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

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 for LIPITOR.
IMPORTANT SAFETY INFORMATION AND INDICATION (continued)

If you take LIPITOR® (atorvastatin calcium) 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® (atorvastatin calcium) 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/terms-conditions. Card will be accepted only at participating pharmacies. Card is not health insurance. No membership fees. Maximum savings of $2,500 per calendar year. This offer is not valid for prescriptions that are reimbursed, in whole or in part, by Medicaid or other federal or state health programs, and cannot be used in conjunction with use of Medicare Part D prescription benefit for LIPITOR. For further information, call 1-800-314-7957, or write: LIPITOR Savings Card, 2250 Perimeter Park Drive, Suite 300, Morrisville, NC 27560.

Please see accompanying full Prescribing and Patient Information for LIPITOR.
LIPITOR® (atorvastatin calcium) tablets, for oral use

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**INDICATIONS AND USAGE**

LIPITOR is an HMG-CoA reductase inhibitor indicated as an adjunct therapy to diet to:

- Reduce the risk of MI, stroke, revascularization procedures, and angina in adult patients without CHD, but with multiple risk factors (1.1).
- Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF, and angina in adult patients with CHD (1.1).
- Reduce elevated total-C, LDL-C, apo B, and TG levels and increase HDL-C in adult patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (1.2).
- Reduce elevated TG in adult patients with hypertriglyceridemia and primary dysbetalipoproteinemia (1.2).
- Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH) after failing an adequate trial of diet therapy (1.2).
- Reduce elevated total-C, LDL-C, and apo B levels in pediatric patients, 10 years to 17 years of age, with heterozygous familial hypercholesterolemia (HeFH) after failing an adequate trial of diet therapy (1.2).

**Limitations of Use**

LIPITOR has not been studied in Friedrickson Types I and V dyslipidemias (1.3).

**DOSAGE AND ADMINISTRATION**

- **Dose range**: 10 to 80 mg once daily (2.1).
- **Recommended start dose**: 10 or 20 mg once daily (2.1).
- **Patients requiring large LDL-C reduction (>45%)** may start at 40 mg once daily (2.1).

**DOSAGE FORMS AND STRENGTHS**

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

**CONTRAINdications**

- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels (4).
- Hypersensitivity to any component of this medication (4).
- Pregnancy (4.1, 8.3).
- Lactation (4.8, 2).

**WARNINGS AND PRECAUTIONS**

- Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): Risks increase when higher doses are used concomitantly with cyclosporine and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, HIV protease inhibitors). Predisposing factors include advanced age (>65), uncontrolled hyperthyroidism, and renal impairment. Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported. Advise patients to promptly report to their physician unexplained and/or persistent muscle pain, tenderness, or weakness. LIPITOR therapy should be discontinued if myopathy is diagnosed or suspected (5.1, 8.5).
- Other Lipid-Lowering Medications: Use with fibrate products or lipid-modifying doses 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 (7.8).
- Oral Contraceptives: Values for norethindrone and ethinyl estradiol may be increased (7.9).
- Rifampin should be simultaneously co-administered with LIPITOR (7.7).

**8 USE IN SPECIFIC POPULATIONS**

- Hepatic impairment: Plasma concentrations markedly increased in patients with chronic alcoholic liver disease (8.6).
- Females of reproductive potential: Advise females of reproductive potential to use effective contraception during treatment with LIPITOR (8.3).

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**11 DESCRIPTION**

**12 CLINICAL PHARMACOLOGY**

**13 NONCLINICAL TOXICOLOGY**

**14 CLINICAL STUDIES**

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- Liver enzyme abnormalities: Persistent elevations in hepatic transaminases can occur. Check liver enzyme tests before initiating therapy and as clinically indicated thereafter (5.2).
- A higher incidence of hemorrhagic stroke was seen in patients without CHD but with stroke or TIA within the previous 6 months in the LIPITOR 80 mg group vs. placebo (5.5).

