matter most to you. There is space to add your own questions on the next page.

How long does it take for LIPITOR to start working?

What are my latest test results? Does this mean LIPITOR is working for me?

How long should I continue taking my medicine?

What are my cholesterol treatment goals?

How often should I come see you and have my cholesterol levels checked?

What kind of diet can help me manage my cholesterol?

How much exercise is recommended to help me manage my cholesterol?

What other lifestyle changes can I make to help me manage my cholesterol?

What foods and medications should I avoid while taking LIPITOR?

Tell your doctor about all your medical conditions and all the medicines you take, including prescription, non-prescription, vitamins, and herbal supplements. Especially tell your doctor if you take medicines for your immune system, cholesterol, infections, birth control, heart failure, HIV, or AIDS. My current medications:

What are possible side effects of LIPITOR, and when should I call my doctor? (ie, muscle pain, tenderness, weakness, etc)

IMPORTANT SAFETY INFORMATION AND INDICATIONS

LIPITOR® (atorvastatin calcium) tablets are not for everyone, including anyone who has previously had an allergic reaction to LIPITOR. It is not for those with liver problems. And it is not for women who are nursing, pregnant, or may become pregnant. If you get pregnant, stop taking LIPITOR and call your doctor right away.

Please see accompanying Important Safety Information and Indication continued on following page. Please see accompanying Full Prescribing and Patient Information.
IMPORTANT SAFETY INFORMATION AND INDICATIONS (continued)

If you take LIPITOR tablets, tell your doctor if you feel any new muscle pain or weakness. This could be a sign of rare but serious muscle problems that can lead to kidney problems, including kidney failure.

Tell your doctor about all your medical conditions and all medications you take. This may help avoid serious drug interactions. Your doctor should do blood tests to check your liver function before starting LIPITOR and during your treatment if you have symptoms of liver problems. Call your doctor right away if you have the following symptoms of liver problems - feel tired or weak or have a loss of appetite, upper belly pain, dark amber colored urine or yellowing of your skin or the whites of your eyes.

Tell your doctor if you have diabetes. Elevated blood sugar levels have been reported with statins, including LIPITOR. Common side effects are diarrhea, upset stomach, muscle and joint pain, and changes in some blood tests. Talk to your healthcare provider if you have side effects that bother you or that will not go away.

INDICATIONS

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

LIPITOR can lower the risk for heart attack, stroke, certain types of heart surgery, and chest pain in patients who have heart disease or risk factors for heart disease such as age, smoking, high blood pressure, low HDL-C, or heart disease in the family. LIPITOR can lower the risk for heart attack or stroke in patients with diabetes and risk factors such as eye problems, kidney problems, smoking, or high blood pressure.

Limitations of Use: LIPITOR has not been studied in people who have an increase of chylomicrons (Fredrickson Types I and V).

*Eligibility required. Terms and conditions apply. Full terms and conditions can be found at LIPITOR.com/savings-terms. Savings Offer will be accepted only at participating pharmacies. Savings Offer is not health insurance. No membership fees. Maximum savings of $1,800 per calendar year. This offer is not valid for prescriptions that are eligible to be reimbursed, in whole or in part, by Medicaid, Medicare or other federal or state healthcare programs. This offer is not valid for prescriptions that are eligible to be reimbursed in whole by private insurance plans or other health or pharmacy benefit programs. For help with LIPITOR Savings Offer, call 1-800-314-7957, visit LIPITOR.com, or write: LIPITOR Savings Offer, 2250 Perimeter Park Drive, Suite 300, Morrisville, NC 27560.

Please see accompanying Full Prescribing and Patient Information.
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) tablets, for oral use
Initial U.S. Approval: 1996

1. INDICATIONS AND USAGE

1.1 Prevention of Cardiovascular Disease in Adults
1.2 Hyperlipidemia
1.3 Limitations of Use

2. DOSAGE AND ADMINISTRATION

2.1 Hyperlipidemia and Mixed Dyslipidemia
2.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10 Years to 17 Years of Age)
2.3 Homozygous Familial Hypercholesterolemia
2.4 Concomitant Lipid-Lowering Therapy
2.5 Dosage in Patients with Renal Impairment
2.6 Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors

3. DOSAGE FORMS AND STRENGTHS

Tablets: 10, 20, 40, and 80 mg of atorvastatin (3).

4. CONTRAINDICATIONS

4.1 Skeletal Muscle
4.2 Liver Dysfunction
4.3 Endocrine Function
4.4 CNS Toxicity
4.5 Use in Patients with Recent Stroke or TIA

5. WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle
5.2 Liver Dysfunction
5.3 Endocrine Function
5.4 CNS Toxicity
5.5 Use in Patients with Recent Stroke or TIA

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience
6.2 Postmarketing Experience

7. DRUG INTERACTIONS

7.1 Strong Inhibitors of CYP 3A4
7.2 Grapefruit Juice
7.3 Cyclosporine
7.4 Gleevec and Pibrantavir; Elbasvir and Grazoprevir
7.5 Gemfibrozil
7.6 Other Fibrates
7.7 Niacin
7.8 Rifampin or other Inducers of Cytochrome P450 3A4

FULL PRESCRIBING INFORMATION: CONTENTS*

1. INDICATIONS AND USAGE
1.1 Prevention of Cardiovascular Disease in Adults
1.2 Hyperlipidemia
1.3 Limitations of Use

2. DOSAGE AND ADMINISTRATION
2.1 Hyperlipidemia and Mixed Dyslipidemia
2.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10 Years to 17 Years of Age)
2.3 Homozygous Familial Hypercholesterolemia
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5.1 Skeletal Muscle
5.2 Liver Dysfunction
5.3 Endocrine Function
5.4 CNS Toxicity
5.5 Use in Patients with Recent Stroke or TIA

6. ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience

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7.1 Strong Inhibitors of CYP 3A4
7.2 Grapefruit Juice
7.3 Cyclosporine
7.4 Gleevec and Pibrantavir; Elbasvir and Grazoprevir
7.5 Gemfibrozil
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*Sections or subsections omitted from the full prescribing information are not listed.

