CENTERS FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 20-702/S012

Trade Name: Lipitor

Generic Name: Atorvastatin calcium

Sponsor: Parke-Davis Research and Development

Approval Date: June 3, 1998
## Reviews / Information Included in this NDA Review.

<table>
<thead>
<tr>
<th>Reviews / Information</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval Letter</td>
<td>X</td>
</tr>
<tr>
<td>Approvable Letter</td>
<td></td>
</tr>
<tr>
<td>Labeling</td>
<td></td>
</tr>
<tr>
<td>Medical Review(s)</td>
<td></td>
</tr>
<tr>
<td>Chemistry Review(s)</td>
<td></td>
</tr>
<tr>
<td>Pharmacology Review(s)</td>
<td></td>
</tr>
<tr>
<td>Statistical Review(s)</td>
<td></td>
</tr>
<tr>
<td>Microbiology Review(s)</td>
<td></td>
</tr>
<tr>
<td>Clinical Pharmacology/ Biopharmaceutics Review(s)</td>
<td></td>
</tr>
<tr>
<td>Administrative/Correspondence Document(s)</td>
<td>X</td>
</tr>
</tbody>
</table>
APPLICATION NUMBER:
NDA 20-702/S012

APPROVAL LETTER
Dear Mr. Parker:

Please refer to your supplemental new drug application dated March 2, 1998, received March 3, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.70(c) for Lipitor (atorvastatin calcium) Tablets.

The supplemental application contains final printed labeling (#0155G025) that was implemented on or about March 2, 1998. Supplement -012 provides for changes in the “Post introduction Reports” subsection of the ADVERSE REACTIONS section of the Lipitor package insert to include rhabdomyolysis following “edema” as an adverse reaction.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use with the revision listed below. Accordingly, the supplemental application is approved effective on the date of this letter. The revision is as follows:

Delete the entire “Other Concomitant Therapy” paragraph from the “Drug Interactions” subsection of the PRECAUTIONS section of the package insert. This revision is a term of the supplemental NDA approval.

Should a letter communicating important information about this drug product (i.e., a “Dear Doctor” letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.
If you have any questions, please contact Margaret Simoneau, R.Ph., Regulatory Management Officer, at (301) 827-6418.

Sincerely yours,

[Signature]

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-702/S012

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
Labeling Review

Application Number: NDA 20-702/S-012

Name of Drug: Lipitor (atorvastatin calcium) Tablets

Sponsor: Parke-Davis

Materials Reviewed: December 3, 1997 (S-004) last approved labeling and March 2, 1998 revised draft labeling. Review was done on May 8, 1998 by Jena Weber and Margaret Simoneau.

Background and Summary Descriptions: The submission dated March 2, 1998 included FPL (#0155G025) from S-004 and changes being effected for S-012.

Rhabdomyolysis is added as an ADVERSE REACTION.

On March 2, 1998 all manufacturers of marketed of HMG-CoA reductase inhibitors were sent comments about the deletion of Other Concomitant Therapy from the PRECAUTIONS, Drug Interactions section of the current approved labeling. This was NOT done and will be noted in the approval letter with the revision noted.

Submission dated March 2, 1998 with FPL has been accepted by the reviewing team members. This is Lipitor (#0155G025).

Medical Team Leader: 5-8-98

Chemistry Team Leader: 

Pharmacology Team Leader: 5/8/98

Chemistry reviewer: C. More 5/8/98

Project manager: 

Chief, Project Manager: 

Project manager, Margaret Simoneau: 

Chief, Project Manager: 

cc: NDA 20-702/S-012
cc:
Original NDA 20-702
HFD-510/Div. files
HFD-510/CSO/M. Simoneau
HFD-510/D. Orloff/X. Ysenn/S. Moore/R. Steigerwalt/E. Galliers
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling)
HFI-20/Press Office (with labeling)

Drafted by: Mas/May 8, 1998/20702.12
Initialed by: D. Orloff 5.8.98/S. Moore 5.8.98/R. Steigerwalt 5.8.98/E. Galliers 6.2.98
final: Mas 6.2.98

APPROVAL (AP)
March 2, 1998

NDA 20-702,
Lipitor® (atorvastatin calcium) Tablets

Re: Special Supplement- Changes Being Effected - Labeling Supplement

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Sobel:

Reference is made to our approved NDA (20-702) for Lipitor® (atorvastatin calcium) Tablets.

In accordance with 21 CFR §314.70(c)(2)(i), we are submitting a labeling supplement, Changes Being Effected, which revises the Lipitor package insert to include rhabdomyolysis as an adverse reaction. Specifically, we have included this adverse event in the ADVERSE REACTIONS section, Postintroduction Report subsection following "edema".

Inclusion of rhabdomyolysis is based on three post-marketing adverse event reports, copies of which are included herein as follows:

- Attachment 1: Report #001-0981-971742 (2 pages)
- Attachment 2: Report #001-0981-970661 (1 page)
- Attachment 3: Report #049-0981-970134 (2 pages)

Twenty copies of the revised Lipitor package insert, specification number 0155G025 dated February 1998, are included with this submission as Attachment 4.
Solomon Sobel, M.D.
NDA 20-702
March 2, 1998
Page 2

Please note this revised package insert also contains the recent change to the liver monitoring schedule, as approved by FDA on February 2, 1998 (S-004).

If you have any questions or require additional information, please do not hesitate to contact me at 973/540-3113 or FAX 973/540-5972.

