CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-702/S-008

Trade Name: Lipitor Tablets 10 mg, 20 mg, and 40 mg

Generic Name: atorvastatin calcium

Sponsor: Parke Davis Pharmaceutical Research

Approval Date: November 5, 1997
**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER:**

20-702/S-008

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APPLICATION NUMBER: 20-702/S-008

APPROVAL LETTER
Parke-Davis Pharmaceutical Research, Div. of Warner-Lambert Company
Attention: Margaret Uprichard, Pharm.D.
Manager, FDA Liaison, Worldwide Regulatory Affairs
2800 Plymouth Road
P.O. Box 1047
ANN ARBOR, MI 48106-1047

Dear Dr. Uprichard:

Please refer to your supplemental new drug application dated September 5, 1997, received September 8, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lipitor (atorvastatin calcium) Tablets, 10 mg, 20 mg, and 40 mg.

We acknowledge receipt of your submissions dated October 9 and November 5, 1997.

The supplemental application as amended provides for the following additions to the CLINICAL PHARMACOLOGY and the ADVERSE REACTIONS sections of the labeling:

CLINICAL PHARMACOLOGY, "Mechanism of Action," added to the end of the third paragraph--

Although frequently 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.

ADVERSE REACTIONS, the following sentence is added below Table 4--

The events in italics occurred in ≥2% of patients and the events in plain type occurred in ≤2% of patients.

ADVERSE REACTIONS (The following reactions or their italicization is added):
   Chest pain; Nausea; Bronchitis, rhinitis; Insomnia, depression, hypesthesia, hypertonia; Arthritis; Pruritis; Urinary tract infection; angina pectoris, hypertension; Peripheral edema.
ADVERSE REACTIONS (The following subsection is added.):
Postintroduction Reports
Adverse events associated with Lipitor that have been received since market introduction, that are not listed above, and that may have no causal relationship to drug include the following: angioneurotic edema.

We have completed the review of this supplemental application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated November 5, 1997. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on November 5, 1997.

Please submit 16 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 20-702/S-008. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

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, Project Manager, at (301) 827-6418.

Sincerely yours,

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-702
HFD-510/Div. files
HFD-510/CSO/MSimoneau
HFD-510/DOrlloff
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: EMG/November 5, 1997/20702s08.ap
Initialed by: DOrlloff 11/5/97
final: emg/11/5/97

APPROVAL (AP)
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
20-702/S-008

LABELING
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 in the liver, and is an essential step in the biosynthesis of cholesterol. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and methanol, and freely soluble in ethanol.

Lipitor tablets for oral administration contain 10, 20, or 40 mg atorvastatin and the following inactive ingredients: cornstarch, magnesium stearate, colloidal silicon dioxide, and lactose monohydrate.

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 to cholesterol. Inhibiting this enzyme decreases cholesterol synthesis in the liver and results in decreased levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides. Atorvastatin also increases levels of high-density lipoprotein cholesterol (HDL-C).

CLINICAL STUDIES
The efficacy of Lipitor was assessed in two multicenter, placebo-controlled, double-blind, randomized, parallel-group studies in patients with primary hypercholesterolemia (types IIa or IIb) and hypertriglyceridemia. In the primary hypercholesterolemia study, 24 weeks of treatment with Lipitor resulted in statistically significant reductions from baseline in total cholesterol, LDL-C, and triglycerides.

CONTRAINdications
Hypersensitivity to atorvastatin or any of the excipients of Lipitor tablets.

WARNINGS
Liver Function Tests
Liver function tests should be obtained before treatment with Lipitor and periodically during continued therapy. Atorvastatin is rapidly absorbed after oral administration, and plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to dosage. The bioavailability of atorvastatin is approximately 11% and is not affected by food.

Precautions
Liver function tests should be obtained before treatment with Lipitor and periodically during continued therapy. Atorvastatin is rapidly absorbed after oral administration, and plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to dosage. The bioavailability of atorvastatin is approximately 11% and is not affected by food.

Adverse Reactions
The most common adverse reactions reported in clinical trials with Lipitor were myalgia, nasopharyngitis, and diarrhea.

Drug Interactions
Atorvastatin is extensively metabolized by the cytochrome P450 3A4/5 (CYP3A4/5) system in the liver. Therefore, atorvastatin may be extensively coadministered with other drugs that are also extensively metabolized by this system. The following drugs were coadministered with atorvastatin in trials: nifedipine, warfarin, digoxin, cyclosporine, phenytoin, and sulfonylureas.

DOSAGE AND ADMINISTRATION
Lipitor tablets are indicated for the treatment of adults with primary hypercholesterolemia (types IIa or IIb) or mixed dyslipidemia (types IV or V) or as a adjunctive therapy to diet to reduce total cholesterol, LDL-C, triglycerides, and, in patients with type IIa or IIb hyperlipidemia, HDL-C.

CONTRAINDICATIONS
Hypersensitivity to atorvastatin or any of the excipients of Lipitor tablets.
LIPITOR™ (Atorvastatin Calcium) Tablets

Metabolism: Atorvastatin is extensively metabolized to other hydroxyarylpropionate derivatives and various beta carbon oxidation products. In vitro, inhibition of HMG-CoA reductase by atorvastatin metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating radiolabeled activity for HMG-CoA reductase is attributable to active metabolites. In vitro studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, which is increased with concomitant use of drugs that inhibit this enzyme (see Drug Interactions). In animals, the hydroxyaryl metabolite undergoes further glucuronidation.