ADVERSE REACTIONS
The most commonly reported adverse reactions (incidence > 2%) in patients treated with LIPITOR in placebo-controlled trials regardless of causality were: nasopharyngitis, arthralgia, diarrhea, pain in extremity, and urinary tract infection (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer at (1-800-438-1985 and www.pfizer.com) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis (2.6, 5.1, 7, 12.3)

Interacting Agents
Prescribing Recommendations
Cyclosporine, tipranavir plus ritonavir, glecaprevir plus pibrentasvir
Avoid atorvastatin
Clarithromycin, itraconazole, saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, elbasvir plus grazoprevir
Do not exceed 20 mg atorvastatin daily
Nelfinavir
Do not exceed 40 mg atorvastatin daily
Lopinavir plus ritonavir, simprevir, fibrinic acid derivatives, erythromycin, azole antifungals, lipid-modifying doses of niacin, colchicine
Use with caution and lowest dose necessary

Other Lipid-Lowering Medications: Use with fibrate products or lipid-modifying doses (≥ 1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with LIPITOR (7).

Digoxin: Patients should be monitored appropriately (7.9).

Oral Contraceptives: Values for norethindrone and ethinyl estradiol may be increased (7.10).

Rifampin should be simultaneously co-administered with LIPITOR (7.8).

USE IN SPECIFIC POPULATIONS

Hepatic impairment: Plasma concentrations markedly increased in patients with chronic alcoholic liver disease (8.1, 12.3).

Females of reproductive potential: Advise females of reproductive potential to use effective contraception during treatment with LIPITOR (8.3).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 4/2019
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Drug therapy is recommended as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate. In patients with CHD or multiple risk factors for CHD, LIPITOR can be started simultaneously with diet.

1.1 Prevention of Cardiovascular Disease in Adults

In adult patients with clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, LIPITOR is indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke
- Reduce the risk for revascularization procedures and angina

In adult patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, LIPITOR is indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke

In adult 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

1.2 Hyperlipidemia

LIPITOR is indicated:

- As an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in adult patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb).
- As an adjunct to diet for the treatment of adult patients with elevated serum TG levels (Fredrickson Type IV).
- For the treatment of adult patients with primary dysbetalipoproteinemia (Fredrickson Type III) who do not respond adequately to diet.
- To reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH) as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.
- As an adjunct to diet to reduce total-C, LDL-C, and apo B levels in pediatric patients, 10 years to 17 years of age, with heterozygous familial hypercholesterolemia (HeFH) 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

1.3 Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Hyperlipidemia and Mixed Dyslipidemia

The recommended starting dose of LIPITOR is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of LIPITOR is 10 to 80 mg once daily. LIPITOR can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of LIPITOR should be individualized according to patient characteristics such as goal of therapy and response. After initiation and/or upon titration of LIPITOR, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

2.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10 Years to 17 Years of Age)

The recommended starting dose of LIPITOR is 10 mg/day; the usual dose range is 10 to 20 mg orally once daily [see Clinical Studies (14.6)]. Doses should be individualized according to the recommended goal of therapy [see Indications and Usage (1.2) and Clinical Pharmacology (12)]. Adjustments should be made at intervals of 4 weeks or more.

2.3 Homozygous Familial Hypercholesterolemia

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

2.4 Concomitant Lipid-Lowering Therapy

LIPITOR may be used with bile acid resins. The combination of HMG-CoA reductase inhibitors (statins) and fibrates should generally be used with caution [see Warnings and Precautions (5.1) and Drug Interactions (7)].

2.5 Dosage in Patients with Renal Impairment

Renal disease does not affect the plasma concentrations nor LDL-C reduction of LIPITOR; thus, dosage adjustment in patients with renal dysfunction is not necessary [see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)].

2.6 Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors

In patients taking cyclosporine or the HIV protease inhibitor tipranavir plus ritonavir or the hepatitis C virus (HCV) protease inhibitor glecaprevir plus pibrentasvir, therapy with LIPITOR should be avoided. In patients with HIV taking lopinavir plus ritonavir, use the lowest dose necessary of LIPITOR. In patients taking clarithromycin, itraconazole, elbasvir plus grazoprevir, 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 used. In patients taking the HIV protease inhibitor nelfinavir therapy with LIPITOR should be limited to 40 mg. When co-prescribing atorvastatin with other protease inhibitors, appropriate clinical assessment is recommended to ensure that the lowest dose necessary of LIPITOR is used [see Warnings and Precautions (5.1) and Drug Interactions (7)].

3 DOSAGE FORMS AND STRENGTHS

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

Table 1: LIPITOR Tablet Strengths and Identifying Features

<table>
<thead>
<tr>
<th>Tablet Strength</th>
<th>Identifying Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg of atorvastatin</td>
<td>“PD 155” on one side and “10” on the other</td>
</tr>
<tr>
<td>20 mg of atorvastatin</td>
<td>“PD 156” on one side and “20” on the other</td>
</tr>
<tr>
<td>40 mg of atorvastatin</td>
<td>“PD 157” on one side and “40” on the other</td>
</tr>
<tr>
<td>80 mg of atorvastatin</td>
<td>“PD 158” on one side and “80” on the other</td>
</tr>
</tbody>
</table>

4 CONTRAINDICATIONS

LIPITOR is contraindicated in patients with active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels, hypersensitivity to any component of this medication, pregnancy [see Use in Specific Populations (8.1)], or lactation [see Use in Specific Populations (8.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with LIPITOR and with other drugs in this class. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects. Atorvastatin, like other statins, occasionally causes myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN. The concomitant use of higher doses of atorvastatin with certain drugs such as cyclosporine and strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., clarithromycin, itraconazole, and HIV and HCV protease inhibitors) increases the risk of myopathy/rhabdomyolysis.