Sincerely,

James A. Parker, Jr.
Director
Advertising & Labeling
Worldwide Regulatory Affairs

REVIEWED COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

JPlsv\rm

Attachments

To be converted into section S-005 and S-007
NDA 20-702/S-012

PARKE -DAVIS RESEARCH AND DEVELOPMENT
WARNER-LAMBERT COMPANY
2800 Plymouth Road
Ann Arbor, MI 48105

Attention: James A. Parker, Jr., Director, Advertising & Labeling Worldwide Regulatory Affairs

Dear Mr. J. A. Parker:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: LIPITOR (atorvastatin calcium) Tablets
NDA Number: 20-702
Supplement Number: S-012
Date of Supplement: March 2, 1998
Date of Receipt: March 3, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on May 2, 1998, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

[Signature]

End Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
cc:
Original NDA 20-702/S-012
HFD-510/Div. Files
HFD-510/CSO/M. Simoneau

filename:
SUPPLEMENT ACKNOWLEDGEMENT
Lipitor®
(Atorvastatin Calcium) Tablets

DESCRIPTION
Atorvastatin calcium 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)-4,4-dihydroxy-6-(1-methylbutyl)-3-phenyl-1-(phenylmethylcarboxyl)-1H-pyrrole-1-carboxylic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is C_{35}H_{30}F_{6}CaO_{4}N_{2}S and its molecular weight is 728.62. Its structural formula is:

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{N} & \quad \text{CO}_2 \text{H} \\
\text{C}_6 \text{H}_4 & \quad \text{CH}_2 \text{CH}_2 \text{CH}_2 \text{CH}_2 \\
& \quad \text{CH}_3 \\
\text{C}_6 \text{H}_4 & \quad \text{CH}_3 \\
\text{C}_6 \text{H}_4 & \quad \text{CH}_3 \\
\end{align*}
\]

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 acetone/MeOH, slightly soluble in ethanol, and freely soluble in methanol.

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

CLINICAL PHARMACOLOGY
Mechanism of Action

Atorvastatin 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, diglycerides, and triglycerides. After inhibition, these compounds are then de novo synthesized into LDL (low-density lipoproteins), VLDL (very-low-density lipoproteins), and HDL (high-density lipoproteins). Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote atherogenesis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

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 LPL production and the number of LPL particles. Lipitor reduces LDL-C in some patients with homozygous familial hypercholesterolemia (FH), a population that rarely responds to other lipid-lowering medication(s).

A variety of clinical studies have demonstrated that elevated levels of total-C, LDL-C, and apo B are membrane complex for LDL-C and its transport complex, apo A-I are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C, and inversely with the level of HDL-C. Although often found in association with low HDL-C, elevated plasma TG has not been established as an independent risk factor for coronary heart disease. The independent effect of raising HDL-C or lowering TG on the risk for coronary and cardiovascular morbidity and mortality has not been established.

Lipitor reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous FH, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Lipitor also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-I. The effect of Lipitor on cardiovascular morbidity and mortality has not been determined.
Pharmacodynamics
Atorvastatin is a potent and selective inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis. Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibition activity is approximately 29%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin 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).

Distribution: Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin 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, atorvastatin is likely to be secreted in human milk (see INDICATIONS, Pregnancy and Lactation, and PRECAUTIONS, Nursing Mothers).

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

Special Populations
Geriatric: Plasma concentrations of atorvastatin are higher (approximately 40% for Cmax and 36% for AUC) in healthy elderly subjects (age ≥66 years) than in young adults. LDL-C reduction is comparable to that seen in younger patient populations given equal doses of Lipitor.

Pediatric: Pharmacokinetic data in the pediatric population are not available.

Gender: Plasma concentrations of atorvastatin in women differ from those in men (approximately 25% higher for Cmax and 18% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with Lipitor between men and women.

Renal Insufficiency: Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, dose adjustment in patients with renal dysfunction is not necessary (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: While studies have not been conducted in patients with end-stage renal disease, hemodialysis is expected to significantly enhance clearance of atorvastatin since the drug is extensively bound to plasma proteins. Furthermore, in patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. Cmax and AUC are each 6-fold greater in patients with Childs Pugh B disease, respectively; patients with Childs Pugh B disease (see CONTRAINDICATIONS).

Clinical Studies
Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types I, IIa and IIb)
Lipitor reduces total-C, LDL-C, VLDL-C, apo B, and TG, and increases HDL-C in patients with hypercholesterolemia and mixed dyslipidemia. 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 hypercholesterolemia, with and without hypertriglyceridemia, in men and women, and in the elderly. Experience in pediatric patients has been limited to patients with heterozygous FH.

In two multicenter, placebo-controlled, dose-response studies in patients with hypercholesterolemia, 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 1).
TABLE 1. Dose-Response in Patients With Primary Hypercholesterolemia (Adjusted Mean % Change From Baseline)*

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th>TC</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>Placebo</td>
<td>21</td>
<td>4</td>
<td>6</td>
<td>3</td>
<td>10</td>
<td>-3</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>22</td>
<td>-29</td>
<td>-29</td>
<td>-32</td>
<td>-19</td>
<td>6</td>
<td>-34</td>
</tr>
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<td>20</td>
<td>20</td>
<td>-33</td>
<td>-33</td>
<td>-35</td>
<td>-26</td>
<td>9</td>
<td>-41</td>
</tr>
<tr>
<td>40</td>
<td>21</td>
<td>-37</td>
<td>-50</td>
<td>-42</td>
<td>-29</td>
<td>6</td>
<td>-45</td>
</tr>
<tr>
<td>80</td>
<td>22</td>
<td>-45</td>
<td>-52</td>
<td>-50</td>
<td>-37</td>
<td>5</td>
<td>-53</td>
</tr>
</tbody>
</table>

*Results are pooled from two dose-response studies.

