

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**20-702/S-022**

***Trade Name:*** Lipitor

***Generic Name:*** atorvastatin calcium

***Sponsor:*** Parke-Davis Pharmaceutical Research

***Approval Date:*** April 7, 2000

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-702/S-022**

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**APPROVAL LETTER**



NDA 20-702/S-022

Parke-Davis Pharmaceutical Research  
Attention: Sean Brennan, PhD  
VP Worldwide Regulatory Affairs  
2800 Plymouth Road  
P.O. Box 1047  
Ann Arbor, MI 48106-1047

APR - 7 2000

Dear Dr. Brennan:

Please refer to your supplemental new drug application dated December 6, 1999, received December 7, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lipitor (atorvastatin calcium) Tablets.

We acknowledge receipt of your submissions dated December 8, 1999 (2), and February 1 and April 4, 2000.

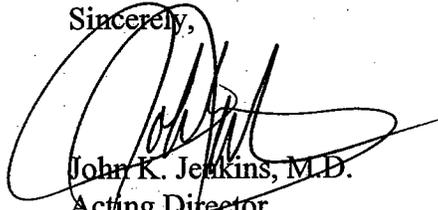
This supplemental new drug application provides for a new strength tablet, 80 mg Lipitor (atorvastatin calcium) Tablets.

We have completed the review of this supplemental application and it is approved.

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, call Margaret Simoneau, R.Ph., Regulatory Management Officer, at (301) 827-6418.

Sincerely,



John K. Jenkins, M.D.

Acting Director

Division of Metabolic and Endocrine

Drug Products, HFD-510

Office of Drug Evaluation II

Center for Drug Evaluation and Research



NDA 20-702/S-022

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Division of Metabolic and Endocrine  
Drug Products, HFD-510  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

cc:

Archival NDA 20-702

HFD-510/Div. Files

HFD-510/M. Simoneau

HFD-510/DOrloff/RSteigerwalt/XYsern/SMoore/RShore/HAhn

HFD-095/DDMS-IMT

HFD-820/DNDC Division Director

DISTRICT OFFICE

Drafted by: Mas/April 6, 2000

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RSteigerwalt4.6.00/RShore4.6.00/HAhn4.6.00/EGalliers4.6.00

final: Mas4.6.00

filename: 20702.22

APPROVAL (AP)

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**20-702/S-022**

**LABELING**

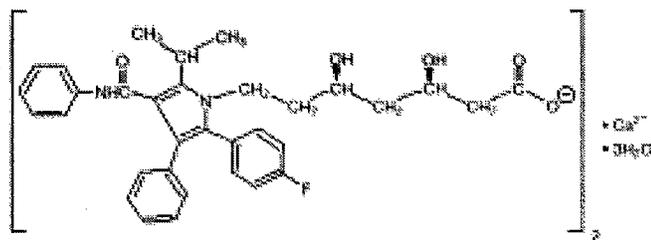
# Lipitor®

## (Atorvastatin Calcium) Tablets

### DESCRIPTION

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 [R-(R\*, R\*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is  $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$  and its molecular weight is 1209.42. Its structural formula is:



Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

Lipitor tablets for oral administration contain 10, 20, 40, or 80 mg atorvastatin and the following inactive ingredients: calcium carbonate, USP; candelilla wax, FCC; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1-7040 (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. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-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 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 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 medication(s).

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.

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-1. Lipitor reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. Lipitor reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia. The effect of Lipitor on cardiovascular morbidity and mortality has not been determined.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and 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 clearance. Drug dosage rather than systemic drug concentration correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response (see DOSAGE AND ADMINISTRATION).

### **Pharmacokinetics and Drug Metabolism**

**Absorption:** 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 inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by C<sub>max</sub> and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for C<sub>max</sub> 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 CONTRAINDICATIONS, Pregnancy and Lactation, and PRECAUTIONS, Nursing Mothers).

**Metabolism:** Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this isozyme (see PRECAUTIONS, Drug Interactions). In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

**Excretion:** Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of 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 C<sub>max</sub> and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults (see PRECAUTIONS section; Geriatric Use subsection).

**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 for C<sub>max</sub> and 10% 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).

**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 alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. C<sub>max</sub> and AUC are each 4-fold greater in patients with Childs-Pugh A disease. C<sub>max</sub> and AUC are approximately 16-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 patients has been limited to patients with homozygous 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)<sup>a</sup>**

Dose	N	TC	LDL-C	ApoB	TG	HDL-C	Non-HDL-C/ HDL-C
Placebo	21	4	4	3	10	-3	7
10	22	-29	-39	-32	-19	6	-34
20	20	-33	-43	-35	-26	9	-41
40	21	-37	-50	-42	-29	6	-45
80	23	-45	-60	-50	-37	5	-53

<sup>a</sup>Results are pooled from 2 dose-response studies

In patients with *Fredrickson* Types IIa and IIb hyperlipoproteinemia pooled from 24 controlled trials, the median (25<sup>th</sup> and 75<sup>th</sup> percentile) percent changes from baseline in HDL-C for atorvastatin 10, 20, 40, and 80 mg were 6.4 (-1.4, 14), 8.7 (0, 17), 7.8 (0, 16), and 5.1 (-2.7, 15), respectively. Additionally, analysis of the pooled data demonstrated

consistent and significant decreases in total-C , LDL-C, TG, total-C/HDL-C, and LDL-C/HDL-C.

In three multicenter, double-blind studies in patients with 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 2. Mean Percent Change From Baseline at End Point  
(Double-Blind, Randomized, Active-Controlled Trials)**

Treatment (Daily Dose)	N	Total-C	LDL-C	ApoB	TG	HDL-C	Non-HDL-C/ HDL-C
<i>Study 1</i>							
Atorvastatin 10 mg	707	-27 <sup>a</sup>	-36 <sup>a</sup>	-28 <sup>a</sup>	-17 <sup>a</sup>	+7	-37 <sup>a</sup>
Lovastatin 20 mg	191	-19	-27	-20	-6	+7	-28
95% CI for Diff <sup>f</sup>		-9.2,-6.5	-10.7,-7.1	-10.0,-6.5	-15.2,-7.1	-1.7,2.0	-11.1,-7.1
<i>Study 2</i>							
Atorvastatin 10 mg	222	-25 <sup>b</sup>	-35 <sup>b</sup>	-27 <sup>b</sup>	-17 <sup>b</sup>	+6	-36 <sup>b</sup>
Pravastatin 20 mg	77	-17	-23	-17	-9	+8	-28
95% CI for Diff <sup>f</sup>		-10.8,-6.1	-14.5,-8.2	-13.4,-7.4	-14.1,-0.7	-4.9,1.6	-11.5,-4.1
<i>Study 3</i>							
Atorvastatin 10 mg	132	-29 <sup>c</sup>	-37 <sup>c</sup>	-34 <sup>c</sup>	-23 <sup>c</sup>	+7	-39 <sup>c</sup>
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff <sup>f</sup>		-8.7,-2.7	-10.1,-2.6	-8.0,-1.1	-15.1,-0.7	-4.3,3.9	-9.6,-1.9

<sup>f</sup>A negative value for the 95% CI for the difference between treatments favors atorvastatin for all except HDL-C, for which a positive value favors atorvastatin. If the range does not include 0, this indicates a statistically significant difference.