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing LIPITOR. LIPITOR therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of the drugs listed in Table 2. Physicians considering combined therapy of LIPITOR with any of these drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy reduction or if LDL-C remains ≥ 190 mg/dL or ≥ 180 mg/dL after a 40 mg once daily dose of LIPITOR. Lower starting and maintenance doses of atorvastatin should be considered when taken concomitantly with the aforementioned drugs [see Drug Interactions (7)]. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. Prescribing recommendations for interacting agents are summarized in Table 2 [see Dosage and Administration (2.6), Drug Interactions (7), and Clinical Pharmacology (12.3)].

Table 2. Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

<table>
<thead>
<tr>
<th>Interacting Agents</th>
<th>Prescribing Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine, tijranavir plus ritonavir, glecaprevir plus pibrentasvir</td>
<td>Avoid atorvastatin</td>
</tr>
<tr>
<td>Clarithromycin, itraconazole, saquinavir plus ritonavir*, darunavir plus ritonavir, fosamprenavir plus ritonavir, elbasvir plus grazoprevir</td>
<td>Do not exceed 20 mg atorvastatin daily</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Do not exceed 40 mg atorvastatin daily</td>
</tr>
<tr>
<td>Lopinavir plus ritonavir, sipemprevir, fibrac acid derivatives, erythromycin, azole antifungals, lipid-modifying doses of niacin, colchicine</td>
<td>Use with caution and lowest dose necessary (12.3)</td>
</tr>
</tbody>
</table>

*Use the lowest dose necessary (12.3)

LIPITOR therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to myoglobinuria (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).
5.2 Liver Dysfunction

Statins, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases 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 function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminases returned to or near pretreatment levels. In several trials of 18 to 24 months duration, eighteen of 30 patients with persistent LFT elevations continued treatment at a reduced dose of LIPITOR.

It is recommended that liver enzyme tests be obtained prior to initiating therapy with LIPITOR and repeated as clinically indicated. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including atorvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with LIPITOR, promptly interrupt therapy. If an alternate etiology is not found, do not restart LIPITOR.

LIPITOR should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of LIPITOR. [See Contraindications (4)].

5.3 Endocrine Function

Increases in hba1c and fasting glucose levels have been reported with HMG-CoA reductase inhibitors, including LIPITOR.

Statins interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that LIPITOR does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of statins on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if a statin is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

5.4 CNS Toxicity

Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vaculization were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 200 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single toxic convection was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg/day.

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Walkerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose.

5.5 Use in Patients with Recent Stroke or TIA

In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study where LIPITOR 80 mg vs. placebo was administered in 4,731 subjects without CHD who had a stroke or TIA within the preceding 6 months, a higher incidence of hemorrhagic stroke was seen in the LIPITOR 80 mg group compared to placebo (55, 2.3% atorvastatin 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 LIPITOR vs. placebo). The incidence of non-fatal hemorrhagic strokes was significantly greater in the atorvastatin group compared to placebo (55/2365, 2.3% vs. 33/2366, 1.4%; p=0.0168). The incidence of fatal hemorrhagic stroke was similar across treatment groups (17 vs. 18 LIPITOR vs. placebo). The incidence of non-fatal hemorrhagic strokes was significantly greater in the atorvastatin group compared to placebo (55/2365, 2.3% vs. 33/2366, 1.4%; p=0.0168).

5.6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Other adverse reactions reported in placebo-controlled studies 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: transaminase increase, liver function test abnormal, blood alkaline phosphatase increase, creatine phosphokinase increase, hyperglycemia; Nervous system: embolism; Respiratory system: epistaxis; Skin and appendages: urticaria; Special senses: vision blurred, tinnitus; Urinary system: white blood cells urine positive.

- Other adverse reactions reported in placebo-controlled studies include:
  - Body as a whole: asartosis; Digestive system: abdominal discomfort, abdominal pain, anorexia, distension, nausea, flatulence, hepatobiliary system: abnormal liver function tests, increase in transaminases, decrease in bilirubin; Endocrine system: diabetes mellitus, peripheral edema, polycythemia; Hematopoietic system: anemia, leukopenia; Metabolism and nutrition: hypoglycemia; Musculoskeletal system: myalgia, back pain, muscle cramps, tendinitis; Nervous system: dizziness, somnolence; Respiratory system: asthma, bronchitis, dyspnea, epistaxis, laryngitis, pharyngitis, sinusitis, upper respiratory tract infection; Skin and appendages: pruritus, rash; Special senses: taste perversion; Vascular system: peripheral blood circulation disorders, peripheral edema.

- Other adverse reactions reported in placebo-controlled studies include:
  - Body as a whole: nasopharyngitis; Digestive system: abdominal pain, diarrhea, dyspepsia, flatulence, nausea, vomiting, dyspepsia, diarrhea.
  - Endocrine system: diabetes mellitus, polycythemia, hypoglycemia, hyperglycemia.
  - Hematopoietic system: anemia, leukopenia, neutropenia.
  - Musculoskeletal system: myalgia, back pain, muscle cramps, tendinitis.
  - Nervous system: dizziness, somnolence.
  - Respiratory system: bronchitis, rhinitis.
  - Skin and appendages: pruritus, rash.
  - Special senses: taste perversion.
  - Vascular system: peripheral blood circulation disorders, peripheral edema.

6. ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

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 clinical practice.

In the LIPITOR placebo-controlled clinical trial database of 16,066 patients (8755 LIPITOR vs. 7311 placebo; age range 10–93 years, 29% women, 91% Caucasians, 3% Blacks, 2% Asians, 4% other) with a median treatment duration of 53 weeks, 9.7% of patients on LIPITOR and 9.5% of the patients on placebo discontinued due to adverse reactions regardless of causality. The five 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%).

The most commonly reported adverse reactions (incidence ≥ 2% and greater than placebo) regardless of causality, in patients treated with LIPITOR in placebo-controlled trials (n=8755) were: nasopharyngitis (8.3%), arthralgia (6.9%), diarrhea (6.8%), pain in extremity (6.0%), and urinary tract infection (5.7%).

Table 3 summarizes the frequency of clinical adverse reactions, regardless of causality, reported in ≥ 2% and at a rate greater than placebo in patients treated with LIPITOR (n=8755), from seventeen placebo-controlled trials.

<table>
<thead>
<tr>
<th>Adverse Reaction*</th>
<th>Any dose</th>
<th>10 mg</th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=8755</td>
<td>8755</td>
<td>8750</td>
<td>8748</td>
<td>8742</td>
<td>8745</td>
<td>8751</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>8.3</td>
<td>12.9</td>
<td>5.3</td>
<td>7.0</td>
<td>4.2</td>
<td>8.2</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>6.9</td>
<td>8.9</td>
<td>11.7</td>
<td>10.6</td>
<td>4.3</td>
<td>6.5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.8</td>
<td>7.3</td>
<td>6.4</td>
<td>14.1</td>
<td>5.2</td>
<td>6.3</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6.0</td>
<td>8.5</td>
<td>3.7</td>
<td>9.3</td>
<td>3.1</td>
<td>5.9</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5.7</td>
<td>6.9</td>
<td>6.4</td>
<td>8.0</td>
<td>4.1</td>
<td>5.6</td>
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<tr>
<td>Dyspepsia</td>
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<td>5.9</td>
<td>3.2</td>
<td>6.0</td>
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<td>3.7</td>
<td>7.1</td>
<td>3.8</td>
<td>3.5</td>
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<tr>
<td>Musculoskeletal pain</td>
<td>3.8</td>
<td>5.2</td>
<td>3.2</td>
<td>5.1</td>
<td>2.3</td>
<td>3.6</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>3.6</td>
<td>4.6</td>
<td>4.8</td>
<td>5.1</td>
<td>2.4</td>
<td>3.0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3.5</td>
<td>3.6</td>
<td>5.9</td>
<td>8.4</td>
<td>2.7</td>
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</tr>
<tr>
<td>Insomnia</td>
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<tr>
<td>Pharyngitis</td>
<td>2.3</td>
<td>3.9</td>
<td>1.6</td>
<td>2.8</td>
<td>0.7</td>
<td>2.1</td>
</tr>
</tbody>
</table>

* Adverse Reaction ≥ 2% in any dose greater than placebo
7.2 Grapefruit Juice

Grapefruit juice is reported to increase LIPITOR concentrations by up to 30% [see Warnings and Precautions (5.1)].

7.6 Other Fibrates

The concomitant administration of fibrates, such as fenofibrate, gemfibrozil, or fenofibrates, with LIPITOR should be avoided due to the risk of myopathy. However, if a concomitant fibrate is required, it should be used with caution [see Warnings and Precautions (5.1)].

7.7 Nicin

Nicin is a medication that is known to interact with statins and fibrates. It is important to monitor for signs of myopathy, particularly in patients on high-dose LIPITOR.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

LIPITOR is contraindicated for use in pregnant women since safety in pregnant women has not been established. There have been rare reports of immune-mediated necrotizing myopathy associated with statin use [see Warnings and Precautions (5.1)].

8.6 Other Fibrates

Combination therapy with fibrates and statins may increase the risk of myopathy. Patients should be monitored closely for signs of myopathy.

8.7 Rifampin or other Inducers of Cytochrome P450 3A4

Rifampin or other strong inducers of CYP 3A4 (e.g., phenobarbital, phenytoin) may increase the metabolism of atorvastatin and decrease its efficacy [see Clinical Pharmacology (12.3)].
8.4 Pediatric Use

Heterozygous Familial Hypercholesterolemia (HeFH)

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

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

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

- A placebo-controlled clinical trial of 6 months duration in 187 boys and postmenarchal girls, 10 years to 17 years of age. Patients treated with mg or 20 mg daily LIPITOR had an adverse reaction profile generally similar to that of patients treated with placebo. In this limited controlled study, there was no significant effect on growth or sexual maturation in boys or on menstrual cycle length in girls.

- A three year open-label uncontrolled trial that included 163 pediatric patients 10 to 15 years of age with HeFH who were titrated to achieve a target LDL-C < 130 mg/dL. The safety and efficacy of LIPITOR in lowering LDL-C appeared generally consistent with that observed for adult patients, despite limitations of the uncontrolled study design

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

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

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

Homzygous Familial Hypercholesterolemia (HoFH)

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

8.5 Geriatric Use

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

8.6 Hepatic Impairment

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

10 OVERDOSAGE

There is no specific treatment for LIPITOR overdose. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance LIPITOR clearance.