TABLE 2. Mean Percent Change From Baseline at End Point (Double-Blind, Randomized, Active-Controlled Trials)

<table>
<thead>
<tr>
<th>Treatment (Daily Dose)</th>
<th>N 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>
</table>
| Study 1
| Atorvastatin 10 mg    | 767  | -21* | -30* | -29* | -17* | +7              |
| Lovastatin 20 mg       | 191  | -19  | -27   | -20  | -6   | +7              |
| 95% CI for Diff        | -8.2, -4.5 | -10.0, -7.1 | -10.0, -6.5 | -15.2, -7.1 | -17.2, -11.1, -7.1 |
| Study 2
| Atorvastatin 10 mg    | 222  | -29* | -30* | -37* | -17* | +6              |
| Pravastatin 20 mg      | 77   | -17  | -23   | -17  | -9   | +8              |
| 95% CI for Diff        | -10.8, -6.1 | -14.5, -8.2 | -13.4, -7.4 | -14.1, -0.7 | -4.9, 1.6, -11.5, -4.1 |
| Study 3
| Atorvastatin 10 mg    | 132  | -29* | -37* | -34* | -23* | +7              |
| Simvastatin 10 mg      | 45   | -24  | -30   | -33  | -15  | +7              |
| 95% CI for Diff        | -8.7, -2.7 | -10.1, -2.6 | -8.0, -1.1 | -15.1, -0.7 | -4.3, 3.9, -9.6, -1.9 |

*Significantly different from placebo, ANCOVA, p < 0.05.
*Significantly different from pravastatin, ANCOVA, p < 0.05.
*Significantly different from simvastatin, ANCOVA, p < 0.05.

The impact on clinical outcomes of the differences in lipid-altering effects between treatments shown in Table 2 is not known. Table 2 does not contain data comparing the effects of atorvastatin 10 mg and higher doses of lovastatin, pravastatin, and simvastatin. The drugs compared in the studies summarized in the table are not necessarily interchangeable.

In a large clinical study, the number of patients meeting their National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) II target LDL-C levels on 10 mg of Lipitor was assessed. After 16 weeks, 150/167 (90%) of patients with less than 2 risk factors for CHD and baseline LDL-C ≥ 190 mg/dL reached a target of ≤ 100 mg/dL; 14/138 (6%) of patients with 2 or more risk factors for CHD and LDL-C ≥ 190 mg/dL achieved a level of ≤ 100 mg/dL. LDL-C, and 2/113 (19%) of patients with CHD and LDL-C ≥ 130 mg/dL reached a target level of ≤ 100 mg/dL. LDL-C.

Homozygous Familial Hypercholesterolemia

In a study without a concurrent control group, 29 patients ages 6 to 37 years with homozygous FH received maximum daily doses of 29 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 LDL-C reductions of 28%. The remaining 4 patients who had a LDL-C reduction had no significant reduction in LDL-C. The remaining 3 patients had a mean LDL-C reduction of 22%.

INDICATIONS AND USAGE

Lipitor is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb). Lipitor is also indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (eg, LDL apheresis) or if such treatments are unachievable.

Therapy with lipid-altering agents should be a component of multiple-risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol only when the response to diet and other nonpharmacologic measures has been inadequate (see National Cholesterol Education Program (NCEP) Guidelines, summarized in Table 3).
<table>
<thead>
<tr>
<th>Definite Atherosclerotic Disease</th>
<th>Two or More Other Risk Factors*</th>
<th>LDL Cholesterol (mg/dL)</th>
<th>Minimum Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>≥190</td>
<td>&lt;160</td>
</tr>
<tr>
<td>(≥4.9)</td>
<td>(≥4.1)</td>
<td>≥190</td>
<td>&lt;160</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>≥160</td>
<td>&lt;13.4</td>
</tr>
<tr>
<td>(≥4.1)</td>
<td>(≥3.4)</td>
<td>≥190</td>
<td>&lt;160</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes or No</td>
<td>≥130</td>
<td>≤100</td>
</tr>
<tr>
<td>(≥3.4)</td>
<td>(≥2.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Coronary heart disease or peripheral vascular disease including symptomatic carotid artery disease

**Other risk factors for coronary heart disease (CHD) include: age (male 45 years; female ≥55 years or premenopausal women, history of premature CHD in a first-degree relative (i.e., sibling, child, or parent), history of gestational diabetes, high-sensitivity C-reactive protein (hs-CRP) ≥3 mg/L, and diabetes mellitus. Subjects 1 risk factor (hs-CRP <3 mg/L) and diabetes mellitus.

In CHD patients with LDL-C levels 160 to 190 mg/dL, the physician should exercise clinical judgment in deciding whether to initiate drug treatment.

At the time of hospitalization for an acute coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C level is ≥190 mg/dL. (NCEP-ATP II).

Prior to initiating therapy with Lipitor, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C, HDL-C, and TG. For patients with TG <400 mg/dL (≥4.5 mmol/L), LDL-C can be estimated using the following equation: LDL-C = total-C - (0.39 × TG) + HDL-C. For TG levels ≥400 mg/dL (≥4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation.

CONTRAINDICATIONS

Active liver disease or unexplained persistent elevations of serum transaminases.

Hypersensitivity to any component of this medication.