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**DRUG INTERACTIONS**

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

- Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)
- HIV protease inhibitor (lopinavir plus ritonavir)
- Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)
- HIV protease inhibitor (nefuvir) Hepatitis C protease inhibitor (boceprevir)
- Certain Protease Inhibitors
  - Strong Inhibitors of CYP 3A4
  - Concomitant Lipid-Lowering Therapy
  - Dosage in Patients with Renal Impairment
  - Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors
  - Dosage of LIPITOR 80 mg daily in obese patients (12.3)

**Postmarketing Experience**

**17 PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

Revised: 6/2017
In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, therapy with LIPITOR should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of LIPITOR is employed. In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, therapy with LIPITOR should be limited to 40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of LIPITOR is employed [see 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>
<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

- 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)].
- 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 CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, and HIV 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 symptoms and signs 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 cyclosporine, fibrin acid derivatives, erythromycin, clarithromycin, the hepatitis C protease inhibitor telaprevir, combinations of HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, fosamprenavir, and fosamprenavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with LIPITOR and fibrin acid derivatives, erythromycin, clarithromycin, a combination of saquinavir plus ritonavir, lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamprenavir plus ritonavir, azole antifungals, or lipid-modifying doses of niacin 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 and during any periods of upward dosage titration of either drug. 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, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)</td>
<td>Avoid atorvastatin</td>
</tr>
<tr>
<td>HIV protease inhibitor (lopinavir plus ritonavir)</td>
<td>Use with caution and lowest dose necessary</td>
</tr>
<tr>
<td>Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir), darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)</td>
<td>Do not exceed 20 mg atorvastatin daily</td>
</tr>
<tr>
<td>HIV protease inhibitor (nelfinavir)</td>
<td>Do not exceed 40 mg atorvastatin daily</td>
</tr>
</tbody>
</table>

*Use with caution and with the lowest dose necessary (12.3)

Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine [see Drug Interactions (7.11)].

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 rhabdomyolysis (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, transaminates returned to or near pretreatment levels. Of patients tested, 18 of 30 patients with persistent LFT elevations continued treatment with 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 serum 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 vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 months of escalating doses up to 280 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 tonic convulsion 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 (Wallerian 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/day 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 (5.5% vs. 3.4% for placebo; HR: 1.68, 95% CI: 1.21, 2.31; p=0.00168). The incidence of fatal hemorrhagic stroke was not significantly different between treatment groups (15 vs. 18). The incidence of non-fatal hemorrhagic strokes was significantly greater in the atorvastatin group (19, 3.8%) as compared to placebo (9, 1.8%). Some of the patients were randomized to placebo or atorvastatin 80 mg (n=3,366) in the Collaborative Atorvastatin Diabetes Study (CARDS).

In CARDS [see Clinical Studies (14.1)] involving 10,305 participants (age range 40–80 years, 19% women; 94.6% Caucasians, 2.6% Africans, 1.5% South Asians, 1.3% mixed or other) treated with LIPITOR 10 mg daily (either LIPITOR or placebo) (n=4,173), the safety and tolerability profile of the group treated with LIPITOR was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.

5.6 Use in Patients with a Recent MI

In a 26-week controlled study in boys and postmenarchal girls with HeFH (ages 10 years to 17 years) experiencing cardiovascular death were numerically smaller in the LIPITOR 80 mg group (3.3%) than in the placebo group (4.7%). The proportions of subjects who experienced cardiovascular death were numerically smaller in the LIPITOR 80 mg group (3.3%) than in the placebo group (4.1%). The proportions of subjects who experienced non-cardiovascular death were numerically larger in the LIPITOR 80 mg group (5.0%) than in the placebo group (4.0%).

Adverse Reactions from Clinical Studies of LIPITOR in Pediatric Patients

In a 26-week controlled study in boys and postmenarchal girls with HeFH (ages 10 years to 17 years) (n=140, 31% female; 92% Caucasians, 1.6% Blacks, 1.6% Asians, 4.8% other), the safety and tolerability profile of LIPITOR 10 to 20 mg daily, as an adjunct to diet to reduce total cholesterol, LDL-C, and apo B levels, was generally similar to that of placebo [see Use in Special Populations (8.4) and Clinical Studies (14.6)].
7.10 Warfarin
LIPITOR had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

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

8 USE IN SPECIFIC POPULATIONS

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

Human Data
Limited published data on atorvastatin calcium from observational studies, meta-analyses and case reports have not shown an increased risk of major congenital malformations or miscarriage. Rare reports of congenital anomalies have been received following intrauterine exposure to other HMG-CoA reductase inhibitors. In a review of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or lovastatin, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/s stillbirths did not exceed what would be expected in the general population. The number of cases is small and does not allow reliable estimates of risk. A spontaneous abortion occurred in a woman treated with atorvastatin. In a study in pregnant rats administered 20, 100, or 225 mg/kg/day from gestation day 7 through 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; pinna 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.