<sup>a</sup>Significantly different from lovastatin, ANCOVA,  $p \leq 0.05$

<sup>b</sup>Significantly different from pravastatin, ANCOVA,  $p \leq 0.05$

<sup>c</sup>Significantly different from simvastatin, ANCOVA,  $p \leq 0.05$

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 daily was assessed. After 16 weeks, 156/167 (93%) of patients with less than 2 risk factors for CHD and baseline LDL-C  $\geq 190$  mg/dL reached a target of  $\leq 160$  mg/dL; 141/218 (65%) of patients with 2 or more risk factors for CHD and LDL-C  $\geq 160$  mg/dL achieved a level of  $\leq 130$  mg/dL LDL-C; and 21/113 (19%) of patients with CHD and LDL-C  $\geq 130$  mg/dL reached a target level of  $\leq 100$  mg/dL LDL-C.

#### **Hypertriglyceridemia (Fredrickson Type IV)**

The response to Lipitor in 64 patients with isolated hypertriglyceridemia treated across several clinical trials is shown in the table below. For the atorvastatin-treated patients, median (min, max) baseline TG level was 565 (267-1502).

**TABLE 3. Combined Patients With Isolated Elevated TG:  
Median (min, max) Percent Changes From Baseline**

	Placebo (N=12)	Atorvastatin 10 mg (N=37)	Atorvastatin 20 mg (N=13)	Atorvastatin 80 mg (N=14)
Triglycerides	-12.4 (-36.6, 82.7)	-41.0 (-76.2, 49.4)	-38.7 (-62.7, 29.5)	-51.8 (-82.8, 41.3)
Total-C	-2.3 (-15.5, 24.4)	-28.2 (-44.9, -6.8)	-34.9 (-49.6, -15.2)	-44.4 (-63.5, -3.8)
LDL-C	3.6 (-31.3, 31.6)	-26.5 (-57.7, 9.8)	-30.4 (-53.9, 0.3)	-40.5 (-60.6, -13.8)
HDL-C	3.8 (-18.6, 13.4)	13.8 (-9.7, 61.5)	11.0 (-3.2, 25.2)	7.5 (-10.8, 37.2)
VLDL-C	-1.0 (-31.9, 53.2)	-48.8 (-85.8, 57.3)	-44.6 (-62.2, -10.8)	-62.0 (-88.2, 37.6)
non-HDL-C	-2.8 (-17.6, 30.0)	-33.0 (-52.1, -13.3)	-42.7 (-53.7, -17.4)	-51.5 (-72.9, -4.3)

### Dysbetalipoproteinemia (*Fredrickson* Type III)

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

**TABLE 4. Open-Label Crossover Study of 16 Patients  
With Dysbetalipoproteinemia (*Fredrickson* Type III)**

	Median (min, max) at Baseline mg/dL)	Median % Change (min, max)	
		Atorvastatin 10 mg	Atorvastatin 80 mg
Total-C	442 (225, 1320)	-37 (-85, 17)	-58 (-90, -31)
Triglycerides	678 (273, 5990)	-39 (-92, -8)	-53 (-95, -30)
IDL-C + VLDL-C	215 (111, 613)	-32 (-76, 9)	-63 (-90, -8)
non-HDL-C	411 (218, 1272)	-43 (-87, -19)	-64 (-92, -36)

### 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 Lipitor. The mean LDL-C reduction in this study was 18%. Twenty-five patients with a reduction in LDL-C had a mean response of 20% (range of 7% to 53%, median of 24%); the remaining 4 patients had 7% to 24% increases in LDL-C. Five of the 29 patients had absent LDL-receptor function. Of these, 2 patients also had a portacaval shunt and had no significant reduction in LDL-C. The remaining 3 receptor-negative patients had a mean LDL-C reduction of 22%.

### INDICATIONS AND USAGE

Lipitor is indicated:

1. as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous

familial and nonfamilial) and mixed dyslipidemia ( *Fredrickson* Types IIa and IIb);

2. as an adjunct to diet for the treatment of patients with elevated serum TG levels (*Fredrickson* Type IV);
3. for the treatment of patients with primary dysbetalipoproteinemia ( *Fredrickson* Type III) who do not respond adequately to diet;
4. 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 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 5).

**TABLE 5. NCEP Guidelines for Lipid Management**

Definite Atherosclerotic Disease <sup>a</sup>	Two or More Other Risk Factors <sup>b</sup>	LDL-Cholesterol mg/dL (mmol/L)	
		Initiation Level	Minimum Goal
No	No	≥190 (≥4.9)	<160 (<4.1)
No	Yes	≥160 (≥4.1)	<130 (<3.4)
Yes	Yes or No	≥130 <sup>c</sup> (≥3.4)	≤100 (≤2.6)

<sup>a</sup>Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).

<sup>b</sup>Other risk 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; confirmed HDL-C <35 mg/dL (<0.91 mmol/L); and diabetes mellitus. Subtract 1 risk factor if HDL-C is ≥60 mg/dL (≥1.6 mmol/L).

<sup>c</sup>In CHD patients with LDL-C levels 100 to 129 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 ≥130 mg/dL (NCEP-ATP II).

Prior to initiating therapy with Lipitor, secondary causes for hypercholesterolemia (eg, poorly controlled diabetes mellitus, hypothyroidism, 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 - (0.20 x [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.

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

## 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 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 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. Eighteen of 30 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 (eg, 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**

**Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class.**

Uncomplicated myalgia has been reported in atorvastatin-treated patients (see ADVERSE REACTIONS). Myopathy, 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 marked elevation of CPK. Patients should be advised to report promptly 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 drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibric 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 (eg, severe acute infection, hypotension, major surgery, 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 drugs of this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin (nicotinic acid), erythromycin, azole antifungals (see WARNINGS, Skeletal Muscle).

**Antacid:** When atorvastatin and Maalox® TC suspension were coadministered, plasma concentrations of atorvastatin decreased approximately 35%. However, LDL-C reduction was not altered.

**Antipyrine:** Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes 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.

**Cimetidine:** Atorvastatin plasma concentrations and LDL-C reduction were not altered by coadministration of cimetidine.

**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.

### **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 endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

### **CNS Toxicity**

Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was

sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg/day.

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

#### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

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

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 aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for 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 or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m<sup>2</sup>).

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 maturity 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 (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human 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 lovastatin 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 50% 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

The safety and efficacy of atorvastatin (10-80 mg) in the geriatric population ( $\geq 65$  years of age) was evaluated in the ACCESS study. In this 54-week open-label trial 1,958 patients initiated therapy with atorvastatin 10 mg. Of these, 835 were elderly ( $\geq 65$  years) and 1,123 were non-elderly. The mean change in LDL-C from baseline after 6 weeks of treatment with atorvastatin 10 mg was -38.2% in the elderly patients versus -34.6% in the non-elderly group.

The rates of discontinuation due to adverse events were similar between the two age groups. There were no differences in clinically relevant laboratory abnormalities between the age groups.