Pregnancy and Lactation

Atherogenic diets are a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may pose a fetal hazard when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors should be discontinued during pregnancy and in nursing mothers. Atorvastatin should be administered contraindicated during pregnancy and in nursing mothers. Atorvastatin should be administered only to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Dysfunction

HMG-CoA reductase inhibitors, 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 atorvastatin 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, transaminase levels returned to or near pretreatment levels without sequelae. Elevations of 2 to 3 times ULN occurred in 1.8% of patients, 1.7% of patients, and 1.5% of patients treated with 10, 20, and 40 mg, respectively. Elevations of 4 times ULN occurred in 0.1% of patients, 0.1% of patients, and 0.0% of patients treated with 10, 20, and 40 mg, respectively. For patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin.

It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of ≥3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended.

Atorvastatin 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 atorvastatin (see CONTRAINDICATIONS).

Skeletal Muscle

Rhabdomyolysis with acute renal failure secondary to myoglobinuria has been reported with other drugs in this class.

Uncomplicated myalgia is an entity that has been reported in atorvastatin treated patients (see ADVERSE REACTIONS). Myalgia is defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN in some patients. Myalgia, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly.
Liptor® (Atorvastatin Calcium) Tablets

unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with other drugs in this class is increased with concurrent administration of cyclosporine, fibrin acid derivatives, erythromycin, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibrin acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering 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. 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.

Atorvastatin 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, such as severe acute infection, hypotension, hypothyroidism, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures.

PRECAUTIONS

General

Before instituting therapy with atorvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Information for Patients

Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Drug Interactions

The risk of myopathy during treatment with other drugs in this class is increased with concurrent administration of cyclosporine, fibrin acid derivatives, niacin (nicotinic acid), erythromycin, azole antifungals (see WARNINGS, Skeletal Muscle).

Antacids: When atorvastatin and Meacox® TC suspension were coadministered, plasma concentrations of atorvastatin decreased approximately 20%. However, LDL-C reduction was not altered.

Antipruritic: Because atorvastatin does not affect the pharmacokinetics of antipruritic, interactions with other drugs metabolized via the same cytochrome isoenzymes are not expected.

Colestipol: Plasma concentrations of atorvastatin decreased approximately 25% when colestipol and atorvastatin were coadministered. However, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone.

Genodermatitis: Atorvastatin plasma concentrations and LDL-C reduction were not altered by coadministration of simvastatin.

Digoxin: When multiple doses of atorvastatin and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.

Erythromycin: In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4 (see WARNINGS, Skeletal Muscle).

Oral Contraceptives: Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

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

Other Concomitant Therapy: In clinical studies, atorvastatin was used concomitantly with antihypertensive agents and estrogen replacement therapy without evidence of clinically significant adverse interactions. Interaction studies with specific agents have not been conducted.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors 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 an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of HMG-CoA reductase, e.g., ketoconazole, spironolactone, and corticosteroids.
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 mid-limb banding after 1 week of dosing at 380 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 convolution 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. There 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 (Wallenberg degeneration of retino-genetic 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.

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: one, there was a rhabdomyosarcoma and, in another, there was a osteosarcoma. 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 carcinogeticity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with Salmonella typhimurium and Escherichia coli, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the in vivo mouse micronucleus test.

Studies in 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 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); testes 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 mobility, spermatozoon head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on seminal parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS

Safety in pregnant women has not been established. Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 1000 mg/kg/day or in rabbits up to 100 mg/kg/day. These doses result in exposures of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m²).

In a study in rats given 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and puberty in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (intraventricular performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day.

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took atorvastatin with dextroamphetamine sulfate during the first trimester of pregnancy. Lipitor should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking Lipitor, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers

Nursing rat pups had plasma and liver drug levels of 60% and 40%, respectively, of that in their mother’s milk. Because of the potential for adverse reactions in nursing infants, women taking Lipitor should not breast-feed (see CONTRAINDICATIONS).

Pediatric Use

Treatment experience in a pediatric population is limited to doses of Lipitor up to 80 mg/day for 1 year in 8 patients with homozygous FH. No clinical or biochemical abnormalities were reported in these patients. None of these patients was below 9 years of age.

Geriatric Use

Treatment experienced in adults age ≥70 years with doses of Lipitor up to 80 mg/day has been evaluated in 221 patients. The safety and efficacy of Lipitor in this population were similar to those of patients <70 years of age.

ADVERSE REACTIONS

Lipitor is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies of 2602 patients, <2% of patients were discontinued due to adverse experiences attributable to atorvastatin. The most frequent adverse events thought to be related to atorvastatin were constipation, flatulence, dyspepsia, and abdominal pain.
Lipitor® (Atorvastatin Calcium) Tablets

Clinical Adverse Experiences

Adverse experiences reported in ≥2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment, are shown in Table 4.

<table>
<thead>
<tr>
<th>Table 4. Adverse Events in Placebo-Controlled Studies (% of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BODY SYSTEM</strong>/Adverse Event</td>
</tr>
<tr>
<td><strong>BODY AS A WHOLE</strong></td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Accidental Injury</td>
</tr>
<tr>
<td>Flu Syndrome</td>
</tr>
<tr>
<td>Abdominal Pain</td>
</tr>
<tr>
<td>Back Pain</td>
</tr>
<tr>
<td>Allergic Reaction</td>
</tr>
<tr>
<td>Asthenia</td>
</tr>
</tbody>
</table>

**DIGESTIVE SYSTEM**

| Constipation | 1.8 | 2.1 | 0.0 | 2.5 | 1.1 |
| Diarrhea | 1.5 | 2.7 | 0.0 | 3.8 | 5.3 |
| Dyspepsia | 4.1 | 2.3 | 2.8 | 1.3 | 2.1 |
| Flatulence | 3.3 | 2.1 | 2.8 | 1.3 | 1.1 |