Excretion: Atorvastatin and its metabolite are excreted primarily in bile following hepatic and 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 radiolabeled activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of glucuronide 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 39% for AUC) in healthy elderly subjects (age 65 years) than in young adults. LDL-C reduction is comparable to that seen in younger patient populations given equal doses of Lipitor.

Pediatric: Long-term pharmacokinetic data in the pediatric population are not available.

Gender: Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for Cmax and 10% lower for AUC), however, there is no clinically significant difference in LDL-C reduction with Lipitor between men and women.

Renal Insufficiency: Recent disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; dose 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 elimination of atorvastatin since the drug is extensively bound to plasma proteins.

Hepatic Insufficiency: In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. Cmax and AUC are each 4-fold greater in patients with Child-Pugh A disease, 37 and 44-fold greater in patients with Child-Pugh B disease (see CONTRAINDICATIONS).

Clinical Studies

Hypertrohlesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Friedlaiden Type IIa and IIIb)

Lipitor reduced total-C, LDL-C, VLDL-C, apo B, and TG, and increased 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 homozygous FH.

In two multicenter, placebo-controlled, dose-response studies in patients with hypercholesterolemia, Lipitor was compared to placebo and 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 concomitant agent (Table 1).

TABLE 1. Dose Response in Patients With Primary Hypercholesterolemia

<table>
<thead>
<tr>
<th>Treatment (Fixed 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>210</td>
<td>154</td>
<td>5</td>
<td>19</td>
<td>3</td>
<td>43</td>
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<tr>
<td>10</td>
<td>22</td>
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<td>6</td>
<td>19</td>
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<td>20</td>
<td>21</td>
<td>210</td>
<td>138</td>
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<td>20</td>
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<td>21</td>
<td>180</td>
<td>122</td>
<td>6</td>
<td>19</td>
<td>6</td>
<td>12</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 concomitant agent (Table 2).

TABLE 2. Mean Percent Change from Baseline at End Point

<table>
<thead>
<tr>
<th>Treatment (Fixed Dose)</th>
<th>N</th>
<th>Total-C</th>
<th>LDL-C</th>
<th>Apo B</th>
<th>TG</th>
<th>HDL-C</th>
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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 concomitant agent (Table 2).
INDICATIONS AND USAGE
Lipitor is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, and TG levels in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemias (Fredrickson Types IIa and IV).
Lipitor is also indicated to reduce total-C and LDL-C in patients with homozgous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.
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 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>
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<tbody>
<tr>
<td><strong>Definite Atherosclerotic Disease</strong></td>
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<td>-----------------------------------------</td>
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<td>No</td>
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<tr>
<td>Yes</td>
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</table>

*Defined as heart disease or peripheral vascular disease including syncope or reduced ankle artery flow.

Other factors for coronary heart disease (CHD) include age (males 45 years, females 55 years or premature menopause without estrogen replacement therapy), family history of premature CHD, current cigarette smoking, hypertension, and diabetes. For CHD patients with LDL-C levels 190 to 250 mg/dL, the physician should exercise clinical judgment in deciding whether to initiate therapy.

At the time of hospitalization for an acute coronary event, combination can be given to initiating drug therapy at discharge if the LDL-C level is ≥130 mg/dL (≥3.4 mmol/L). For patients with TG levels of 400 mg/dL (4.5 mmol/L) or higher, LDL-C can be estimated using the following equation: LDLC = total-C - 20 x (TG/5 + 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 ultrafiltration.

CONTRAINDICATIONS
Active liver disease or unexplained persistent elevations in serum transaminases.

HYPERSENSITIVITY TO ANY COMPONENT OF THIS MEDICATION

Pregnancy and Lactation
Atorvastatin may be 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 certain steroids and cell membrane. Since HMG-CoA reductase 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 reductase inhibitors are contraindicated during pregnancy and in nursing mothers.

ATORVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILD-REARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO COMPLY AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient informed of the potential hazards 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 upper limit of normal) occurring on 2 or more occasions in serum transaminases occurred in 0.37% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.4%, 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. In a group of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin.

It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation in dose, and periodically thereafter. Liver enzyme changes generally occur in the first 6 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 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 has been reported in atorvastatin-treated patients (see ADVERSE REACTIONS). Myalgia, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values ≥10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or mental signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward or downward dosage adjustments 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 (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disturbances, and uncontrolled acid-base abnormalities).
LIPITOR™ (Atorvastatin Calcium) Tablets

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

Drug Interactions

The risk of myopathy during treatment with other drugs of this class is increased with concurrent administration of cyclosporine, fibrinolytic derivatives, niacin, niacinamide, or anistreplase, or angiotensin-converting enzyme (ACE) inhibitors (see WARNINGS: Skeletal Muscle).

Antidepressants: When antidepressants, such as fluoxetine, citalopram, or paroxetine were co-administered, plasma concentrations of atorvastatin decreased approximately 25%. However, LDL-C reduction was not altered.

Antihypertensives: Because atorvastatin does not affect the pharmacokinetics of antihypertensives, interactions with other drugs that require the same cytochrome P450 isoenzymes are not expected.

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

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

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

Endocrine: In healthy individuals, plasma concentrations of atorvastatin increased approximately 20% with oral administration of atorvastatin and glibenclamide, a known inhibitor of cytochrome P450 3A4 (see WARNINGS: Skeletal Muscle).