## ADVERSE REACTIONS

Lipitor is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies of 2502 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.

### Clinical Adverse Experiences

Adverse experiences reported in  $\geq 2\%$  of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment, are shown in Table 6.

**TABLE 6. Adverse Events in Placebo-Controlled Studies  
(% of Patients)**

BODY SYSTEM/ Adverse Event	Placebo N=270	Atorvastatin 10 mg N=863	Atorvastatin 20 mg N=36	Atorvastatin 40 mg N=79	Atorvastatin 80 mg N=94
<b>BODY AS A WHOLE</b>					
Infection	10.0	10.3	2.8	10.1	7.4
Headache	7.0	5.4	16.7	2.5	6.4
Accidental Injury	3.7	4.2	0.0	1.3	3.2
Flu Syndrome	1.9	2.2	0.0	2.5	3.2
Abdominal Pain	0.7	2.8	0.0	3.8	2.1
Back Pain	3.0	2.8	0.0	3.8	1.1
Allergic Reaction	2.6	0.9	2.8	1.3	0.0
Asthenia	1.9	2.2	0.0	3.8	0.0
<b>DIGESTIVE SYSTEM</b>					
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
<b>RESPIRATORY SYSTEM</b>					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
<b>SKIN AND APPENDAGES</b>					
Rash	0.7	3.9	2.8	3.8	1.1
<b>MUSCULOSKELETAL SYSTEM</b>					
Arthralgia	1.5	2.0	0.0	5.1	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  $\geq 2\%$  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.

**Digestive System:** *Nausea*, gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, 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 paralysis, hyperkinesia, depression, hypesthesia, hypertonia.

**Musculoskeletal System:** *Arthritis*, leg cramps, bursitis, tenosynovitis, myasthenia, tendinous 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, impotence, 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, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion.

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

**Metabolic and Nutritional Disorders:** *Peripheral edema*, hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia.

**Hemic and Lymphatic System:** Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia.

### **Postintroduction Reports**

Adverse events associated with Lipitor therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), and rhabdomyolysis.

### **OVERDOSAGE**

There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance 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 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 5). 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 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**

Lipitor is supplied as white, elliptical, film-coated tablets of atorvastatin calcium containing 10, 20, 40, and 80 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 5000

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

**80 mg tablets:** coded "PD 158" on one side and "80" on the other.  
N0071-0158-23 bottles of 90

**Storage**

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

**Rx only**

Revised June 2001

Manufactured by:

**Warner-Lambert Export, Ltd.** © 1998-'00  
Dublin, Ireland

Distributed by:

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

Marketed by:

**PARKE-DAVIS**  
Div of Warner-Lambert Co and  
**PFIZER Inc.**  
New York, NY 10017  
0155G247-2

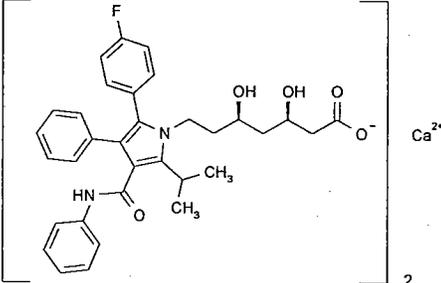
**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**20-702/S-022**

**CHEMISTRY REVIEW(S)**

APR - 5 2000

CHEMIST'S REVIEW		
<b>1. Organization</b> CDE/HFD-510 Division Of Metabolism And Endocrine Drug Products		<b>2. NDA #</b> 20-702 Approved: 17-Dec-1996
<b>3. Name and Address of Applicant</b> Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company 2800 Plymouth Road P.O. Box 1047 Ann Arbor, MI 48106-1047 (313) 966-5000		<b>4. Supplement</b> SCF-022 Doc. 06-DEC-1999 Rec. 07-DEC-1999
		<b>5. Name of the Drug</b> Lipitor Tablets
		<b>6. Nonproprietary Name</b> Atorvastatin Calcium
<b>7. Supplement provides for a new strength tablet, 80-mg Lipitor (Atorvastatin Calcium) Tablets.</b>		<b>8. Amendment</b> Doc. 08-DEC-1999 Rec. 09-DEC-1999 Doc. 04-APR-2000
<b>9. Pharmacological Category</b> Lipid Modifier. HMG-CoA reductase inhibitor/ Antihyperlipoproteinemic agent.		<b>10. How Dispensed</b> Rx
		<b>11. Related</b> -N. A.-
<b>12. Dosage Form</b> Tablet		<b>13. Potency</b> 10-, 20-, 40- and 80-mg
<b>14. Chemical Name and Structure</b>		
<p>Atorvastatin Calcium (C<sub>33</sub>H<sub>34</sub>FN<sub>2</sub>O<sub>5</sub>)<sub>2</sub>Ca FW = 2 x 557.7 + 40.0 = 1155.38 (anhydrous calcium salt) CAS 134523-03-8 CAS 134523-00-5 (atorvastatin) FW free acid C<sub>33</sub>H<sub>34</sub>FN<sub>2</sub>O<sub>5</sub> = 558.66 FW calcium salt trihydrate (C<sub>33</sub>H<sub>34</sub>FN<sub>2</sub>O<sub>5</sub>)<sub>2</sub>Ca H<sub>2</sub>O = 1209.42</p>		
<p>[R-(R*,R*)]-2-(4-fluorophenyl)-β, -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1)</p>		
<b>15. Comments:</b> The 80-mg daily (QD) dose is currently delivered by administration of two 40-mg tablets. This supplement, SCF-022, provides for a <b>new strength tablet, 80-mg Lipitor (Atorvastatin Calcium) Tablets</b> , which would provide a more convenient means to deliver this dose.		
<p>satisfactory stability data from three batches stored in the commercial packaging for six months (accelerated conditions) and at ... Post-approval stability protocol for commercial batches is adequately provided (Stability Commitment).</p>		
<b>16. Conclusions and Recommendations</b> Adequate CMC information has been provided to assure the quality of the proposed 80-mg strength tablets. <b>Issue Approval Letter:</b>		
<b>17. Reviewer Name (and Signature)</b> <i>Xavier Ysern</i> Xavier Ysern, PhD		<b>Date Completed</b> 05-APR-1999
<b>R/D INITIATED BY</b>		
filename: /nda/20702s22.doc		
DISTRIBUTION: Original: NDA 20-702 cc: HFD-510 Division File / MooreS/ WeberJ/ YsernX		

AP

*Stephen Mauer*  
4/15/2000

5 Page(s) Withheld

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

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Application: NDA 20702/022 Priority: 1P Org Code: 510  
Stamp: 07-DEC-1999 Regulatory Due: 07-APR-2000 Action Goal: District Goal: 03-MAR-2000  
Applicant: WARNER LAMBERT EXPOR Brand Name: LIPITOR (ATORVASTATIN  
C/O PARKE DAVIS PHARMACEUTIC. CALCIUM)10/20/40MG  
2800 PLYMOUTH RD Established Name:  
ANN ARBOR, MI 481061047 Generic Name: ATORVASTATIN CALCIUM  
Dosage Form: TAB (TABLET)  
Strength: 10, 20, 40 AND 80 MG