**RESPIRATORY SYSTEM**

| Sinusitis | 2.8 | 2.8 | 0.0 | 2.5 | 6.4 |
| Pharyngitis | 1.5 | 2.5 | 0.0 | 1.3 | 2.1 |

**SKIN AND APPENDAGES**

| Rash | 0.7 | 3.9 | 2.8 | 3.8 | 1.1 |

**MUSCULOSKELETAL SYSTEM**

| Arthralgia | 1.5 | 2.0 | 0.0 | 6.1 | 0.0 |
| Myalgia | 1.1 | 3.2 | 5.6 | 1.3 | 0.0 |

The following adverse events were reported, regardless of causality assessment in patients treated with atorvastatin in clinical trials. The events in italics occurred in 2% of patients and the events in plain type occurred in <2% of patients.

Body as a Whole: Chest pain, face edema, fever, neck rigidity, malaise, photosensitivity reaction, paresthesia, phlebitis, edema.

Digestive System: Nausea, gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, epistaxis, enacation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cholecystitis, diarrhea, enteritis, melena, gum hemorrhage, stomach ulcer, teneuritis, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice.

Respiratory System: Bronchitis, rhinitis, pneumonia, dyspnea, asthma, epistaxis.

Nervous System: Insomnia, dizziness, paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysys, hyperkinesia, depression, hypotension, hypertension.

Musculoskeletal System: Arthritis, leg cramps, bursitis, tenosynovitis, myasthenia, tendinious contracture, myositis.

Skin and Appendages: Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer.

Urogenital System: Urinary tract infection, urinary frequency, cystitis, hematuria, incontinence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, albuminuria, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage.

Special Senses: Amblyopia, sinusitis, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, paresthesia, taste loss, taste perversion.

Cardiovascular System: Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, thrombosis, angina pectoris, hypertension.
Metabolic and Nutritional Disorders: Peripheral edema, hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypercholesterolemia.

Hematologic System: Ectromyositis, anemia, lymphadenopathy, thrombocytopenia, pancytopenia, neutropenia.

Adverse events associated with Liptor that have been reported since market introduction, that are not listed above, and that may have no causal relationship to drug include the following: angioneurotic edema and rhabdomyolysis.

OVERDOSE

There is no specific treatment for atorvastatin 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 atorvastatin clearance.

DOSEAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving Liptor and should continue on this diet during treatment with Liptor.

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIB and IHD)

The recommended starting dose of Liptor is 10 mg once daily. The dosage range is 10 to 80 mg once daily. Liptor can be administered as a single dose at any time of the day, with or without food. Therapy should be individualized according to goal of therapy and response (see NCEP Guidelines, summarized in Table 1). After initiation or adjustment of Liptor, lipid levels should be analyzed within 2 to 4 weeks of therapy. Dosage adjusted accordingly.

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should total-C be used to monitor therapy.

Homozygous Familial Hypercholesterolemia

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

Concomitant Therapy

Atorvastatin may be used in combination with a bile acid binding resin for additive effect. The combination of HMG-CoA reductase inhibitors and fibrates should generally be avoided (see WARNINGS, Skeletal Muscle, and PRECAUTIONS, Drug Interactions for other drug-drug interactions).

Dosage in Patients With Renal Insufficiency

Renal disease does not affect the plasma concentrations nor LDL-C reduction of atorvastatin; thus, dosage adjustment in patients with renal dysfunction is not necessary (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

HOW SUPPLIED

Liptor is supplied as white, elliptical, film-coated tablets of atorvastatin calcium containing 10, 20, and 40 mg atorvastatin.

10 mg tablets: coded “PD 156” on one side and “10” on the other.
N0071-0155-23 bottles of 90
N0071-0155-34 bottles of 600
N0071-0155-40 10 x 10 unit dose blister strips

20 mg tablets: coded “PD 156” on one side and “20” on the other.
N0071-0155-23 bottles of 90
N0071-0155-40 10 x 10 unit dose blister strips

40 mg tablets: coded “PD 167” on one side and “40” on the other.
N0071-0157-23 bottles of 90

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

Revised February 1998

Manufactured by:
Warner-Lambert Export, Ltd © 1998
Dublin, Ireland

Distributed by:
PARKE-DAVIS
- Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA
MADE IN GERMANY

Marketed by:
PARKE-DAVIS
- Div of Warner-Lambert Co and
PFIZER Inc.
New York, NY 10017
0155G025
Lipitor® (atorvastatin calcium) 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 a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

Mechanism of Action
Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A (3-HMG-CoA) to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), LDL (low-density lipoprotein), IDL (intermediate-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is esterified primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

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. Lipitor reduces LDL-C in some patients with homozygous familial hypercholesterolemia (FH), a population that rarely responds to other lipid-lowering medications. A variety of clinical studies have demonstrated that elevated levels of total-C, LDL-C, and apo B (a membrane complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-C and its transport component apo A-I are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. Although the exact relationship between cholesterol and cardiovascular morbidity and mortality has not been established, Lipitor reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous FH, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Lipitor also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-I. The effect of Lipitor on cardiovascular morbidity and mortality has not been determined.

Pharmacodynamics
Atorvastatin 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 catabolism. 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).

Pharmacokinetics and Drug Metabolism
Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to the atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% to 15% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 29%. The low systemic availability is attributed to pre-systemic clearance in gastrointestinal mucosa and 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 atorvastatin is given with or without food. Plasma atorvastatin 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).