Ovarian contraceptives: Co-administration 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 antipertensive agents and cholesterol-lowering 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 impair adrenal and gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal function. The effects of HMG-CoA reductase inhibitors on in vitro hCG-stimulated progesterone production by cultured human granulosa cells have been reported. Adequate studies in patients have not been studied in adequate numbers of patients. This effect is not likely to play a significant role in patients with severe hepatic disease, such as liver transplanted patients and patients with severe hepatic disease, such as liver transplanted patients or patients with severe hepatic disease, such as liver transplanted patients.

CNS Function

Brain hemorrhage was seen in a female dog treated for 2 months at 120 mg/kg/day and in a male dog treated for 1 month at 120 mg/kg/day. Brain hemorrhage and nervous system hemorrhage were seen in another female dog that was sacrificed in a nonclinical condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure (AUC) approximately 10 times the human plasma area under the curve (AUC 0-24 hours) based on the maximum concentration was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 1-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 50 mg/kg/day in mice at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mice) and 8 to 18 times (rats) the human AUC (0-24) based on the maximum recommended human dose of 80 mg/day.

CNS vascular lesions, characterized by petechial hemorrhages, adhesions, and meningeal cell infiltration of pia-arachnoid spaces, have been observed in beagle dogs treated with other members of this class. A category 1 drug in this class produce optic nerve degeneration (Wallerian degeneration of retinal ganglion cells) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels 9 times higher than the mean drug level in humans taking the highest recommended doses.

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 tumors were found in male high-dose females: one there was a mammary gland adenoma and, in another, there was a fibroadenoma. This dose represents a plasma AUC (0-24) value of approximately 10 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 neoplasms 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.

Intrahepatic cholestasis 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 mutagenesis 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 (13 times the human exposure) produced no changes in fertility. There was a decrease in sperm motility in the epididymis of male rats treated with 100 mg/kg of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose). Testicular weights were significantly lower at 20 mg/kg, while epididymal weights were lower at 50 mg/kg. Male rats given 100 mg/kg for 11 weeks prior to mating had decreased sperm motility, sperm number, and concentration, and increased sperm abnormality. Administration 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

SAFETY CONSIDERATIONS

Safety in pregnant women has not been established. Atorvastatin crosses the rat placenta and reaches a level in fetal plasma equivalent to that of maternal plasma. Atorvastatin was teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of at least 15 times human exposure based on body surface area (BSA) in rats or 40 times human exposure based on BSA in rabbits. In studies in which atorvastatin was administered to pregnant mice at multiples of 0.4, 2, or 10 times human exposure, no adverse effect on the offspring was noted. However, in studies in which atorvastatin was administered to pregnant rats at multiples of 0.4, 2, or 10 times human exposure, evidence of fetal malformations was found. The mechanism responsible for this effect is not known. Therefore, the use of atorvastatin during pregnancy should be avoided if possible. If the patient becomes pregnant while taking atorvastatin, the patient should be informed of the potential risk to the fetus. If atorvastatin is used, it should be discontinued as soon as pregnancy is detected.
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 serious 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 9 years of age or younger.

Geriatric Use
Treatment experience in adults age 70 years and with Lipitor up to 80 mg/day has been evaluated in 213 patients. The safety and efficacy of Lipitor in this population were similar to that 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 2,502 patients, 2% of patients were discontinued due to adverse events attributable to Lipitor. The most frequent adverse events thought to be related to Lipitor were increases in serum cholesterol, flushing, dyspepsia, and abdominal pain.

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 4. Adverse Events in Placebo-Controlled Studies (\% of Patients) |  |
|---|---|---|---|---|---|
| BODY AS A WHOLE | | | | | |
| | Placebo | Atorvastatin 10 mg | Atorvastatin 20 mg | Atorvastatin 40 mg | Atorvastatin 80 mg | 
| N = 210 | N = 883 | N = 36 | N = 79 | N = 94 | 
| Infection | 10.0 | 10.3 | 9.8 | 10.1 | 7.4 | 
| Headache | 7.0 | 5.4 | 16.7 | 2.5 | 6.4 | 
| Acute Asthma | 3.7 | 4.2 | 0.0 | 1.3 | 3.7 | 
| Flu Syndrome | 1.9 | 2.2 | 0.0 | 2.5 | 2.2 | 
| Abdominal Pain | 0.7 | 2.8 | 0.0 | 3.8 | 2.1 | 
| Back Pain | 3.0 | 2.6 | 0.0 | 2.8 | 1.1 | 
| Allergic Reaction | 2.6 | 0.5 | 2.8 | 1.2 | 0.0 | 
| Anemia | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 
| DIGESTIVE SYSTEM | | | | | |
| | Placebo | Atorvastatin 10 mg | Atorvastatin 20 mg | Atorvastatin 40 mg | Atorvastatin 80 mg | 
| N = 210 | N = 883 | N = 36 | N = 79 | N = 94 | 
| Constipation | 1.8 | 2.1 | 0.0 | 2.5 | 1.1 | 
| Diarrhea | 1.5 | 2.7 | 0.0 | 2.8 | 3.3 | 
| Dyspepsia | 4.1 | 2.3 | 2.8 | 1.3 | 2.1 | 
| Fluoride | 3.3 | 2.1 | 2.8 | 1.3 | 1.1 | 
| RESPIRATORY SYSTEM | | | | | |
| | Placebo | Atorvastatin 10 mg | Atorvastatin 20 mg | Atorvastatin 40 mg | Atorvastatin 80 mg | 
| N = 210 | N = 883 | N = 36 | N = 79 | N = 94 | 
| Sinusitis | 2.6 | 2.8 | 0.0 | 2.5 | 6.4 | 
| Pharyngitis | 1.5 | 2.0 | 0.0 | 1.3 | 2.1 | 
| SKIN AND APPENDAGES | | | | | |
| | Placebo | Atorvastatin 10 mg | Atorvastatin 20 mg | Atorvastatin 40 mg | Atorvastatin 80 mg | 
| N = 210 | N = 883 | N = 36 | N = 79 | N = 94 | 
| Rash | 0.7 | 3.9 | 2.8 | 3.8 | 1.1 | 
| MUSCULOSKELETAL SYSTEM | | | | | |
| | Placebo | Atorvastatin 10 mg | Atorvastatin 20 mg | Atorvastatin 40 mg | Atorvastatin 80 mg | 
| N = 210 | N = 883 | N = 36 | N = 79 | N = 94 | 
| Arthralgia | 1.5 | 2.0 | 0.0 | 5.1 | 0.0 | 
| Myalgia | 1.1 | 2.7 | 3.6 | 1.2 | 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, chest discomfort, headache, malaise, photosensitivity reaction, generalized edema.