11 DESCRIPTION

LIPITOR is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, 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 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 pre-systemic 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 [see [Dosage and Administration (2)]).

Distribution: Mean volume of distribution of LIPITOR is approximately 38.1 liters. LIPITOR is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, LIPITOR is likely to be secreted in human milk [see Contraindications (4) and Use in Specific Populations (8.2)].

Metabolism: LIPITOR is extensively metabolized to ortho- and para-hydroxylated derivatives and various beta-oxidation products. In vitro inhibition of HMG-CoA reductase by ortho- and para-hydroxylated 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. Clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults [see Use in Specific Populations (8.5)].

Pediatric: Apparent oral clearance of atorvastatin in pediatric subjects appeared similar to that of adults when scaled allometrically by body weight as the body weight was the only significant covariate in the analysis. Mean apparent oral clearance of atorvastatin in pediatric patients was similar to that of adults.

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

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

Hepatic Impairment: In patients with chronic alcoholic liver disease, plasma concentrations of LIPITOR and its active metabolites are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction in these patients was similar to that observed in subjects with normal liver function [see Contraindications (4)].

Drug Interaction Studies

Atorvastatin is a substrate of the hepatic transporters, OATP1B1 and OATP1B3 transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporter BCRP, which may limit the intestinal absorption and biliary clearance of atorvastatin.
TABLE 4. Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin

<table>
<thead>
<tr>
<th>Co-administered drug and dosing regimen</th>
<th>Atorvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose (mg)</td>
</tr>
<tr>
<td>*Cyclosporine 5.2 mg/kg/day, stable dose</td>
<td>10 mg QD* for 28 days</td>
</tr>
<tr>
<td>*Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days</td>
<td>10 mg, SD</td>
</tr>
<tr>
<td><em>Gliclazide 400 mg QD/pibrentasvir 120 mg QD</em>, 7 days</td>
<td>10 mg QD for 7 days</td>
</tr>
<tr>
<td>*Telaprevir 750 mg QD, 10 days</td>
<td>20 mg, SD</td>
</tr>
<tr>
<td><em>Saquinavir 400 mg BID/ ritonavir 400 mg BID</em>, 15 days</td>
<td>40 mg QD for 4 days</td>
</tr>
<tr>
<td><em>Ebsavir 50 mg QD/grazoprevir 200 QD</em>, 13 days</td>
<td>10 mg SD</td>
</tr>
<tr>
<td><em>Simprevir 150 mg QD</em>, 10 days</td>
<td>40 mg SD</td>
</tr>
<tr>
<td><em>Clarithromycin 500 mg BID</em>, 5 days</td>
<td>80 mg QD for 5 days</td>
</tr>
<tr>
<td><em>Darunavir 300 mg BID/ritonavir 100 mg BID</em>, 9 days</td>
<td>10 mg QD for 4 days</td>
</tr>
<tr>
<td><em>Itraconazole 200 mg QD</em>, 4 days</td>
<td>40 mg SD</td>
</tr>
<tr>
<td><em>Fosapenampravir 700 mg BID/ritonavir 100 mg BID</em>, 14 days</td>
<td>10 mg QD for 4 days</td>
</tr>
<tr>
<td><em>Fosapenampravir 1400 mg BID</em>, 14 days</td>
<td>10 mg QD* for 4 days</td>
</tr>
<tr>
<td><em>Nelfinavir 1250 mg BID</em>, 14 days</td>
<td>10 mg QD* for 28 days</td>
</tr>
<tr>
<td><em>Grapefruit Juice, 240 mL QD</em>*</td>
<td>40 mg, SD</td>
</tr>
<tr>
<td><em>Diltiazem 240 mg QD</em>, 28 days</td>
<td>40 mg, SD</td>
</tr>
<tr>
<td><em>Erythromycin 750 mg QD</em>, 7 days</td>
<td>10 mg, SD</td>
</tr>
<tr>
<td>*Amiodipine 10 mg, single dose</td>
<td>80 mg</td>
</tr>
<tr>
<td><em>Cimetidine 500 mg QD</em>, 2 weeks</td>
<td>10 mg QD for 2 weeks</td>
</tr>
<tr>
<td><em>Colestipol 10 g BID</em>, 24 weeks</td>
<td>40 mg QD for 8 weeks</td>
</tr>
<tr>
<td><em>Maluex TC® 30 mL QD</em>, 17 days</td>
<td>10 mg QD for 15 days</td>
</tr>
<tr>
<td><em>Erlotinivir 600 mg QD</em>, 14 days</td>
<td>10 mg QD for 3 days</td>
</tr>
<tr>
<td><em>Rilpamivir 600 mg QD</em>, 7 days (co-administered)</td>
<td>40 mg SD</td>
</tr>
<tr>
<td><em>Rilpamivir 600 mg QD</em>, 5 days (doses separated)</td>
<td>40 mg SD</td>
</tr>
<tr>
<td><em>Gemfibrozil 600 mg BID</em>, 7 days</td>
<td>40 mg SD</td>
</tr>
<tr>
<td><em>Fenofibrate 160 mg QD</em>, 7 days</td>
<td>40 mg SD</td>
</tr>
<tr>
<td><em>Boceprevir 800 mg TID</em>, 7 days</td>
<td>40 mg SD</td>
</tr>
</tbody>
</table>

* Represents ratio of treatments (co-administered drug plus atorvastatin vs. atorvastatin alone).
* 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.