Distribution: Mean volume of distribution of atorvastatin is approximately 351 liters. Atorvastatin is 34% 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, atorvastatin is likely to be excreted in human milk (see DOSAGE AND ADMINISTRATION).
Absorption: Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-glucuronides. In vitro inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is 80% of that of atorvastatin. Approximately 10% of circulating inhibitory activity for HMG-CoA reductase is contributed to active metabolites. In vivo studies suggest the importance of atorvastatin, hydroxycarboxylic monoesters, as well as those with increased plasma concentrations of atorvastatin in humans following coadministration with omeprazole, a known inhibitor of this drug, and less than 10% of active metabolites. There is less than 1% of active metabolites.

Special Populations

Geriatric: Plasma concentrations of atorvastatin in elderly persons (age 65 years) are comparable to those detected in younger patients, and atorvastatin exposure is not significantly affected by age. Atorvastatin reduction in LDL-C is comparable to that seen in younger patients populations of equal dose of Lipitor.

Pediatric: Pharmacokinetic data in the pediatric population are not available.

Gender: Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher in women). Low-density lipoprotein cholesterol reduction with Lipitor is similar in both men and women.

Renal Insufficiency: Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, dosage adjustment in patients with renal dysfunction is not necessary (see DOSAGE AND ADMINISTRATION).

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

Hepatic Insufficiency: In patients with chronic alcoholics or liver disease, plasma concentrations of atorvastatin are markedly increased. Cmax and AUC are each 4-fold greater in patients with Childs-Pugh A disease. Cmax and AUC are approximately 10-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease (see CONTRAINDICATIONS).

Clinical Studies

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIA and IIB)

Lipitor reduces total-C, LDL-C, VLDL-C, apo B, and TG, and increases HDL-C in patients with hypercholesterolemia and mixed dyslipidemia. 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 hypercholesterolemia, with and without hypertriglyceridemia, in men and women, and in the elderly. Experience in pediatric population has been limited to patients with homocysteinemia.

In two multicenter, placebo-controlled, dose-response studies in patients with hypercholesterolemia, Lipitor given as a single dose over 5 weeks significantly reduced total-C, LDL-C, apo B, and TG (Table 1). Results are provided in Table 1.

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th>TC</th>
<th>LDL-C</th>
<th>Apo B</th>
<th>TG</th>
<th>HDL-C</th>
<th>Non-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>
</tr>
<tr>
<td>10</td>
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<td>-19</td>
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<td>-50</td>
<td>-37</td>
<td>5</td>
<td>-53</td>
<td></td>
</tr>
</tbody>
</table>

*Results are pooled from 2 dose-response studies.

In three multicenter, double-blind studies in patients with hypercholesterolemia, Lipitor was compared to other HMG-CoA reductase inhibitors. After randomization, patients were treated for 16 weeks with either Lipitor 10 mg per day or a fixed dose of the comparative agent (Table 2).

<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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>21</td>
<td>-29</td>
<td>-39</td>
<td>-32</td>
<td>-19</td>
<td>6</td>
<td>-34</td>
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<td>10</td>
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<td>-50</td>
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<td>5</td>
<td>-53</td>
<td></td>
</tr>
</tbody>
</table>

*Results are pooled from 2 dose-response studies.
The impact of the outcomes of the differences in lipid-lowering effects between treatments shown in Table 2 is not known. Table 2 does not contain data comparing the effects of atorvastatin 10 mg and higher doses of pravastatin, pravastatin, and simvastatin. The drugs compared in the studies summarized in the table are not necessarily interchangeable.

In a large clinical study, the number of patients meeting their National Cholesterol Education Program—Adult Treatment Panel (NCEP-ATP II) target LDL-C levels on 10 mg of Lipitor daily was assessed. After 16 weeks, 10,916/7 (60%) of patients with less than 2 risk factors for CHD and baseline LDL-C ≤ 160 mg/dL reached a target of ≤ 160 mg/dL. 12,712/8 (66%) of patients with 2 or 3 risk factors for CHD and LDL-C ≤ 160 mg/dL achieved a level of ≤ 160 mg/dL. LDL-C, and 21,172 (19%) of patients with CHD and LDL-C ≥ 130 mg/dL reached a target of ≤ 160 mg/dL. LDL-C.

Homozygous Familial Hypercholesterolemia

In a study without a concurrent control group, 252 patients ages 6 to 37 years with homozygous FH received maximum daily doses of 20 to 60 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 33%), median of 24%; the remaining 4 patients had 7% to 24% increases in LDL-C. Five of the 28 patients had absent LDL-cholesterol function. Of these, 2 patients also had a perivalvular shunt and had no significant reduction in LDL-C. The remaining 2 receptor-negative patients had a mean LDL-C reduction of 32%.

INDICATIONS AND USAGE

Lipitor is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, age B and TG levels in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Freudstein Type IIa and IIb).

Lipitor is also indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (eg, LDL apheresis) or if such treatments are unavalaible.

Therapy with Lipitor agents should be a component of multiple-risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-lowering agents should be used in addition to a diet restricted in saturated and cholesterol only when the response to diet and other nonpharmacological measures has been inadequate (see National Cholesterol Education Program (NCEP) Guidelines, summarized in Table 3).

<table>
<thead>
<tr>
<th>TABLE 3. NCEP Guidelines for Lipid Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite Atherosclerotic Disease</td>
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<td>Yes or No</td>
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</tbody>
</table>

*Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).

At the time of hospitalization for an acute coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C level is ≥ 130 mg/dL (NCEP-ATP II).