Digestive System: Nausea, gastrointestinal complaints, alanine transaminase abnormal, colitis, vomiting, diarrhea, flatulence, dry mouth, rectal hemorrhage, anorexia, increased appetite, gastrointestinal disorder, diarrhea, abdominal pain, flatulence, vomiting, anorexia, dyspepsia, abnormal stools, melena, hematemesis.

Respiratory System: Hoarseness, rhinitis, pharyngitis, nausea, dyspnea, pharyngitis.

Nervous System: Dizziness, headache, dizziness, headache, migraine, peripheral neuropathy, dizziness, facial paresthesia, hypokinesia, abnormal vision.

Musculoskeletal System: Arthropathy, bursitis, tendinitis, myalgia, tendinopathy, contracture, myalgia.

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


Special Sensations: Arthralgia, tinnitus, dry eyes, urticaria, food intolerance, eye hemorrhage, rhinorrhea, glossitis, pancreatitis, back pain, chest pain, taste perversion.

Cardiovascular System: Palpitation, vasodilatation, syncope, migraine, chest pain, hypertension, paresthesia.

Gastrointestinal System: Hepatic steatosis, cholestasis, gastrointestinal hemorrhage, rectal hemorrhage.

Metabolic and Nutritional Disorders: Paronychia, dental, hyperglycemia, creatine phosphokinase increased, weight gain.

Pediatric Use: Children with homozygous FH.

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

OVERDOSAGE: There is no specific treatment for Lipitor overdose. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to oral bioavailability, plasma levels are not expected to significantly enhance atorvastatin elimination.
**DOSAGE AND ADMINISTRATION**

The patient should be placed 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 40 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 the 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.

**Homogenous Familial Hypercholesterolemia**

The dosage of Lipitor in patients with homozygous FH is 10 to 40 mg daily. Lipitor should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients if such treatments are available.

**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 niacin should generally be avoided (see WARNINGS, Skeletal Muscles, 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 PHARMACOKINETICS).

**HOW SUPPLIED**

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

10 mg tablet coated "PD 155" on one side and "311" on the other.

N0071-0155-23 bottles of 90
N0071-0153-34 boxes of 5000.
N0071-0153-40 10 x 10 unit dose blisters

20 mg tablet coated "PD 156" on one side and "700" on the other.

N0071-0166-23 bottles of 90
N0071-0166-40 10 x 10 unit dose blisters

40 mg tablet coated "PD 157" on one side and "400" 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].

Caution – Federal law prohibits dispensing without prescription.
APPLICATION NUMBER:
20-702/S-008

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
NDA 20-702/S-008

Parke-Davis Pharmaceutical Research, agent for
Warner-Lambert Export, Limited
Attention: Byron Scott, R.Ph.
Director Worldwide Regulatory Affairs
2800 Plymouth Road
Ann Arbor, MI 48105

SEP 4 1998

Dear Mr. Scott:

We acknowledge the receipt of your April 18 and December 10, 1997, submissions containing final printed labeling in response to our letters approving your new drug application (NDA) and supplemental application, S-008, respectively, for Lipitor (atorvastatin calcium) Tablets.

We note that your additional supplemental applications S-003 and S-005, approved on July 10, 1998, supersede these applications. Therefore, we will not review these applications but they will be retained in our files.

If you have any questions, contact Margaret Simoneau, R.Ph., Regulatory Management Officer, at (301)827-6418.

Sincerely,

[Signature]

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
cc:
Archival NDA 20-702
HFD-510/Div. Files
HFD-510/M. Simoneau
HF-2/Medwatch
HFD-102/ADRA
HFD-40/DDMAC
HFD-95/DDMS
HFD-613/OGD
HFD-735/OPDRA
DISTRICT OFFICE

Drafted by: Mas/August 28, 1998
Initialed by: E. Galliers 8.31.98
final: Mas 8.31.98
filename: 20702.AR

ACKNOWLEDGE AND RETAIN (AR)
April 18, 1997 (N-doc-FA)
Dec. 10, 1997 (S-008)
December 10, 1997

NDA 20-702
Ref. No. 55
Lipitor® (atorvastatin calcium) Tablets

Re: FINAL PRINTED LABELING for Approved Supplemental NDA 20-702/5-008

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.

Reference is also made to your letter of November 5, 1997, which approved our labeling supplement (S-008) submitted on September 5, 1997. This supplement provided for additions to the CLINICAL PHARMACOLOGY and ADVERSE REACTIONS sections of the labeling. In your approval letter, you requested sixteen copies of final printed labeling as soon as it was available.

Per your request, we are providing you with sixteen copies of the final printed labeling in Attachment 1. The specification number of this package insert is 0155G023 and the revision date is November 1997.