FDA Contacts: M. SIMONEAU (HFD-510) 301-827-6418 , Project Manager  
X. YSERN (HFD-510) 301-827-6420 , Review Chemist  
S. MOORE (HFD-510) 301-827-6430 , Team Leader

Overall Recommendation:

**ACCEPTABLE on 05-APR-2000 by J. D AMBROGIO (HFD-324) 301-827-0062**  
**WITHHOLD on 05-APR-2000 by J. D AMBROGIO (HFD-324) 301-827-0062**

Establishment: / DMF No:  
**PARKE DAVIS DIV WARNER LAMBE** AADA No:  
**KM 19 RD 689**  
**VEGA BAJA, PR 00763**

Profile: TCM OAI Status: NONE Responsibilities: /  
Last Milestone: OC RECOMMENDATION (/)  
Milestone Date: 06-MAR-2000 (/)  
Decision: ACCEPTABLE (/)  
Reason: DISTRICT RECOMMENDATION (/)

Establishment: ( DMF No:  
**WARNER LAMBERT CO** AADA No:  
**182 & 201 TABOR ROAD**  
**MORRIS PLAINS, NJ 07950**

Profile: CTL OAI Status: NONE Responsibilities: /  
Last Milestone: OC RECOMMENDATION (/)  
Milestone Date: 30-MAR-2000 (/)  
Decision: ACCEPTABLE (/)  
Reason: DISTRICT RECOMMENDATION (/)

Establishment: ( DMF No:  
AADA No:

Profile: TCM OAI Status: NONE Responsibilities: /  
Last Milestone: OC RECOMMENDATION (/)

05-APR-2000

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

Page 2 of 2

Milestone Date: **22-FEB-2000**  
Decision: **ACCEPTABLE**  
Reason: **BASED ON PROFILE**

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**20-702/S-022**

**PHARMACOLOGY REVIEW**

53.1

JAN - 5 2000

NDA 20-702/s022BL

Date of Review: December 23, 1999

Sponsor: Parke-Davis; Ann Arbor, MI

**DRUG** Atorvastatin, Lipitor™

**CATEGORY:** Lipid lowering (HMG CoA reductase inhibitor)

**PHARMACOLOGY REVIEW OF NDA SUPPLEMENT 20-702/S022**

**PHARMACOLOGY COMMENTS:** There were no preclinical data submitted under supplement #022 BL. Therefore, no pharmacology review is necessary for this supplement. There were no labeling changes made to the previously approved preclinical sections of the label.

*Ronald W. Steigerwalt*

Ronald W. Steigerwalt, Ph.D.

1/5/00

cc: NDA Arch  
HFD510  
HFD510/Steigerwalt/Simoneau  
20702.022.000  
**Recommendation code: AP**

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**20-702/S-022**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**



ratio of Cmax values (77.6%-101%) is not contained within the 80%-125% interval. However, DMEDP concluded that this diminished Cmax would not negatively impact efficacy. Therefore, the 80mg tablet is found to be acceptable to OCPB. This recommendation should be sent to the sponsor.

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*(Appendices and/or Attachments available from DMEDP filing room or DFS, if not included)*

**BACKGROUND:**

Lipitor (atorvastatin 10, 20, and 40mg tablets), an HMG-CoA reductase inhibitor approved on 17-DEC-96, is indicated for treatment of various dyslipidemias. Currently, Lipitor labeling indicates doses ranging from 10 to 80mg once daily. The sponsor believes that the 80mg tablet would be a more convenient means to deliver the 80mg dose, which is currently 2x40mg tablets. The sponsor has conducted a bioequivalence study comparing 1x80mg and 2x40mg tablets.

**STUDY SUMMARY INDEX**

<b>Protocol Number</b>	<b>Title</b>	<b>Page</b>
981-386	A single-dose bioequivalence study comparing 80-mg atorvastatin tablets prepared from the current formulation to 40-mg marketed Lipitor tablets	p. 8

**DRUG FORMULATION:**

**Were the lots used in the submitted bioequivalence study acceptable?**

The 80mg lot (CV1450799[81169V]) used in the bioequivalence study was of commercial size produced at an approved commercial site (Vega Baja, PR). The 40mg tablets were from marketed lots.

The formulation of the 80mg tablet is / -

Components	Theoretical Quantities per Tablet (mg)
<b>Core Ingredients</b>	
Atorvastatin Calcium	
Calcium Carbonate	
Microcrystalline Cellulose	
Lactose Monohydrate	
Croscarmellose Sodium	
Polysorbate 80	
Hydroxypropyl Cellulose	
<hr/>	
Magnesium Stearate	
Total	
<b>Film Coating Ingredients</b>	
Opadry White YS-1-7040	
Simethicone Emulsion	
<hr/>	
Total	

- <sup>a</sup> Equivalent to 80.00 mg of atorvastatin per tablet  
<sup>b</sup> Removed during processing and does not appear in final product.

The lots used in the bioequivalence study were acceptable.

**DISSOLUTION:**

**Does the 80mg tablet meet the current dissolution spec?**

The current dissolution method/spec is Apparatus 2 (paddle) at 75RPM, 900mL of 0.05M phosphate buffer, pH=6.8, NLT ~~(Q)~~ (Q) in 15 minutes. The sponsor conducted dissolution testing on 2 commercial 40mg tablets per vessel and 1 TBM 80mg tablet per vessel. The Office of Clinical Pharmacology and Biopharmaceutics does not accept dissolution data generated with two units per vessel; however, the 40mg dissolution data is irrelevant in determining if the 80mg tablet meets the currently approved dissolution spec. The 80mg tablet dissolution data included in the submission are shown below:

Sample No.	Dissolution Profiles of Batches Used in Bioequivalency Studies							
	Percent of Label Claim Dissolved							
	80-mg Tablet (Batch 81169V, Pan 1)				80-mg Tablet (Batch 81169V, Pan 2)			
	10 min	15 min	30 min	45 min	10 min	15 min	30 min	45 min
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	94	96	98	98	94	95	96	97
Min								
Max								

The 80mg tablet does meet the current dissolution spec.

**ANALYTICAL METHODOLOGY:**

Is the analytical method valid?

The table below summarizes the assay data:

Summary of Sample Analysis for Atorvastatin  
in Plasma (Protocol 981-386)

<b>Analytical Laboratory</b>  Supervisor Analyst(s) Software	/
<b>Parke-Davis Data Reviewer</b> <b>Method Description</b> Type of method Validation report(s)  Deviations from validated method Sample volume Analytical range: Lower limit of quantitation (LLOQ)  Upper limit of quantitation (ULOQ)  Long-term stability under storage conditions Stability Reference	William Bullen, BS  LC/MS/MS    ng/mL, all analytes  ng/mL, all analytes  3
<b>Study Assay Performance; QC Samples</b> PDM Sample Analysis SOP Accuracy (%relative error for quality controls)  Precision (%RSD for quality controls)	September 9, 1998 -9.573% to 3.022% (all analytes)  ≤6.77% (all analytes)
<b>Condition of samples on receipt</b> Longest interval between collection and analysis of a sample.	
<b>Parke-Davis References</b> Databook(s)	

Details of the assay are located in Appendix 2. The analytical methods were valid.

**HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES:**

**Bioavailability/Bioequivalence**

Do the 90%CI for the ratios of back-transformed least-squares means demonstrate bioequivalence between 2x40mg tablets and 1x80mg tablet of Lipitor?

A non-blind, single-dose, randomized, 2-way crossover study in healthy adult volunteers was conducted.

Subjects fasted for 8 hours before each treatment and remained fasting for 4 hours post-dose. There was a 15 day washout between periods. Blood sampling occurred up to 72 hours post-dose. Cmax was observed, AUC0-t was calculated using the linear trapezoidal rule; and AUC0-inf was extrapolated using LDC/ $\lambda_z$ .

Parameter values were generated through WinNonlin Pro Version 2.1 and evaluated using ANOVA with a model incorporating sequence, subject within sequence, period, and treatment effects. Thirty-six subjects were enrolled but subject 7 discontinued between periods.

The results as submitted by the sponsor are summarized below:

Parameter	Geometric Mean Values		Ratio (Test/Ref)	90%CI
	Reference 2x40mg (n=36)	Test 1x80mg (n=35)		
Cmax, ng/mL	36.7	32.5	88.5	77.6 - 101
Tmax, hr#	0.79	0.92	115	Not applicable
AUC0-t, ng•hr/mL	148	145	98.1	90.6 - 106
AUC0-inf, ng•hr/mL	156	152	97.5	90.3 - 105
T $\frac{1}{2}$ , hr#	12.3	10.2	83.0	Not applicable

# - Arithmetic means

The 90%CI for the ratios of back-transformed least-squares means fail to demonstrate bioequivalence between 2x40mg tablets and 1x80mg tablet of Lipitor – the 90%CI for Cmax falls outside the 80%-125% interval.

### DISCUSSION:

Bioequivalence is established when the 90%CI of the ratios of AUC and Cmax are contained within the 80%-125% interval. Since the parent compound atorvastatin is active and detectable in plasma at concentrations high enough, and for a time period long enough, to accurately estimate its AUC and Cmax, this parent compound should be used to establish bioequivalence; metabolite data should not be used in this case.

The 90%CI for the ratios of AUC0-t (90.6%-106%) as well as AUC0-inf (90.3%-105%) for atorvastatin fall within the 80%-125% interval. However, the 90%CI for the ratios of Cmax is **77.6%-101%**. Therefore, the results fail to demonstrate bioequivalence between the ~~40mg~~<sup>2x</sup> and 80mg Lipitor tablets ✓

It is possible that the two 40mg tablets dissolved more rapidly in the stomach perhaps due to greater surface area versus the one 80mg tablet and thus resulted in a greater Cmax and earlier Tmax (median Tmax for the 2x40mg and 1x80mg doses was 34 and 60 minutes, respectively) but comparable AUC.

The currently approved Lipitor labeling indicates:

'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...'

In discussing the decreased Cmax of the 80mg tablet with the medical officer it was concluded that this diminution would not negatively impact efficacy. It is important, however, to realize that the Cmax with the

80mg tablet may be decreased an additional 11% from other sources of diminution already noted.

---

Robert M. Shore, Pharm.D.  
Division of Pharmaceutical Evaluation II  
Office of Clinical Pharmacology and Biopharmaceutics

*Robert M. Shore*

23-FEB-00

RD initialed by Hae-Young Ahn, Ph.D., Team Leader \_\_\_\_\_

FT initialed by Hae-Young Ahn, Ph.D., Team Leader \_\_\_\_\_

*Hae-Young Ahn*

2/28/00

CC: NDA 20-702/SCF-022 (orig., 1 copy), HFD-510(Simoneau, Orloff), HFD-870(WeiX, Ahn, HuangS),  
HFD-850(Lesko) CDR (~~Barbara Murphy~~).

Code: AP

**Appendix 1. Study summaries**

Name of Company: <b>Warner-Lambert</b>	<b>INDIVIDUAL STUDY</b> <b>TABLE</b>	(For National Authority Use Only)
Name of Finished Product: <b>Lipitor</b>	Referring to Part of the Dossier	
Name of Active Ingredient: <b>Atorvastatin</b>	Volume: Page:	

**Title of Study:** A Single-Dose Bioequivalence Study Comparing 80-mg Atorvastatin Tablets Prepared from the Current Formulation to 40-mg Marketed Lipitor Tablets: Protocol 981-386

**Investigators:** / \_\_\_\_\_ /

**Study Center:** { \_\_\_\_\_ }

**Publication (reference):** none

**Studied Period (years):** 08/09/99 to 09/03/99      **Clinical Phase:** 4

**Objective:** To determine whether 80-mg atorvastatin tablets prepared from the current formulation are bioequivalent to two 40-mg marketed atorvastatin tablets.

**Methodology:** Nonblind, single-dose, randomized, 2-way crossover study in healthy volunteers

**Number of Subjects:** Planned enrollment was 36 subjects.

**Criteria for Inclusion:** Healthy adult male and female volunteers

**Reference Product, Dose and Mode of Administration, Batch Number:** 2 × 40-mg marketed Lipitor tablets (Lot CG 0170898), administered orally following an 8-hour overnight fast

**Test Product, Dose and Mode of Administration, Batch Number:** 1 × 80-mg atorvastatin tablet (Lot CV 1450799 [81169V]), administered orally following an 8-hour overnight fast

**Duration of Treatment:** Single oral doses on Days 1 and 15

**Pharmacokinetic Sampling and Analysis:** Plasma samples collected serially for 72 hours after each treatment were assayed for atorvastatin, \_\_\_\_\_

\_\_\_\_\_ concentration by a LC/MS/MS validated from \_\_\_\_\_  
\_\_\_\_\_ ng/mL, the lower limit of quantitation, to \_\_\_\_\_ g/mL for atorvastatin: \_\_\_\_\_

Name of Company: <b>Warner-Lambert</b>	<b>INDIVIDUAL STUDY TABLE</b>	(For National Authority Use Only)
Name of Finished Product: <b>Lipitor</b>	Referring to Part of the Dossier	
Name of Active Ingredient: <b>Atorvastatin</b>	Volume: Page:	

**Protocol CI-981 (Page 2)**

**Criteria for Evaluation:** Subjects providing adequate concentration-time data were included in the pharmacokinetic analysis. All subjects were included in the safety analysis.

**Pharmacokinetic and Statistical Analysis:** Pharmacokinetic parameter values were estimated using standard noncompartmental methods. Results from ANOVA of log-transformed C<sub>max</sub> and AUC values were used to calculate 90% confidence intervals for the ratio of treatment means. Confidence intervals derived from ANOVA results of atorvastatin C<sub>max</sub> and AUC values were used to evaluate bioequivalence.

### SUMMARY - CONCLUSIONS:

**Subject Characteristics and Disposition:** Thirty-six subjects enrolled in and 35 completed this study; 14 of the enrolled were males and 22 were females. The mean (range) age was 38.5 (20-61) years and the mean (range) weight was 78.4 (50.2-124.4) kg.