Prior to initiating therapy with Lipitor, secondary causes for hypercholesterolemia (eg, poorly controlled diabetes mellitus, hypoprotrominemia, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other drug therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C, HDL-C, and TG. For patients with TG ≥ 400 mg/dL (4.5 mmol/L), LDL-C can be estimated using the following equation: LDL-C = total-C - (0.20 × [TG] + HDL-C). For TG levels > 400 mg/dL (4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation.

CONTRAINDICATIONS

Active liver disease or unexplained persistent elevations of serum transaminases. Hypersensitivity to any component of this medication.

Pregnancy and Lactation

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reduclease inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductases inhibitors are contraindicated during pregnancy and in nursing mothers. ATOVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF-childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.
It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter.
Warfarin: Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving warfarin treatment.

Other Concomitantly used concomitantly with antihypertensive agents and diuretic therapy without evidence of clinically significant adverse interactions. Interaction studies specific agents have not been conducted.

Endocrine Function

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

CNS Toxicity

Brain hemorrhage was seen in a male dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolization were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 340 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-units (AUC, 0-24 h) based on the maximum human dose of 80 mg/day. A single toxic convulsion was seen in a male dog (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 rats at doses up to 100 mg/kg/day. These doses were 8 and 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 (Wallenberg degeneration of retinal ganglion cell fibers) in clinically normal dogs in a dose-dependent fashion at doses that produced plasma drug levels about 20 times higher than the mean drug level in humans taking the highest recommended dose.

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 tumors were found in mice 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 8 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 S. 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.

Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was a decrease in the number of viable eggs in the 200 mg/kg group in a 1-month study. In a 1-month study, the body weight was significantly lower at 100 and 300 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg for 11 weeks prior to mating had decreased sperm motility. Spermatid head condensation, 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.

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m²).

In a study in rats given 20, 100, or 250 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 250 mg/kg/day. Body weight was decreased on days 4 and 51 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 81 at 250 mg/kg/day. Pup development was delayed (pup performance at 100 mg/kg/day and weanling start at 225 mg/kg/day; plasma destruction and eye opening at 300 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (250 mg/kg) the human AUC at 80 mg/kg.

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bone deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took atorvastatin with dextroamphetamine sulfate during the first trimester of pregnancy. Liptor should be discontinued and the patient advised to avoid the potential hazards to the fetus.

Nursing Mothers

Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking Liptor should not breastfeed (see CONTRAINDICATIONS).

Pediatric Use

Treatment experience in a pediatric population is limited to doses of Liptor up to 80 mg/day for a year in 8 patients with homozygous FH. No clinical or biochemical abnormalities were reported in these patients. None of these patients was below 8 years of age.

Geriatric Use

Treatment experience in adults age 70 years with doses of Liptor up to 80 mg/day has been evaluated in 221 patients. The safety and efficacy of Liptor in this population are similar to those of patients <70
Table 4. Adverse Events in Placebo-Controlled Studies (% of Patients)

<table>
<thead>
<tr>
<th>Body Area (System)</th>
<th>Placebo (N=270)</th>
<th>Atorvastatin 10 mg (N=863)</th>
<th>Atorvastatin 20 mg (N=36)</th>
<th>Atorvastatin 40 mg (N=79)</th>
<th>Atorvastatin 80 mg (N=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infecion</td>
<td>10.0</td>
<td>10.3</td>
<td>2.6</td>
<td>10.1</td>
<td>7.4</td>
</tr>
<tr>
<td>Headache</td>
<td>7.0</td>
<td>5.4</td>
<td>16.7</td>
<td>2.5</td>
<td>6.4</td>
</tr>
<tr>
<td>Accidental Injury</td>
<td>3.7</td>
<td>4.2</td>
<td>0.0</td>
<td>1.3</td>
<td>3.2</td>
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<tr>
<td>Flu Syndrome</td>
<td>1.9</td>
<td>2.2</td>
<td>0.0</td>
<td>2.5</td>
<td>3.2</td>
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<tr>
<td>Abdominal Pain</td>
<td>0.7</td>
<td>2.8</td>
<td>0.0</td>
<td>3.8</td>
<td>2.1</td>
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<tr>
<td>Back Pain</td>
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<td>0.0</td>
<td>3.8</td>
<td>1.3</td>
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<tr>
<td>Allergic Reaction</td>
<td>2.6</td>
<td>2.9</td>
<td>0.0</td>
<td>1.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1.9</td>
<td>2.2</td>
<td>0.0</td>
<td>3.8</td>
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<tr>
<td>Digestive System</td>
<td></td>
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<tr>
<td>Constipation</td>
<td>1.8</td>
<td>2.1</td>
<td>0.0</td>
<td>2.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Diarrhea</td>
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<td>2.7</td>
<td>0.0</td>
<td>3.8</td>
<td>5.3</td>
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<tr>
<td>Dyspepsia</td>
<td>4.1</td>
<td>2.3</td>
<td>2.6</td>
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<td>2.1</td>
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<tr>
<td>Flatulence</td>
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<td>2.1</td>
<td>2.6</td>
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<td>Respiratory System</td>
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<td>Sinusitis</td>
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<td>2.8</td>
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<td>Pharyngitis</td>
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<td>0.0</td>
<td>1.3</td>
<td>2.1</td>
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<tr>
<td>Skin and Appendages</td>
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<tr>
<td>Rash</td>
<td>0.7</td>
<td>3.9</td>
<td>2.6</td>
<td>3.8</td>
<td>1.1</td>
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<td>Musculoskeletal System</td>
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<tr>
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<td>2.0</td>
<td>0.0</td>
<td>5.1</td>
<td>0.0</td>
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<tr>
<td>Myalgia</td>
<td>1.1</td>
<td>3.2</td>
<td>5.6</td>
<td>1.3</td>
<td>0.0</td>
</tr>
</tbody>
</table>

The following adverse events were reported, regardless of causality assessment in patients treated with atorvastatin in clinical trials. The events in italics occurred in ≥2% of patients and the events in plain type occurred in <2% of patients.