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

<table>
<thead>
<tr>
<th>Atorvastatin</th>
<th>Co-administered drug and dosing regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg QD* for 15 days</td>
<td>Antiplate, 600 mg SD</td>
</tr>
<tr>
<td>80 mg QD* for 10 days</td>
<td>* Difoxan 0.25 mg QD; 20 days</td>
</tr>
<tr>
<td>40 mg QD* for 22 days</td>
<td>Oral contraceptive QD; 2 months - norethindrone 1 mg - ethinyl estradiol 35µg</td>
</tr>
<tr>
<td>10 mg, SD</td>
<td>Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days</td>
</tr>
<tr>
<td>10 mg QD* for 4 days</td>
<td>Fosapenampravir 1400 mg BID*, 14 days</td>
</tr>
<tr>
<td>10 mg QD* for 4 days</td>
<td>Fosapenampravir 700 mg BID/ritonavir 100 mg BID*, 14 days</td>
</tr>
</tbody>
</table>

* See Section 7 for clinical significance.
* Once daily
‡ Twice daily
§ Single dose

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in rats at doses 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 Salmomella 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 aspermatia in the epididymides of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the humane 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. Adverse effects on fertility were not seen in male mice treated with up to 40 mg/kg/day of atorvastatin.

14 CLINICAL STUDIES

14.1 Prevention of Cardiovascular Disease

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of LIPITOR on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40–80 years of age (mean of 63 years), without a previous myocardial infarction and with TC levels ≤ 251 mg/dl (6.5 mmol/L).

Additionally, all patients had at least 3 of the following cardiovascular risk factors: male gender (81.1%), age >55 years (84.5%), smoking (33.2%), diabetes (24.3%), history of CHD in a first-degree relative (26%), TC:HDL >6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypertrophy (14.4%), prior cerebrovascular event (9.8%), specific ECG abnormality (14.3%), proteinuria/albuminuria (62.4%). In this double-blind, placebo-controlled study, patients were treated with anti-hypertensive therapy (Goal BP <140/90 mm Hg for non-diabetic patients; <130/80 mm Hg for diabetic patients) and allocated to either LIPITOR 10 mg daily (n=5168) or placebo (n=5137), using a covariate adaptive method which took into account the distribution of baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients were followed for a median duration of 3.3 years.

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

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

Figure 1: Effect of LIPITOR 10 mg/day on Cumulative Incidence of Non-Fatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT-LLA)
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 LIPICTOR 10 mg/day on lipid levels was similar to that seen in previous clinical trials. LIPICTOR significantly reduced the rate of major cardiovascular events (primary endpoint events) (83 events in the LIPICTOR 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 LIPICTOR was seen regardless of age, sex, or baseline lipid levels.

LIPICTOR significantly reduced the risk of stroke by 48% (21 events in the LIPICTOR 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. 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 rate of major cardiovascular events (primary endpoint events) by 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 years) or gender.

The effects of LIPITOR 80 mg/day vs. LIPITOR 10 mg/day were compared in the CARDS trial, which enrolled 5,488 patients. The primary endpoint was death due to CHD, non-fatal myocardial infarction, resuscitated cardiac arrest, and fatal and non-fatal stroke. The mean LDL-C, TC, TG, HDL, and non-HDL cholesterol levels at Week 12 were 78, 145, 115, 45, and 48 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 major coronary event (fatal CHD, non-fatal MI, and resuscitated cardiac arrest): 411 (9.3%) in the LIPITOR group vs. 548 (10.9%) in the ATORVASTATIN 10 mg/day group 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 LIPICTOR.

In the Atorvastatin 80 mg group, the proportions of subjects who experienced CV or non-CV death were similar for the LIPITOR 80 mg group and the simvastatin 20–40 mg group. 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. 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 effects of LIPITOR 80 mg/day vs. 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 LIPICTOR.

The mean LDL-C, TC, TG, HDL, and non-HDL cholesterol levels at Week 12 were 78, 145, 115, 45, and 48 mg/dL during treatment with 80 mg of LIPITOR and 99, 177, 152, 129, and 48 mg/dL during treatment with 10 mg of LIPICTOR. There were 61 deaths in the LIPITOR group vs. 82 deaths in the placebo group (HR 0.73, p=0.059).
In two multicenter, placebo-controlled, dose-response studies in patients with hyperlipidemia, LIPITOR was given as a single dose over 6 weeks, significantly reduced total-C, LDL-C, apo B, and TG. (Pooled results are provided in Table 7.)

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

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th>TC (mg/dL)</th>
<th>LDL-C (mg/dL)</th>
<th>Apo B (mg/dL)</th>
<th>TG (mg/dL)</th>
<th>HDL-C (mg/dL)</th>
<th>Non-HDL-C/ HDL-C</th>
<th>Non-HDL-C/ HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>21</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>10</td>
<td>-3</td>
<td>7</td>
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<td>-53</td>
<td>-53</td>
</tr>
</tbody>
</table>

*Results are pooled from 2 dose-response studies.

In patients with Fredrickson Types IIa and IIb hyperlipoproteinemia pooled from 24 controlled trials, the median (25th and 75th percentile) percent changes from baseline in LDL-C for LIPITOR 10, 20, 40, and 80 mg were 6.4 (-1.4, 14), 8.7 (0.0, 17), 7.8 (0.0, 16), and 5.1 (-2.7, 15), respectively. Additionally, analysis of the pooled data demonstrated consistent and significant decreases in total-C, LDL-C, TG, total-C/HDL-C, and LDL-C/HDL-C.