**Clinical:** Atorvastatin was well-tolerated during this study.

**Pharmacokinetic:** Mean atorvastatin pharmacokinetic parameter values, ratios, and 90% confidence intervals are summarized in the following table. Mean C<sub>max</sub> and AUC values were calculated as the antilogs of least-squares mean log-transformed values (analogous to geometric means). Ratios and confidence intervals for C<sub>max</sub> and AUC values are also based on log-transformed values. Least-squares mean values are presented for all other pharmacokinetic parameters.

Name of Company: <b>Warner-Lambert</b>	<b>INDIVIDUAL STUDY</b> <b>TABLE</b>	(For National Authority Use Only)
Name of Finished Product: <b>Lipitor</b>	Referring to Part of the Dossier	
Name of Active Ingredient: <b>Atorvastatin</b>	Volume: Page:	

**Protocol CI-981 (Page 3)**

Parameter	Mean Values		Ratio	90% Confidence Interval
	Reference (n = 36)	Test (n = 35)		
C <sub>max</sub> , ng/mL	36.7	32.5	88.5	77.6 to 101
t <sub>max</sub> , hr	0.79	0.92	115	Not Applicable
AUC(0-t <sub>l</sub> dc), ng-hr/mL	148	145	98.1	90.6 to 106
AUC(0-∞), ng-hr/mL	156	152	97.5	90.3 to 105
t <sub>1/2</sub> , hr	12.3	10.2	83.0	Not Applicable

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).

90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.

Based on atorvastatin t<sub>max</sub> and C<sub>max</sub> values, the rate of absorption following administration of new 80-mg atorvastatin tablets was similar to that observed for marketed 40-mg Lipitor tablets. The mean t<sub>max</sub> value for the new 80-mg tablet was less than 10 minutes slower (15%) and the mean C<sub>max</sub> value was 11.5% lower than those of marketed 40-mg Lipitor tablets. The lower 90% confidence interval was just below the 80% to 125% range generally required by regulatory agencies for establishing bioequivalence.

Based on atorvastatin AUC(0-∞) values, extent of absorption following administration of new 80-mg atorvastatin tablets was similar to that observed for marketed 40-mg Lipitor tablets. The difference in mean atorvastatin AUC(0-∞) values was 2.5% and the 90% confidence interval was within the 80% to 125% bioequivalence range.

**Conclusions** Based on atorvastatin AUC(0-∞) values, the bioavailability of new 80-mg atorvastatin tablets is 97.5% relative to marketed 40-mg Lipitor tablets. Atorvastatin AUC(0-∞) values meet 90% confidence interval requirements for establishing bioequivalence. Although C<sub>max</sub> values do not meet these criteria, the mean C<sub>max</sub> value following administration of new 80-mg tablets is only 11.5% lower than that observed for marketed 40-mg Lipitor tablets

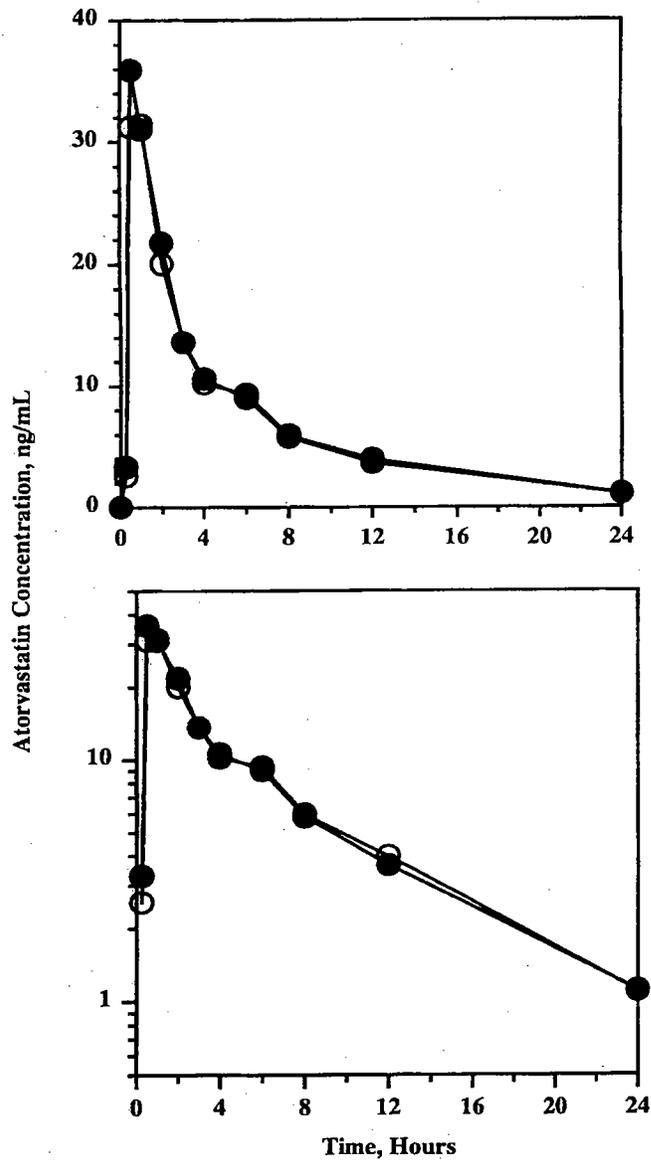


Figure 1. Mean Atorvastatin Plasma Concentration-Time Profiles Following Administration of Marketed 40-mg Lipitor Tablets (Filled Circles) and 80-mg Atorvastatin Tablets Prepared from the                      (Open Circles): Protocol 981-386

Upper and lower panels are linear and semilogarithmic plots, respectively..