Body as a Whole: Chest pain, face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema.

Gastrointestinal: Nausea, gastralgia, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, diarrhea, bile duct, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice.

Respiratory: Bronchitis, minimis, pneumonia, dyspnea, asthma, apnea.

Vascular: Venous insufficiency, blindness, pancreatitis, somnolence, anemia, abnormal dreams, libido decreased, emotional lability, incontinence, peripheral neuropathy, tinnitus, facial paresthesia, hyperkalemia, depression, hypophosphaemia, hyperpigmentation.

Musculoskeletal: Arthritis, leg cramps, bursitis, tenosynovitis, myositis, tendinous contracture, myalgia.

Skin and Appendages: Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, edema, abscess, skin ulcer.

Urogenital: Urinary tract infection, urinary frequency, cystitis, hematuria, impotence, dysuria, kidney calculus, nocturia, epididymitis, thrombocytopenia, breast edema, vaginal hemorrhage, albuminuria, breast engorge, mastalgia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage.

Special Sensation: Amphotropia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, arthrosis, taste loss, taste perversion.

Cardiovascular: Palpitations, vasodilation, hypotension, syncope, migraine, postural hypotension, phlebitis, myocarditis, angina pectoris, hyperextension.

Metabolic and Nutritional Disorders: Peripheral edema, hyperglycemia, creatine phosphokinase increased, rhabdomyolysis.

Dosage and Administration: The usual dose of the drug is 10 mg daily. Dosage may be increased to 20 mg daily after one month if needed.

Overdosage: There is no specific treatment for atorvastatin 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 atorvastatin clearance.
Dosage and Administration

The patient should be on a standard cholesterol-lowering diet before receiving Lipitor and should continue on this diet during treatment with Lipitor.

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemias (Fredrickson Types IIa and IIb)

The recommended starting dose of Lipitor is 10 mg once daily. The dosage range 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. Therapy should be individualized according to goal of therapy and response (see NCEP Guidelines, summarized in Table 1). After initiation and/or upon titration of Lipitor, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should total-C be used to monitor therapy.

Homozygous Familial Hypercholesterolemia

The dosage of Lipitor in patients with homozygous FH is 10 to 80 mg daily. Lipitor should be used as an adjunct to other lipid-lowering treatments (eg, LDL apheresis) in these patients, if such treatments are unavailable.

Concomitant Therapy

Atorvastatin may be used in combination with a bile acid binding resin for additive effect. The combination of HMG-CoA reductase inhibitors and fibrates should generally be avoided (see WARNINGS, Skeletal Muscle, and PRECAUTIONS, Drug Interactions for other drug-drug interactions).

Dosage in Patients With Renal Insufficiency

Renal disease does not affect the plasma concentrations nor LDL-C reduction of atorvastatin; thus, dosage adjustment in patients with renal dysfunction is not necessary (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

How Supplied

Lipitor is supplied as white, elliptical, film-coated tablets of atorvastatin calcium containing 10, 20, and 40 mg atorvastatin.

10 mg tablets: coded *PD 155* on one side and "10" on the other.
NDC7-0155-33 bottles of 90
NDC7-0155-34 bottles of 6000
NDC7-0155-40 10 x 10 unit-dose blisters

20 mg tablets: coded *PD 156* on one side and "20" on the other.
NDC7-0156-33 bottles of 90
NDC7-0156-40 10 x 10 unit-dose blisters

40 mg tablets: coded *PD 157* on one side and "40" on the other.
NDC7-0157-33 bottles of 90

Storage

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

Caution – Federal law prohibits dispensing without prescription.


Revised November 1997

PARKE-DAVIS
Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA
MADE IN GERMANY

Marketed by:
PARKE-DAVIS
Div of Warner-Lambert Co and
PFIZER Inc.
New York, NY 10017

0155G023
USER FEE COVER SHEET

1. APPLICANTS NAME AND ADDRESS

James A. Parker, Jr.
Parke-Davis Regulatory Affairs
201 Tabor Rd.
Morris Plains, NJ 07950

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

Mary E. Taylor, MPH
Parke-Davis Research and Development
Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105

3. TELEPHONE NUMBER (INCLUDE AREA CODE) (313)996-5000

4. PRODUCT NAME

Lipitor® (atorvastatin calcium) Tablets

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA? ☑ NO

6. USER FEE I.D. NUMBER

7. LICENSE NUMBER

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT
APPROVED BEFORE 9/1/92

☐ AN INSULIN PRODUCT SUBMITTED UNDER 506

☐ THE APPLICATION IS SUBMITTED UNDER 505(b)(2)
(See reverse before checking box.)

☐ FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR
TRANSFUSION

☐ A CRUDE ALLERGIC EXTRACT PRODUCT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL
APPLICATION LICENSED BEFORE 9/1/92

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT
LICENSED UNDER 351 OF THE PHS ACT

9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION? ☑ YES ☑ NO

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☑ YES ☑ NO

This completed form must be signed and accompany each new drug or biologic product, original or supplement.

NATURAL OF AUTHORIZED COMPANY REPRESENTATIVE

TITLE

DIRECTOR

ADVERTISING AND LABELING

WORLDWIDE REGULATORY AFFAIRS

DATE

March 2, 1998