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

8.3 Females and Males of Reproductive Potential

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

8.4 Pediatric Use

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

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

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

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

Homozygous Familial Hypercholesterolemia (HoFH)

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

8.5 Geriatric Use

Of the 39,828 patients who received LIPITOR in clinical studies, 15,813 (40%) were ≥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 (12.5)].

10 OVERDOSAGE

There is no specific treatment for LIPITOR overdosage. 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 elimination.

11 DESCRIPTION

LIPITOR is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

Atorvastatin calcium is [(R*,R*)-2-(4-fluorophenyl)-3,3-dihydroxy-5-(1-methylethyl)-3-phenyl-4-(4-phenylaminocarbonyl)-1H-pyrrole-1-heptanolic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is C_{33}H_{34}FN_{2}O_{5}Ca•3H_{2}O and its molecular weight is 1209.42. Its structural formula is:

![Structural formula of atorvastatin calcium](image)

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 pH 4 and below. Atorvastatin calcium is very slightly soluble in aqueous solutions of pH 4 and below.

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 pH 4 and below. Atorvastatin calcium is very slightly soluble in aqueous solutions of pH 4 and below.

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 attributable to presystemic clearance in gastrointestinal mucosa and 30% 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 10% lower for AUC) however, there is no clinically significant difference in LDL-C reduction with LIPITOR between men and women.

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

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

Hepatic Impairment: In patients with chronic alcoholic liver disease, plasma concentrations of LIPITOR are markedly increased. Cmax and AUC are each 4-fold greater in patients with Childs-Pugh A disease. Although data are limited, Cmax and AUC are each 4-fold greater in patients with Childs-Pugh B disease [see Contraindications (4)].