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 and Labeling
Worldwide Regulatory Affairs

Attachment
Liptor® (Atorvastatin Calcium) Tablets

DESCRIPTION
Liptor® (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)-5-(1H-pyrazol-1-yl)-3-[(1R,2R)-4-fluorophenyl]-4,4-dihydroxy-5-(1-methyl-2-naphthalenyl)-2-phenyl-4-(phenyliminooxy)butan-2-yl] propane-2,3-diol, sodium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is C_{49}H_{44}N_{2}O_{13}·NaC_{2}H_{6}O_{6} and its molecular weight is 1209.42. Its structural formula is

![Structural Formula](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 acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

Liptor tablets for oral administration contain 10, 20, or 40 mg atorvastatin and the following inactive ingredients: calcium carbonate, USP; cellulose, FCC; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; and white YS-17040 hydroxypropylmethylcellulose, polyethylene glycol, talo, titanium dioxide, polysorbate 80, NF; and xanthan gum, NF.

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. 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), 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 catalyzed primarily through the high-affinity LDL receptor. Clinical and pathologic studies have demonstrated that LDL is the primary transport form of cholesterol for the liver. Clinical and pathologic studies have shown that LDL is also the primary transport form of cholesterol for the liver.

In animal models, Liptor 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. Liptor also reduces LDL production and the number of LDL particles. Liptor 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 increased 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 complex, apo A) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality very directly with the level of total-C.

Liptor® (Atorvastatin Calcium) Tablets

<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>5</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>22</td>
<td>-29</td>
<td>-39</td>
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<td>20</td>
<td>20</td>
<td>-33</td>
<td>-43</td>
<td>-35</td>
<td>-26</td>
<td>6</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>2</td>
<td>45</td>
</tr>
</tbody>
</table>

*Results are pooled from 2 dose-response studies.*

In three multicenter, double-blind studies in patients with hypercholesterolemia, Liptor was compared to other HMG-CoA reductase inhibitors. After randomization, patients were treated for 18 weeks with either Liptor 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>4</td>
<td>4</td>
<td>3</td>
<td>10</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>10 mg Atorvastatin</td>
<td>22</td>
<td>-29</td>
<td>-39</td>
<td>-52</td>
<td>-19</td>
<td>0</td>
<td>34</td>
</tr>
<tr>
<td>20 mg Atorvastatin</td>
<td>20</td>
<td>-33</td>
<td>-43</td>
<td>-35</td>
<td>-26</td>
<td>6</td>
<td>41</td>
</tr>
<tr>
<td>40 mg Atorvastatin</td>
<td>21</td>
<td>-37</td>
<td>-50</td>
<td>-42</td>
<td>-29</td>
<td>2</td>
<td>45</td>
</tr>
</tbody>
</table>

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

The impact on clinical outcomes of differences in lipid-altering effects between treatments shown in Table 3 is not known. Table 2 does not contain data comparing the effects of Liptor 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 Liptor daily was assessed. After 16 weeks, 159/167 (93%) of patients with less than 2 risk factors for CHD and baseline LDL-C 2 mg/dL reached a target of 2 mg/dL. 145/185 (78%) of patients with 2 or more risk factors for CHD and LDL-C 2 mg/dL achieved a target of 2 mg/dL. 21 (11%) of patients with CHD and LDL-C 2 mg/dL reached a target of 100 mg/dL.

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 20 to 80 mg of Liptor. The mean LDL-C reduction in this study was 18%. Twenty-five patients with a reduction in LDL-C had a mean response of 30% (range of 7% to 83%, 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 those, 2 patients also had a portasomal stunted and had no significant reduction in LDL-C. The remaining 3 receptor-negative patients had a mean LDL-C reduction of 22%.

INDICATIONS AND USAGE
the remaining 4 patients had 7% to 24% increase in LDL-C. Five of the 28 patients had absent LDL-receptor function. Of these, 2 patients also had a portacaval shunt and had no significant reduction in LDL-C. The 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.

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 (e.g., LDL apheresis) if such treatments are unavailable.

Therapy with lipid-altering agents should be a component of multiple risk-factor intervention in all individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-altering agents should be a part of a diet restricted to saturated fat and cholesterol only when the response to diet alone has been inadequate (see National Cholesterol Education Program (NCEP) Guidelines, summarized in Table 3).

**TABLE 3. NCEP Guidelines for Lipid Management**

<table>
<thead>
<tr>
<th>Definite Atherosclerotic Disease</th>
<th>Two or More Other Risk Factors</th>
<th>LDL-Cholesterol mg/dL (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>&lt;100</td>
</tr>
<tr>
<td>(4.8)</td>
<td></td>
<td>(&lt;4.1)</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>&gt;160</td>
</tr>
<tr>
<td>(4.1)</td>
<td></td>
<td>(&gt;3.9)</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes or No</td>
<td>&gt;210</td>
</tr>
<tr>
<td>(4.8)</td>
<td></td>
<td>(≥5.2)</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: smoking, age, family history (first-degree relatives <55 years of age or premature myocardial infarction [MI] 45-54 years of age) and diabetes mellitus. Subclass 1 for TCM = 100-199 mg/dL (2.6-5.2 mmol/L). In CHD patients with TCM from 100 to 129 mg/dL, the physician should exercise clinical judgment in deciding whether to use this drug.

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 ≥200 mg/dL (5.2 mmol/L). If CHD is present, therapy should be initiated according to the NCEP guidelines.