**REVIEWER'S COMMENTS FOR STUDY #1:**

1. Study acceptable. Results fail to demonstrate bioequivalence between 2x40mg and 1x80mg.

**Appendix 2. Assay performance**

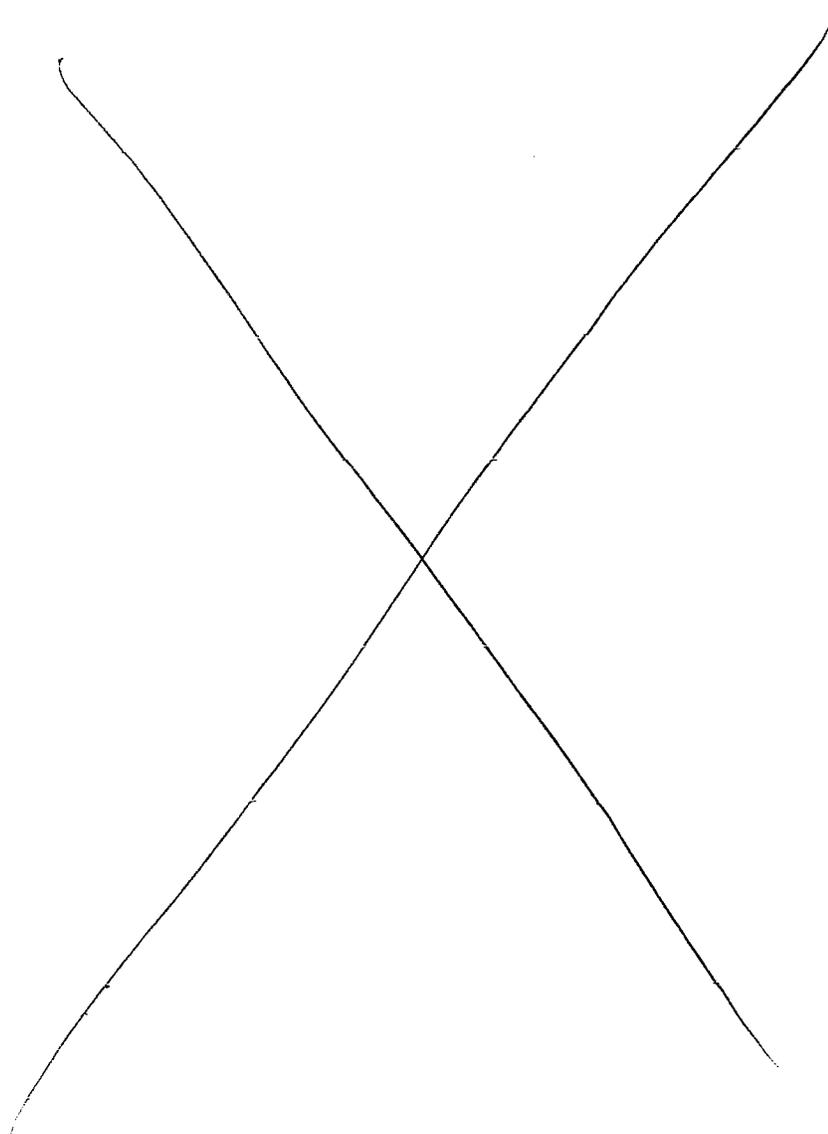
Atorvastatin (and metabolites) was quantified in plasma using a turbo ion spray LC/MS/MS following solid-phase extraction. All samples were analyzed at \_\_\_\_\_ The following methods and validation data apply not only to atorvastatin but also to the \_\_\_\_\_

**2. METHODS**

**2.1. Analytical Procedure(s)**

F

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<b>Sensitivity</b>		<b>LOQ</b>
<b>Linearity</b>		<b>ng/mL</b>
<b>Precision (%RSD)</b>	<b>Standards inter-assay</b>	<b>≤9%</b>
	<b>QC intra-assay</b>	<b>≤9%</b>
<b>Accuracy (%DEV)</b>	<b>Standards intra-assay</b>	<b>-9.6 – 3.0%</b>
	<b>QC intra-assay</b>	<b>-3.2 – 2.4%</b>

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20-702/S-022**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**



John Jenkins, M.D.  
NDA 20-702  
April 4, 2000  
Page 2

The ~~\_\_\_\_\_~~ acceptance criterion for the 80-mg tablets have been revised as follows:

NDA Supplement,  
December 6, 1999 As Amended

~~\_\_\_\_\_~~

These revisions are based on data obtained from production scale demonstration batches manufactured at the approved PDPL facility. Dissolution results obtained on tablets compressed at the upper and lower limits of ~~\_\_\_\_\_~~ ranged from ~~\_\_\_\_\_~~. Individual tablet dissolution profile results are provided in Attachment 1. These results are within the approved dissolution specification of ~~\_\_\_\_\_~~ (Q) in ~~\_\_\_\_\_~~ minutes. The amended acceptance criterion for tablet ~~\_\_\_\_\_~~ will be applied in process validation studies for the 80-mg tablet at PDPL.

In the original supplement, 3 month accelerated stability data were provided on three batches of drug product tablets. Six month accelerated and room temperature results are now available and are provided in Attachment 2 of this amendment.

Should you have any questions concerning this amendment, please feel free to contact me at 734/622-5781 or send a facsimile to 734/622-7890.

Sincerely,



Philip G. Simonson, Ph.D.  
Director, CMC  
Worldwide Regulatory Affairs

PS:kb  
04-04-2000\RN-109\20-702\CI-0981\Letter  
Attachments

Desk Copy: Ms. Regina Brown (New Jersey District Office)  
Dr. Xavier Ysem (HFD-510)





DEC 15 1999

Food and Drug Administration  
Rockville MD 20857

NDA 20-702/S-022

Parke-Davis Pharmaceutical Research  
Warner-Lambert Company  
2800 Plymouth Road, P.O. Box 1047  
Ann Arbor, MI 48106-1047

Attention: Sean Brennan, Ph.D. Vice President  
Worldwide Regulatory Affairs

Dear Dr. Brennan:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Lipitor® (atorvastain calcium) Tablets  
NDA Number: 20-702  
Supplement Number: S-022  
Date of Supplement: December 6, 1999  
Date of Receipt: December 7, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on February 5, 2000, 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

NDA 20-702/S-022

Page 2

cc:

Original NDA 20-702/S-022

HFD-510/Div. Files

HFD-510/CSO/Simoneau

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SUPPLEMENT ACKNOWLEDGEMENT



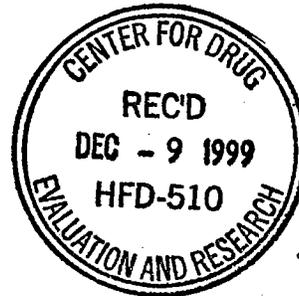
December 8, 1999

NDA 20-702  
Ref. No. 104  
Lipitor® (atorvastatin calcium) Tablets

Re: Amendment to Supplement  
(Ref. No. 103) New 80-mg Strength

Sean Brennan, Ph.D.  
Vice President  
Worldwide Regulatory Affairs

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



*No comment  
1-3-00*

Dear Dr. Sobel:

On behalf of, and as agent for, Warner-Lambert Export, reference is made to approved NDA 20-702 for Lipitor® (atorvastatin calcium) Tablets and to a Supplement (Ref. No. 103) submitted on December 6, 1999. The original supplement provides for a new tablet strength of 80-mg atorvastatin. The purpose of this amendment is to provide copies of draft labeling for the 80-mg tablet.

Copies of the most recently approved labeling for Lipitor Tablets are provided with the proposed changes indicated for the 80-mg strength. New text added is highlighted and changes to the existing labeling are shown by strikethrough. The changes to labeling provided in this amendment are limited to references of how atorvastatin is supplied on pages 1 and 17, the new product code and NDC number for the 80-mg strength on page 17, and the new label specification number on page 18.

Should you have any questions regarding this submission, please contact me at 734/622-7596 or send a facsimile to 734/622-7890.