<table>
<thead>
<tr>
<th>Co-administered drug and dosing regimen</th>
<th>Dose (mg)</th>
<th>Change in Cmax</th>
<th>Change in AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine 5.2 mg/kg/day, stable dose</td>
<td>10 mg QD for 28 days</td>
<td>18.7 fold</td>
<td>110.7 fold</td>
</tr>
<tr>
<td>Tipranavir 500 mg BID/ritonavir</td>
<td>200 mg BID, 7 days</td>
<td>10 mg, SD</td>
<td>19.4 fold</td>
</tr>
<tr>
<td>Telaprevir 750 mg qd, 10 days</td>
<td>20 mg, SD</td>
<td>17.8 fold</td>
<td>110.6 fold</td>
</tr>
<tr>
<td>Saquinavir 400 mg BID/ritonavir</td>
<td>400 mg BID, 15 days</td>
<td>40 mg QD for 4 days</td>
<td>13.9 fold</td>
</tr>
<tr>
<td>Clarithromycin 500 mg BID, 9 days</td>
<td>80 mg QD for 8 days</td>
<td>14.4 fold</td>
<td>15.4 fold</td>
</tr>
<tr>
<td>Darunavir 300 mg BID/ritonavir</td>
<td>100 mg BID, 9 days</td>
<td>10 mg QD for 4 days</td>
<td>13.4 fold</td>
</tr>
<tr>
<td>Itraconazole 200 mg QD, 4 days</td>
<td>40 mg SD</td>
<td>13.3 fold</td>
<td>120%</td>
</tr>
<tr>
<td>Fosamprenavir 700 mg BID/ritonavir</td>
<td>100 mg BID, 14 days</td>
<td>10 mg QD for 4 days</td>
<td>12.53 fold</td>
</tr>
<tr>
<td>Fosamprenavir 1400 mg BID, 14 days</td>
<td>10 mg QD for 4 days</td>
<td>12.3 fold</td>
<td>14.04 fold</td>
</tr>
<tr>
<td>Nefavir 1250 mg BID, 14 days</td>
<td>10 mg QD for 28 days</td>
<td>174%</td>
<td>12.2 fold</td>
</tr>
<tr>
<td>Grapefruit juice, 240 mL QD *</td>
<td>40 mg, SD</td>
<td>137%</td>
<td>116%</td>
</tr>
<tr>
<td>Diltiazem 240 mg, QD, 28 days</td>
<td>40 mg, SD</td>
<td>151%</td>
<td>No change</td>
</tr>
<tr>
<td>Ethromycin 500 mg QD, 7 days</td>
<td>10 mg, SD</td>
<td>133%</td>
<td>138%</td>
</tr>
<tr>
<td>Amiodipine 10 mg, single dose</td>
<td>80 mg, SD</td>
<td>115%</td>
<td>112%</td>
</tr>
<tr>
<td>Cimetidine 300 mg QD, 2 weeks</td>
<td>10 mg QD for 2 weeks</td>
<td>&lt;1%</td>
<td>11%</td>
</tr>
<tr>
<td>Colestipol 10 mg BID, 28 weeks</td>
<td>40 mg QD for 28 weeks</td>
<td>Not determined</td>
<td>26%**</td>
</tr>
<tr>
<td>Mexil TCB 30 mL QD, 17 days</td>
<td>10 mg QD for 15 days</td>
<td>133%</td>
<td>134%</td>
</tr>
<tr>
<td>Efavirenz 600 mg QD, 14 days</td>
<td>10 mg QD for 3 days</td>
<td>41%</td>
<td>11%</td>
</tr>
<tr>
<td>Ritonavir 600 mg QD, 7 days co-administered 1</td>
<td>40 mg SD</td>
<td>130%</td>
<td>12.7 fold</td>
</tr>
<tr>
<td>Ritonavir 600 mg QD, 5 days (doses separated) 1</td>
<td>40 mg SD</td>
<td>130%</td>
<td>12.7 fold</td>
</tr>
<tr>
<td>Gemfibrozil 600 mg, BID, 7 days</td>
<td>40 mg SD</td>
<td>135%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Fenofibrate 160 mg QD, 7 days</td>
<td>40 mg SD</td>
<td>13%</td>
<td>12%</td>
</tr>
<tr>
<td>Bempidine 800 mg TID, 7 days</td>
<td>40 mg SD</td>
<td>12.3 fold</td>
<td>12.6 fold</td>
</tr>
</tbody>
</table>

* Data given as x-fold change represent a simple ratio between co-administration and atorvastatin alone (i.e., 1-fold = no change). Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change).

† See Sections 5 and 7 for clinical significance.

‡ Greater increases in AUC (up to 2.5 fold) and/or Cmax (up to 71%) have been reported with excessive grapefruit consumption (>750 mL - 1.2 liters per day).
The effect of LIPITOR was seen regardless of age, smoking status, obesity, or presence of renal dysfunction. The effect of LIPITOR was significant regardless of age, sex, or baseline lipid levels. Patients were followed for a median duration of two years.

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 micronucleus test.

In female rats, atorvastatin at doses up to 225 mg/kg (56 times the human exposure) did not cause adverse effects. 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 oral dose); tests 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, spermatic head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

13 CLINICAL STUDIES

13.1 Prevention of Cardiovascular Disease

In the Anglo-Sardinian Cardiovascular Outcomes Trial (ASCOT), the effect of LIPITOR on fatal and non-fatal coronary heart disease was assessed in 10,635 hypertensive patients 40–60 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 (32.2%), diabetes (24.3%), history of CHD in 1st-degree relative (23%), hypertension (80%), retinopathy (30%), or macroalbuminuria (9%) or microalbuminuria (3%). Subject recruitment continued until the target population was reached. All patients had at least 3 of the following cardiovascular risk factors: male gender (81.1%), age ≥55 years (84.5%), smoking (32.2%), diabetes (24.3%), history of CHD in 1st-degree relative (23%), hypertension (80%), retinopathy (30%), or macroalbuminuria (9%) or microalbuminuria (3%).