Prior to initiating therapy with a Lipitor, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hyperthyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, and alcoholism) should be excluded, and a lipid profile performed to confirm total-C and triglyceride levels.

For patients with TG <400 mg/dL (4.5 mmol/L), Lipitor can be used to lower TG levels from 400 mg/dL (4.6 mmol/L) to normal or near normal levels. LDL-C reduction is less accurate and total-C concentrations should be determined by ultracentrifugation.

**CONTRAINDICATIONS**

Active liver disease or unexplained persistent elevations of serum transaminases. Hyper sensitivity 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 reductase 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 reductase inhibitors should not be used in women who are or may become pregnant.

**WARNINGS**

Liver Function Tests

HMG-CoA reductase inhibitors, like other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Persistent elevations of liver enzyme (ALT or AST) 3 times the upper limit of normal (ULN) occurring 2 or more times in serum transaminases occurred in 6.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.8%, 0.8%, and 2.3% for 10, 25, 40, and 80 mg, respectively.

One patient in clinical trials developed jaundice. Increases in liver function tests (ALT) 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 within 1-2 weeks. Eighteen of 20 patients with persistent ALT elevations continued treatment with a reduced dose of atorvastatin.

It is recommended that liver function tests be performed before initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation in dose, and periodically (e.g., semiannually) while on therapy. Liver function tests should be performed at the 3rd and 6th 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.

Drugs 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 has been reported in atorvastatin-treated patients (see ADVERSE REACTIONS). Myalgia, defined as diffuse muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values ≤10 times ULN, should be considered in any patient with diffuse myalgias, mild to moderate tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly

0155G023
Lipitor® (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, fibrinic acid derivatives, erythromycin, niacin, or azole antifungals. Physicians considering coadministration of atorvastatin and fibrinic acid derivatives, erythromycin, immunosuppressant 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 (e.g. severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled sepsis).

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, fibrinic acid derivatives, niacin (nicotinic acid), erythromycin, azole antifungals (see WARNINGS, Skeletal Muscle).

Antacid: When atorvastatin and MAO inhibitors were coadministered, plasma concentrations of atorvastatin decreased approximately 30%. However, LDL-C reduction was not altered.

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

Colchicines: Plasma concentrations of atorvastatin decreased approximately 20% when colchicine and atorvastatin were coadministered. However, LDL-C reduction was greater when atorvastatin and colchicine were coadministered than when either drug was given alone.

Atorvastatin plasma concentrations and LDL-C reduction were not altered by coadministration of ciclosporin.

Diazepam: When multiple doses of atorvastatin and diazepam were coadministered, steady-state plasma diazepam concentrations increased by approximately 30%. Patients taking diazepam 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 gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cholesterol or low-density lipoprotein (LDL) levels. The effect of HMG-CoA reductase inhibitors on adrenal and gonadal steroid production is unknown.

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 4. Adverse Events in Placebo-Controlled Studies (% of Patients)

<table>
<thead>
<tr>
<th>BODY SYSTEM</th>
<th>Adverse Event</th>
<th>Placebo</th>
<th>Atorvastatin 10 mg</th>
<th>Atorvastatin 20 mg</th>
<th>Atorvastatin 40 mg</th>
<th>Atorvastatin 80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N = 270</td>
<td>N = 863</td>
<td>N = 36</td>
<td>N = 79</td>
<td>N = 94</td>
</tr>
<tr>
<td>BODY AS A WHOLE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td></td>
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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.

Dermatologic: Noses, gastroenteritis, liver function tests abnormal, colitis, vomit, gastritis, dry mouth, rectal hemorrhage, esophagitis, excretion, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, chills, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice.

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

Nervous System: Insomnia, dizziness, paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, tinnitus, facial paralysis, hypersomnia, depression, hypothyrosism, hyperptonia.

Musculoskeletal System: Arthritis, leg cramps, back pain, tenosynovitis, muscle strain, tendinitis, 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, impotence, dysuria, kidney calculus, nocturia, epididymitis, renal cystic, breast, vaginal hemorrhage, alburnurira, breast enlargement, metronidazole, nephritis, urinary incontinence, urinary retention, urinary urgency, abdominal distention, uterine hemorrhage.
Other Concomitant Therapy: In clinical studies, astrovirus 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 desirable and necessary genital steroid production. Clinical studies have shown that atorvastatin does not reduce basal or stimulated cortisol concentrations. 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 are not known. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels of androgenic steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

CNS

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 morbidity condition after 2 weeks of escalating doses up to 200 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure (AUC, 0-24 hour) based on the maximum human dose of 80 mg/day. A single toxic 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 retinal 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.

Cardiogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in rats at doses of 10, 30, and 100 mg/kg/day, 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.

Studies in rats performed at doses up to 175 mg/kg (10 times the human exposure) produced no changes in fertility. There was aplasia and aspermatogenesis in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months. The mean human plasma exposure at a dose of 80 mg/day is 16 times (C) the human AUC at the 80 mg dose. Testes weights were significantly increased at doses of 10 and 30 mg/kg, and ejaculated weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased sperm abnormality. Male rats showed 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 teratogenic in rats at doses greater than 100 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 20 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 in maturity of pups in mothers dosed with 225 mg/kg/day. Body weight and body weight gains were lower at 100 mg/kg/day. Male pups given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased sperm abnormality. Male rats showed no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

Musculoskeletal System: Arthritis, leg cramps, bursitis, tenosynovitis, myasthenia, tendinopathy, contractures, myalgia.