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

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

<table>
<thead>
<tr>
<th>Treatment (Daily Dose)</th>
<th>N</th>
<th>Total-C</th>
<th>LDL-C</th>
<th>Apo B</th>
<th>TG</th>
<th>HDL-C</th>
<th>Non-HDL-C/ HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIPITOR 10 mg</td>
<td>707</td>
<td>-27</td>
<td>-36</td>
<td>-28</td>
<td>-17</td>
<td>+7</td>
<td>-37</td>
</tr>
<tr>
<td>Lovastatin 20 mg</td>
<td>191</td>
<td>-19</td>
<td>-27</td>
<td>-20</td>
<td>-6</td>
<td>+7</td>
<td>-28</td>
</tr>
<tr>
<td>95% CI for Diff**</td>
<td>-9.2, -6.5</td>
<td>-14.7, -8.2</td>
<td>-13.4, -7.4</td>
<td>-14.1, -0.7</td>
<td>-4.9</td>
<td>1.6</td>
<td>-11.5, -4.1</td>
</tr>
<tr>
<td>LIPITOR 10 mg</td>
<td>222</td>
<td>-25</td>
<td>-35</td>
<td>-27</td>
<td>-17</td>
<td>+6</td>
<td>-36</td>
</tr>
<tr>
<td>Pravastatin 20 mg</td>
<td>77</td>
<td>-17</td>
<td>-23</td>
<td>-17</td>
<td>-9</td>
<td>+8</td>
<td>-28</td>
</tr>
<tr>
<td>95% CI for Diff**</td>
<td>-10.8, -6.1</td>
<td>-14.5, -8.2</td>
<td>-13.4, -7.4</td>
<td>-14.1, -0.7</td>
<td>-4.9</td>
<td>1.6</td>
<td>-11.5, -4.1</td>
</tr>
<tr>
<td>LIPITOR 10 mg</td>
<td>132</td>
<td>-29</td>
<td>-37</td>
<td>-34</td>
<td>-23</td>
<td>+7</td>
<td>-39</td>
</tr>
<tr>
<td>Simvastatin 10 mg</td>
<td>45</td>
<td>-24</td>
<td>-30</td>
<td>-30</td>
<td>-15</td>
<td>+7</td>
<td>-33</td>
</tr>
<tr>
<td>95% CI for Diff**</td>
<td>-8.7, -2.7</td>
<td>-10.1, -2.6</td>
<td>-8.0, -1.1</td>
<td>-15.1, -0.7</td>
<td>-4.3</td>
<td>3.9</td>
<td>-9.6, -1.9</td>
</tr>
</tbody>
</table>

* 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.

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

<table>
<thead>
<tr>
<th>Placebo (N=12)</th>
<th>LIPITOR 10 mg (N=37)</th>
<th>LIPITOR 20 mg (N=15)</th>
<th>LIPITOR 80 mg (N=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG</td>
<td>-2.3 (15.5, 24.4)</td>
<td>-2.3 (15.5, 24.4)</td>
<td>-2.3 (15.5, 24.4)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>3.6 (-31.3, 31.6)</td>
<td>-26.5 (-57.9, 8)</td>
<td>-30.4 (-53.9, 0.3)</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>3.8 (-135.1, 13.4)</td>
<td>13.8 (-97.6, 61.5)</td>
<td>11.0 (-32.2, 25.2)</td>
</tr>
<tr>
<td>non-HDL-C</td>
<td>-1.0 (-31.9, 53.2)</td>
<td>-48.8 (-85.8, 57.3)</td>
<td>-44.6 (-62.2, -9)</td>
</tr>
</tbody>
</table>

14.5 Homozygous Familial Hypercholesterolemia

In a study without a concurrent control group, 29 patients ages 6 years to 37 years with HeFH received maximum daily doses of 20 to 80 mg of LIPITOR. The mean LDL-C reduction in this study was 18%. Twenty-five patients with a reduction in LDL-C had a mean response of 20% (range of 7% to 53%, median of 24%); the remaining 4 patients had 7% to 24% increases in LDL-C. Five of the 29 patients had absent LDL-receptor function. Of these, 2 patients also had a portacaval shunt and had no significant reduction in LDL-C. The remaining 3 receptor-negative patients had a mean LDL-C reduction of 22%. 14.6 Heterozygous Familial Hypercholesterolemia in Pediatric Patients

In a double-blind, placebo-controlled study followed by an open-label phase, 187 boys and post-menarchal girls 10 years to 17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (HeFH) or severe hypercholesterolemia, were randomized to LIPITOR (n=140) or placebo (n=47) for 26 weeks and then all received LIPITOR for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level ≥190 mg/dL or 2) a baseline LDL-C level ≥160 mg/dL and positive family history of FH or documented premature coronary disease in a first or second-degree relative. The mean baseline LDL-C value was 218.6 mg/dL (range: 138.5–385.0 mg/dL) in the LIPITOR group compared to 230.0 mg/dL (range: 160.0–324.5 mg/dL) in the placebo group. The dosage of LIPITOR (once daily) was 10 mg for the first 4 weeks and uptitrated to 20 mg if the LDL-C level was > 130 mg/dL. The number of LIPITOR-treated patients who required up titration to 20 mg after Week 4 during the double-blind phase was 78 (55.7%).