Atorvastatin also significantly decreased the relative risk for revascularization procedures by 42% (incidences of 1.4% for LIPITOR and 2.4% 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=0.01) 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, 66% male), ages 40–75 with type 2 diabetes based on WHO criteria, without prior history of cardiovascular disease and with LDL ≤ 160 mg/dL and TG ≤ 400 mg/dL. In addition to diabetes, subjects had 1 or more of the following risk factors: current smoking (23%), hypertension (31%), retinopathy (30%), or macroalbuminuria (9%) or microalbuminuria (3%). No subjects on hemodialysis were enrolled in the study. In this multicenter, placebo-controlled, double-blind clinical trial, subjects were randomly allocated to either LIPITOR 10 mg daily (1418) 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 HDL-cholesterol 71.1 mg/dL; with LDL-C at baseline: 124 mg/dL; mean estimated residual risk at the 80 mg oral dose.

The effect of LIPITOR 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 28% (38 events in the LIPITOR group vs. 64 events in the placebo group), HR 0.72, 95% CI (0.53, 0.96) (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=0.058).

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, age >65 years) with clinically evident coronary heart disease who had achieved a target LDL-C level <130 mg/dL. In this double-blind, placebo-controlled study, patients were treated with atorvastatin 80 mg/day for 3 months (16 times the human AUC at the 80 mg oral dose). Tests 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, spermatic head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

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.

Atorvastatin was negative in 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 micronucleus test.

In female rats, atorvastatin at doses up to 225 mg/kg (56 times the human exposure) did not cause adverse effects. 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); tests 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, spermatic head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.
The proportions of subjects who experienced noncardiovascular death were numerically larger in the 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 cardiovascular death, including the components of CHD death and heart failure, but not peripheral vascular disease. The reduction in the rate of CHF with hospitalization was only or resuscitated cardiac arrest (Table 6). Of the predefined secondary endpoints, treatment with LIPITOR reduced the rate of non-fatal, non-procedure related MI and fatal and non-fatal stroke, but not CHD death or CV death.

Confidence intervals for the Secondary Endpoints were not adjusted for multiple comparisons. CHF=congestive heart failure; CV=cardiovascular; PVD=peripheral vascular disease; * Secondary endpoints not included in primary endpoint.

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

TABLE 6. Overview of Efficacy Results in TNT

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Atorvastatin 10 mg (N=5006)</th>
<th>Atorvastatin 80 mg (N=4995)</th>
<th>HR* (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY ENDPOINT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First major cardiovascular</td>
<td>548 (10.9)</td>
<td>434 (8.7)</td>
<td>0.78 (0.69, 0.89)</td>
</tr>
<tr>
<td>Components of the Primary Endpoint</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD death</td>
<td>127 (2.5)</td>
<td>101 (2.0)</td>
<td>0.80 (0.61, 1.03)</td>
</tr>
<tr>
<td>Non-fatal, non-procedure related MI</td>
<td>308 (6.2)</td>
<td>243 (4.9)</td>
<td>0.78 (0.66, 0.93)</td>
</tr>
<tr>
<td>Resuscitated cardiac arrest</td>
<td>26 (0.5)</td>
<td>25 (0.5)</td>
<td>0.96 (0.56, 1.67)</td>
</tr>
<tr>
<td>Stroke (fatal and non-fatal)</td>
<td>155 (3.1)</td>
<td>117 (2.3)</td>
<td>0.75 (0.59, 0.96)</td>
</tr>
</tbody>
</table>

SECONDARY ENDPOINTSB

| 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 procedurec | 904 (18.1)                   | 667 (13.4)                 | 0.72 (0.65, 0.80) |
| First documented angina endpoint | 615 (12.3)                   | 545 (10.9)                 | 0.88 (0.79, 0.99) |
| All-cause mortality           | 282 (5.6)                   | 284 (5.7)                  | 1.01 (0.85, 1.19) |

Components of All-Cause Mortality

| Cardiovascular death          | 155 (3.1)                   | 126 (2.5)                  | 0.81 (0.64, 1.03) |
| Noncardiovascular death       | 127 (2.5)                   | 158 (3.2)                  | 1.25 (0.99, 1.57) |
| Cancer death                  | 75 (1.5)                    | 85 (1.7)                   | 1.13 (0.83, 1.55) |
| Other non-CV death            | 43 (0.9)                    | 58 (1.2)                   | 1.35 (0.91, 2.00) |
| Suicide, homicide, and other traumatic non-CV death | 9 (0.2)                   | 15 (0.3)                   | 1.67 (0.73, 3.82) |

a Atorvastatin 80 mg; atorvastatin 10 mg
b Component of other secondary endpoints

* Secondary endpoints not included in primary endpoint

HR=heart-to-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.