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

Urinary System: Renal tract infection, urinary frequency, cystitis, hematuria, impotence, dysuria, kidney calculus, incontinence, epididymitis, fibrosarcoma, vaginal hemorrhage, alopecia, renal enlargement, mentoscaria, nephritis, proteinuria, urinary incontinence, urinary retention, urinary urgency, abnormal urination.

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

Cardiovascular System: Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arthralgia, angina pectoris, hypertension.

Metabolic and Nutritional Disorders: Peripheral edema, hyperglycemia, creating phosphonate increased, gout, weight gain, hypoglycemia.

Hemic and Lymphatic System: Ecchymoses, anemia, lymphadenopathy, thrombocytopenia, petechiae.

PostIntroduction Reports

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

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 placed 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 Dyslipidemia (Fredrickson Types IIa and IIb)

The recommended starting dose of Lipitor is 10 mg once daily. The dosage range is 10 to 80 mg 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 goals of therapy and response (see NCEP Guidelines, summarized in Table 3). 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 monitor treatment response. Only if LDL-C levels are not available, should total-C be used to monitor therapy.

Homocysteine Familial Hypercholesterolemia

The dosage of Lipitor in patients with homocysteine HD 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 or 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).

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.
N0071-0155-23 bottles of 90
N0071-0155-34 bottles of 900
N0071-0155-40 10 x 10 unit dose blisters

20 mg tablets: coded "PD 156" on one side and "20" on the other.
N0071-0156-23 bottles of 90
N0071-0156-40 10 x 10 unit dose blisters

40 mg tablets: coded "PD 157" 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). Caution — Federal law prohibits dispensing without prescription.

Revised November 1997

PARKE-DAVIS
Div of Warner-Lambert Co
LaRx Scientific Inc
7850 USA
MADE IN GERMANY

Marketed by:

PARKE-DAVIS
Div of Warner-Lambert Co and
PFIZER Inc.
New York, NY 10017
0156G023
Enid and Peggy:

As discussed with Irwin Martin today, accompanying this fax, please find the cover letter and the revised labeling for labeling supplement S-008. The third paragraph under CLINICAL PHARMACOLOGY, Mechanism of Action, has been revised to include the wording proposed by Dr. Orloff. A hard copy of the submission will follow.

Please contact me if you have questions.

Maggie
November 5, 1997

NDA 20-702
Ref. No. 51
Lipitor® (atorvastatin calcium) Tablets

Re: Amendment to Labeling
Supplement S-008

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

Dear Dr. Sobel:

Reference is made to approved NDA 20-702 for Lipitor® (atorvastatin calcium) Tablets; to approved labeling supplement S-002 (approved October 28, 1997); to pending supplements and S-008 (Ref. Nos. 47 and 50, submitted September 5, 1997, and amended October 9, 1997); and to today's telephone conversation between Ms. Enid Galliers of your Division and Dr. Irwin Martin of Parke-Davis regarding an amendment to labeling supplement S-008.

... comprised two changes to the labeling: the addition of adverse reactions and...

... both changes were submitted as "Changes Being Effected", and revised labeling was provided with a date of July 1997 (label number 0155G022). On November 4, 1997, I was informed by Ms. Margaret Simoneau of your Division that...

... Labeling supplement S-008 was thus submitted with draft labeling revising the unapproved July 1997 version of the package insert. Since that time, we have also received approval for S-002 which corrected the volume of distribution and absolute bioavailability in the CLINICAL PHARMACOLOGY section.
Solomon Sobel, M.D.
NDA 20-702
November 5, 1997
Page 2

and made the changes as approved in S-002, and are now submitting the attached revised labeling as an amendment to S-008. This change will be implemented as soon as possible when approved by the Division.

If there are any questions or comments regarding this submission, please contact me at 313/996-4906 or FAX 313/998-3283.

Sincerely,

Margaret J. Uprichard, Pharm.D.
Senior Manager, FDA Liaison
Worldwide Regulatory Affairs

MU\rm
t:\nda20-702110597.51

Attachment

Desk Copy: Ms. Enid Galliers (HFD-510)
Ms. Margaret Simoneau (HFD-510)
Page(s) Withheld

☐ § 552(b)(4) Trade Secret / Confidential
☒ § 552(b)(4) Draft Labeling
☐ § 552(b)(5) Deliberative Process
November 5, 1997

NDA 20-702
Ref. No. 51
Lipitor® (atorvastatin calcium) Tablets

Re: Amendment to Labeling
Supplement S-008

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

Dear Dr. Sobel:

Reference is made to approved NDA 20-702 for Lipitor® (atorvastatin calcium) Tablets; to approved labeling supplement S-002 (approved October 28, 1997); to pending supplements and S-008 (Ref. Nos. 47 and 50, submitted September 5, 1997, and amended October 9, 1997); and to today’s telephone conversation between Ms. Enid Galliers of your Division and Dr. Irwin Martin of Parke-Davis regarding an amendment to labeling supplement S-008.

(Comprised two changes to the labeling: the addition of adverse reactions and... Both changes were submitted as “Changes Being Effected”, and revised labeling was provided with a date of July 1997 (label number 0155G022). On November 4, 1997, I was informed by Ms. Margaret Simoneau of your Division that labeling supplement S-008 was thus submitted with draft labeling revising the unapproved July 1997 version of the package insert. Since that time, we have also received approval for S-002 which corrected the volume of distribution and absolute bioavailability in the CLINICAL PHARMACOLOGY section.)
and made the changes as approved in S-002, and are now submitting the attached revised labeling as an amendment to S-008. This change will be implemented as soon as possible when approved by the Division.

If there are any questions or comments regarding this submission, please contact me at 313/996-4906 or FAX 313/998-3283.