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

<table>
<thead>
<tr>
<th>Treatment (Daily Dose)</th>
<th>Median (min, max) at Baseline (mg/dL)</th>
<th>Median % Change From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>442 (225, 1320)</td>
<td>(-44, 13)</td>
</tr>
<tr>
<td>LIPITOR 10 mg</td>
<td>-8 (-85, 17)</td>
<td>-44 (-67, 27)</td>
</tr>
<tr>
<td>LIPITOR 80 mg</td>
<td>-9 (-90, -31)</td>
<td>-9 (21, 0)</td>
</tr>
</tbody>
</table>

14.4 Dysbetalipoproteinemia

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

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

<table>
<thead>
<tr>
<th>Treatment (Daily Dose)</th>
<th>Median (min, max) at Baseline (mg/dL)</th>
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</tr>
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<td>-44 (-67, 27)</td>
</tr>
<tr>
<td>LIPITOR 80 mg</td>
<td>-9 (-90, -31)</td>
<td>-9 (21, 0)</td>
</tr>
</tbody>
</table>

14.7 How Supplied/Storage and Handling

10 mg tablets (10 mg of atorvastatin): coded “PD 157” on one side and “10” on the other. NDC 0071-0157-23 bottles of 80
NDC 0071-0157-34 bottles of 5000
NDC 0071-0157-40 10 x 10 unit dose blisters
NDC 0071-0157-51 bottles of 1000
NDC 0071-0157-55 bottles of 1000
NDC 0071-0157-60 10 x 10 unit dose blisters
NDC 0071-0157-74 bottles of 5000
NDC 0071-0157-80 10 x 10 unit dose blisters
NDC 0071-0157-88 bottles of 2500
NDC 0071-0157-92 8 x 8 unit dose blisters

Storage Store at controlled room temperature 20 - 25°C (68 - 77°F) [see USP].
Advise the patient to read the FDA-approved patient labeling (Patient Information).

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

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

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

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

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

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

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

LIPITOR (lip-i-tor)

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

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

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

LIPITOR can lower the risk for heart attack, stroke, certain types of surgery, and chest pain in patients who have heart disease or risk factors for heart disease such as:
- age, smoking, high blood pressure, low HDL-C, heart disease in the family.
LIPITOR can lower the risk for heart attack or stroke in patients with diabetes and risk factors such as:
- eye problems, kidney problems, smoking, or high blood pressure.
LIPITOR starts to work in about 2 weeks.

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

Who Should Not Take LIPITOR?
- Do not take LIPITOR if you:
  - are pregnant or think you may be pregnant, or are planning to become pregnant. LIPITOR may harm your unborn baby. If you get pregnant, stop taking LIPITOR and call your doctor right away.
  - are breast feeding. LIPITOR can pass into your breast milk and may harm your baby.
  - have liver problems.
  - are allergic to LIPITOR or any of its ingredients. The active ingredient is atorvastatin. See the end of this leaflet for a complete list of ingredients in LIPITOR.
LIPITOR dosing has not been established in children under 10 years of age.

Before You Start LIPITOR
Tell your doctor if you:
- have muscle aches or weakness
- drink more than 2 glasses of alcohol daily
- have diabetes
- have a thyroid problem
- have kidney problems

Some medicines should not be taken with LIPITOR. Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. LIPITOR and certain other medicines can interact causing serious side effects. Especially tell your doctor if you take medicines for:
- your immune system
- cholesterol
- infections
- birth control
- heart failure
- HIV or AIDS
- hepatitis C virus
Know all the medicines you take. Keep a list of them with you to show your doctor and pharmacist.

How Should I Take LIPITOR?
- Take LIPITOR exactly as prescribed by your doctor. Do not change your dose or stop LIPITOR without talking to your doctor. Your doctor may do blood tests to check your cholesterol levels during your treatment with LIPITOR. Your dose of LIPITOR may be changed based on these blood test results.
- Take LIPITOR each day at any time of day about the same time each day. LIPITOR can be taken with or without food.
- Don’t break LIPITOR tablets before taking.
- Your doctor should start you on a low-fat diet before giving you LIPITOR. Stay on this low-fat diet when you take LIPITOR.
- If you miss a dose of LIPITOR, take it as soon as you remember. Do not take LIPITOR if it has been more than 12 hours since you missed your last dose. Wait and take the next dose at your regular time. Do not take 2 doses of LIPITOR at the same time.
- If you take too much LIPITOR or overdose, call your doctor or Poison Control Center right away. Go to the nearest emergency room.

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

What are the Possible Side Effects of LIPITOR?
LIPITOR can cause serious side effects. These side effects have happened only to a small number of people. Your doctor can monitor you for them. These side effects usually go away if your dose is lowered or LIPITOR is stopped. These serious side effects include:
- Muscle problems. LIPITOR can cause serious muscle problems that can lead to kidney problems, including kidney failure. You have a higher chance for muscle problems if you are taking certain other medicines with LIPITOR.
- Liver problems. Your doctor should do blood tests to check your liver before you start taking LIPITOR and if you have symptoms of liver problems while you take LIPITOR. Call your doctor right away if you have the following symptoms of liver problems:
  - feel tired or weak
  - loss of appetite
  - upper belly pain
  - dark amber colored urine
  - yellowing of your skin or the whites of your eyes

Call your doctor right away if you have:
- muscle problems like weakness, tenderness, or pain that happen without a good reason, especially if you also have a fever or feel more tired than usual. This may be an early sign of a rare muscle problem.
- muscle problems that do not go away even after your doctor has advised you to stop taking LIPITOR. Your doctor may do further tests to diagnose the cause of your muscle problems.
- allergic reactions including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing which may require treatment right away.
- nausea and vomiting.
- passing brown or dark-colored urine.
- you feel more tired than usual.
- your skin and whites of your eyes get yellow.
- stomach pain.
- allergic skin reactions.

In clinical studies, patients reported the following common side effects while taking LIPITOR: diarrhea, upset stomach, muscle and joint pain, and alterations in some laboratory blood tests.
The following additional side effects have been reported with LIPITOR: tiredness, tendon problems, memory loss, and confusion.

Talk to your doctor or pharmacist if you have side effects that bother you or that will not go away.
These are not all the side effects of LIPITOR.
Ask your doctor or pharmacist for a complete list.

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

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

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

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

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