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

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

In the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study (IDEAL), treatment with LIPITOR 80 mg/day was compared to treatment with simvastatin 20–40 mg/day in 8,888 subjects up to 80 years of age with a history of CHD to assess whether reduction in CV risk could be achieved.

In three multicenter, double-blind studies in patients with hyperlipidemia, LIPITOR was compared to other approved lipid-lowering agents. The pooled data demonstrated consistent and significant decreases in total-C, LDL-C, TG, total-C/HDL-C, and LDL-C/HDL-C.

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

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

**14.2 Hyperlipidemia and Mixed Dyslipidemia**

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

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

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

**14.3 Hypertriglyceridemia**

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

**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).
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 LIPICTOR. 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 LIPICTOR (n=140) or placebo (n=47) for 26 weeks and then all received LIPICTOR 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 cardiovascular disease in a first or second-degree relative. The mean baseline LDL-C value was 218.6 mg/dL (range: 138.5–385.0 mg/dL) in the LIPICTOR group compared to 230.0 mg/dL (range: 160.0–324.5 mg/dL) in the placebo group. The dosage of LIPICTOR (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 LIPICTOR-treated patients who required uptitration to 20 mg after Week 4 during the double-blind phase was 78 (55.7%). LIPICTOR signicantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26-week double-blind phase (see Table 11).

TABLE 11. Lipid-altering Effects of LIPICTOR in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia (Mean Percentage Change From Baseline at Endpoint in Intention-to-Treat Population)

<table>
<thead>
<tr>
<th>DOSAGE</th>
<th>N</th>
<th>Total-C</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
<th>Apolipoprotein B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>47</td>
<td>-1.5</td>
<td>-0.4</td>
<td>-1.9</td>
<td>1.0</td>
<td>0.7</td>
</tr>
<tr>
<td>LIPICTOR</td>
<td>140</td>
<td>-31.4</td>
<td>-39.6</td>
<td>-12.0</td>
<td>-34.0</td>
<td></td>
</tr>
</tbody>
</table>

The mean achieved LDL-C value was 130.7 mg/dL (range: 70.0–242.0 mg/dL) in the LIPICTOR group compared to 228.5 mg/dL (range: 152.0–385.0 mg/dL) in the placebo group during the 26-week double-blind phase.

Atorvastatin was also studied in a three year open-label, uncontrolled trial that included 163 patients with HeFH who were 10 years to 15 years old (82 boys and 81 girls). All patients had a clinical diagnosis of HeFH confirmed by genetic analysis (if not already confirmed by family history). Approximately 86% were Caucasian, and less than 1% were Black or Asian. Mean LDL-C at baseline was 232 mg/dL. The starting atorvastatin dosage was 10 mg once daily and doses were adjusted to achieve a target of < 130 mg/dL LDL-C. The reductions in LDL-C from baseline were generally consistent across age groups within the trial as well as with previous clinical studies in both adult and pediatric placebo-controlled trials. The long-term efficacy of LIPICTOR therapy in childhood to reduce morbidty and mortality in adulthood has not been established.
PATIENT INFORMATION

LIPITOR (lip-ih-tore)

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

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

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

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

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

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

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

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

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

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

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

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

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

In clinical studies, patients reported the following common side effects while taking LIPITOR: diarrhea, upset stomach, muscle and joint pain, and alterations in some laboratory blood tests.
The following additional side effects have been reported with LIPITOR: tiredness, tendon problems, memory loss, and confusion.
Talk to your doctor or pharmacist if you have side effects that bother you or that will not go away.
These are not all the side effects of LIPITOR. Ask your doctor or pharmacist for a complete list.

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

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

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

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

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