Sincerely,

[Signature]

Margaret J. Uprichard, Pharm.D.
Senior Manager, FDA Liaison
Worldwide Regulatory Affairs

Attachment

Desk Copy:  Ms. Enid Galliers (HFD-510)
            Ms. Margaret Simoneau (HFD-510)
Page(s) Withheld

☐ § 552(b)(4) Trade Secret / Confidential

☒ § 552(b)(4) Draft Labeling

☐ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative 20-702
5068
September 5, 1997

NDA 20-702
Ref. No. 47
Lipitor® (atorvastatin calcium) Tablets

Re: Labeling Supplement

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

Dear Dr. Sobel:

Reference is made to approved NDA 20-702 for Lipitor® (atorvastatin calcium) Tablets and to my telephone conversations with Dr. David Orloff of your Division on August 26, 28, and September 3, 1997, regarding modifications to the CLINICAL PHARMACOLOGY section of the package insert which would place atorvastatin's effects on plasma triglycerides into perspective. As suggested verbatim by Dr. Orloff, we propose the following modification (in italic type) to the third paragraph of the CLINICAL PHARMACOLOGY, “Mechanism of Action” section:

“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 complex, apo A) 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 frequently 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.”

In accordance with 21 CFR 314.70(b)(3), we are submitting for your review and approval the above proposed revision. This change will not be implemented until approved by the Division.
If there are any questions or comments regarding this submission, please contact me at 313/996-4906 or FAX 313/998-3283.

Sincerely,

Margaret J. Uprichard, Pharm.D.
Manager, FDA Liaison
Worldwide Regulatory Affairs

MU\rm
c:\nda\20-702\090597-47

[Handwritten notes: Noted. Change approved 9/22/97]
NDA 20-702/S-008

PARKE-DAVIS PHARMACEUTICAL RESEARCH
DIVISION of WARNER-LAMBERT COMPANY
2800 Plymouth Road P. O. BOX 1047
Ann Arbor, MI 48106-1047

Attention: Margaret J. Uprichard, Ph.D., Manager, FDA Liaison Worldwide Regulatory Affairs

Dear Dr. M. J. Uprichard:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: LIPIITOR TABLETS

NDA Number: 20-702

Supplement Number: S-008

Date of Supplement: September 5, 1997

Date of Receipt: September 8, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on November 7, 1997, 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,

Enid 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-008
HFD-510/Div. Files
HFD-510/CSO/A-Rhee, M. Simoneau

filename:
SUPPLEMENT ACKNOWLEDGEMENT
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

Liptor® (atorvastatin calcium) Tablets

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA?

☐ YES ☑ 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

☐ 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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

Title
Director Advertising and Labeling Worldwide Regulatory Affairs

DATE
December 10, 1997
USER FEE DATA ENTRY/VALIDATION FORM

NDA # 80-702  DOCUMENT ID/LETTER DATE  SLR-008  9/5/97
APPLICANT NAME  PARKE-DOUGLAS PHARMACEUTICAL RESEARCH
PRODUCT NAME  Lipitor Tablets

FORM MUST BE COMPLETED ASAP

1. YES  User Fee Cover Sheet Validated?

NOTE TO DOCUMENT ROOM:
PLEASE MAKE THE FOLLOWING CHANGES TO THE COMIS DATA ELEMENTS

---

2. YES NO  CLINICAL DATA?
[Check YES if contains study reports or literature reports of what are explicitly or implicitly represented by the applicant to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).

REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION?

3. YES NO  NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (OTHER THAN BUNDLING)? IF YES, list ALL NDA numbers, review divisions & indicate those for which application fees apply.
NDA #  DIVISION
N ---  FEE  NO FEE
N ---  FEE  NO FEE

4. YES NO  BUNDLING POLICY APPLIED CORRECTLY? NO DATA ENTRY REQUIRED FOR ELEMENT
[Check YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Check NO if application should be split into more than one application or submitted as an original instead of a supplement. IF NO, list resulting NDA numbers, and review divisions.]
NDA #  DIVISION
N ---  N

5. P S  PRIORITY OR STANDARD?

6. CSO SIGNATURE/DATE  EFCalls 9/18/97
SCSO CONCURRENCE SIGNATURE/DATE

COPY DISTRIBUTION: ORIGINAL TO ARCHIVAL AFTER DATA ENTRY, ONE COPY EACH TO DIVISION FILE AND CDBR, ASSOCIATE DIRECTOR FOR POLICY HPD-5
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<th>2. USER FEE BILLING NAME, ADDRESS, AND CONTACT</th>
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<tr>
<td>2800 Plymouth Rd.</td>
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<tr>
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<td>Mary E. Taylor, MPH</td>
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</table>

**IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM**

<table>
<thead>
<tr>
<th>6. TR FEE I.D. NUMBER</th>
<th>7. LICENSE NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-702</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92</td>
</tr>
<tr>
<td>□ AN INSULIN PRODUCT SUBMITTED UNDER 506</td>
</tr>
<tr>
<td>□ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION</td>
</tr>
<tr>
<td>□ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9.a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION?</th>
<th>□ YES</th>
<th>□ NO</th>
</tr>
</thead>
</table>

(See reverse if answered YES)

<table>
<thead>
<tr>
<th>9.b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?</th>
<th>□ YES</th>
<th>□ NO</th>
</tr>
</thead>
</table>

(See reverse if answered YES)

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

**SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE**

Mary E. Taylor

**TITLE**

Director

Worldwide Regulatory Affairs

**DATE**

September 5, 1997