Sincerely,

*Sean Brennan*  
Sean Brennan

*APL 4-7-00  
mas*

SB:kb  
12-08-1999\RN-104\20-702\CI-0981\Letter  
Attachments

ORIGINAL

NEW CORRESPONDENCE  
SNC



December 8, 1999

Sean Brennan, Ph.D.  
Vice President  
Worldwide Regulatory Affairs

NDA 20-702  
Lipitor® (atorvastatin calcium) Tablets

Re: Response to FDA Request for Information

Ms. Margaret Simoneau  
CSO, Reviewer  
Division of Metabolism and Endocrine Drug Products (HFD-510)  
Document Control Room 14B-04  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Parklawn Building  
5600 Fishers Lane  
Rockville, Maryland 20857



Proprietary Review D. Q. Ahn 12-15-99

Dear Ms. Simoneau:

On behalf of, and as agent for, Warner-Lambert Export Limited, reference is made to approved NDA 20-702 for Lipitor® (atorvastatin calcium) Tablets. Reference is also made to our submission dated December 6, 1999 (Ref. No. 103) for a new 80-mg tablet strength supplement. At the request of Ms. Enid Galliers, we are resubmitting Volume 1 which now includes an index of the summaries and reports that were included in the December 6, 1999 submission.

Should you have any questions regarding this submission, please contact me at at 734/622-7596 or send a facsimile to 734/622-7890.

Sincerely,

*Sean Brennan*  
Sean Brennan, Ph.D.

REVISIONS COMPLETED  
APL 4/2/00  
CSO ACTION  
 LETTER  MEMO  
Mas  
CSO INITIALS DATE

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12-08-1999\20-702\CI-0981\Letter

Attachments

Desk Copy: Ms. Regina Brown, North Brunswick FDA District Office (HFR-CE350)  
Dr. Xavier Ysern (HFD-510)  
Dr. Hae Young Ahn (HFD-870)

Pharmaceutical  
Research

2800 Plymouth Road  
Ann Arbor, MI  
48105

Phone: (734) 622-7596  
Facsimile: (734) 622-7890

NDA NO. 20-702 REF. NO. 032  
NDA NUMBER FOR SCF

**PARKE-DAVIS**

Sean Brennan, Ph.D.  
Vice President  
Worldwide Regulatory Affairs

**CRIMINAL**

December 6, 1999

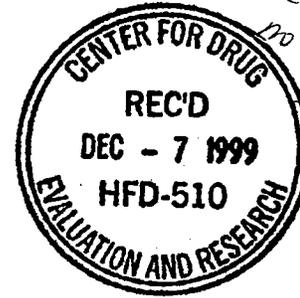
NDA 20-702

Ref. No. 103

Lipitor® (atorvastatin calcium) Tablets

**Re: Supplement: New 80-mg Tablet  
Strength**

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



*to make the 80-425%  
45% CI up to 10% reduction  
by 1x 80  
w. 2x 40mg strength  
no impact  
clinical efficacy  
D&D  
↓  
N.A. Clinical  
Bases  
D&D  
4/2/00*

Dear Dr. Sobel:

On behalf of, and as agent for, Warner-Lambert Export Limited, reference is made to approved NDA 20-702 for Lipitor® (atorvastatin calcium) Tablets. The purpose of this supplement is to provide for an 80-mg tablet, which is \_\_\_\_\_ to the commercial 10-, 20-, and 40-mg tablet strengths.

Atorvastatin calcium tablets are marketed in 10-, 20-, and 40-mg strengths, with an approved maximum daily dose of 80-mg of atorvastatin. The 80-mg QD dose is currently delivered by administration of two 40-mg tablets. In order to provide a more convenient means to deliver this dose, an 80-mg tablet has been developed.

A randomized, single dose, 2-way crossover bioequivalence study was conducted comparing the proposed 80-mg tablet to two 40-mg marketed Lipitor tablets. Data were collected from 35 subjects who completed the study, as well as 1 subject who received 40-mg marketed Lipitor tablets only, before withdrawing. The bioavailability of the proposed 80-mg tablets is 97.5% relative to 2 marketed 40-mg Lipitor tablets based on atorvastatin AUC (0-∞) values. AUC (0-∞) values meet 90% confidence interval requirements for establishing bioequivalence.

REVIEWS COMPLETED <i>AP Rk 4-7-00</i>
CSD ACTION: <input checked="" type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO <i>Mus 4-7-00</i>
CSD INITIALS _____ DATE _____

Solomon Sobel, M.D.  
NDA 20-702  
December 6, 1999  
Page 2

Based on atorvastatin  $t_{max}$  and  $C_{max}$  values, the rate of absorption following administration of the proposed 80-mg atorvastatin tablets was similar to that observed for marketed 40-mg Lipitor tablets. The mean  $t_{max}$  value for the new 80-mg tablet was less than 10 minutes slower (15%) and the mean  $C_{max}$  value was 11.5% lower than marketed 40-mg Lipitor tablets. The lower limit of the 90% confidence interval for atorvastatin  $C_{max}$  values extends slightly below the 80-125% range generally employed to establish bioequivalence.

Although  $C_{max}$  values do not meet strict bioequivalence criteria, the mean  $C_{max}$  value following administration of new 80-mg tablets is only 11.5% lower than that observed for marketed 40-mg Lipitor tablets. The reduction in  $C_{max}$  of the parent compound indicates no concern for safety or clinical efficacy of the 80-mg atorvastatin tablet. The clinical significance of the reduced  $C_{max}$  of the new 80-mg tablets has been evaluated and a clinical assessment based on this evaluation is provided in Attachment 1A (RR-REG 720-04438).

A complete report describing the bioequivalence study conducted to compare the proposed 80-mg tablet to two 40-mg Lipitor tablets is provided in Attachment 1B (RR-744-00512).

The composition of the 80-mg tablet is [redacted]. Additionally, the film coat used for the 80-mg tablet is [redacted].

[redacted] The new tablet strength will be manufactured at the approved Parke-Davis Pharmaceuticals, Limited (PDPL) facility located in Vega Baja, Puerto Rico. A Drug Product Technical Summary describing the complete manufacturing and control of the 80-mg tablets at PDPL is provided in Attachment 2 (RR-REG 956-00267).

The commercial container/closure systems for the 80-mg tablets will remain unchanged from those currently approved in NDA 20-702: [redacted] bottles of 90 tablets and unit-dose foil/foil blisters. A [redacted] bottle has been added to accommodate the larger size of the 80-mg tablet.

In support of this supplement, three batches of Lipitor 80-mg tablets [redacted] batches manufactured at the Morris Plains, NJ facility and one [redacted] batch manufactured at the PDPL facility) have been manufactured, packaged in the approved container/closure systems, and placed on stability. Three-month accelerated stability data for 80-mg tablets manufactured at both Morris Plains and PDPL facility are also included in Attachment 2. Stability results obtained to date are similar to those

Solomon Sobel, M.D.

NDA 20-702

December 6, 1999

Page 3

observed during development and on the commercial product. Based on these results, and the excellent stability history of the currently marketed tablet strengths, an expiration period of 24 months is proposed for the 80-mg tablets. The proposed expiration period is the same as that approved for the currently marketed strengths.

Should you have any questions regarding this submission, please contact me at at 734/622-7596, or send a facsimile to 734/622-7890.

Sincerely,

*Sean Brennan*  
Sean Brennan, Ph.D.

PS\kb

12-06-1999\RN-103\20-702\CI-0981\Letter

**Attachments**

Desk Copy: Ms. Regina Brown, North Brunswick FDA District Office (HFR-CE350)  
Dr. Xavier Ysern (HFD-510)  
Dr. Hae Young Ahn (HFD-870)