CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-702/S039

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-702/S-039

Pfizer Inc., US Agent for
Pfizer Ireland Pharmaceuticals
Attention: Madeleine M. Jester
Director, US Regulatory Affairs
235 East 42nd Street
New York, NY 10017

Dear Ms. Jester:

Please refer to your supplemental new drug application dated September 30, 2003, received October 1, 2003, 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 July 16, 26, 28 (email), and 30 (email), 2004.

This supplemental New Drug Application provides for new indications, based on the results of the Anglo-Scandinavian Cardiovascular Outcomes Trial Lipid Lowering Arm (ASCOT-LLA), for the use of atorvastatin in adult patients without clinically evident coronary heart disease (but with multiple risk factors for coronary heart disease such as age $\geq$ 55 years, smoking, hypertension, low HDL-C or a family history of early coronary heart disease), to reduce the risk of myocardial infarction, and to reduce the risk for revascularization procedures and angina. In addition, this supplemental application provides for changes to the CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE and ADVERSE EVENTS sections of the LIPITOR package insert.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

We note your commitment to submit the full study report for ASCOT, the parent trial for ASCOT-LLA, within one year of completion or termination of ASCOT.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted July 30, 2004)(copy enclosed).

Please submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDAs*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-702/S-039." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Margaret Simoneau, M.S. R.Ph., Regulatory Project Manager, at (301) 827-6411.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Eric Colman
7/30/04 11:55:44 AM
Eric Colman for David Orloff

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-702/S039

LABELING

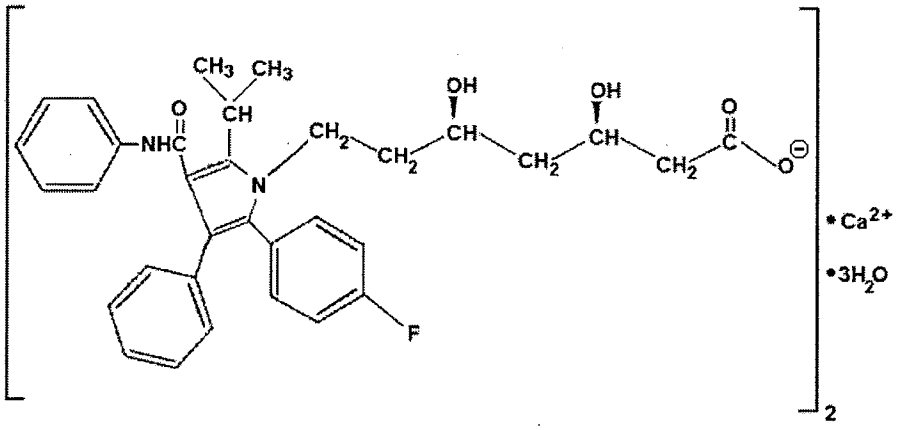
69-5884-00-4.1

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)-ß, 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 (hypromellose, 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.

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 Cmax and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration (see DOSAGE AND ADMINISTRATION).

Distribution: Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be secreted in human milk (see 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 Cmax and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults.Clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults (see 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 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: 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. Cmax and AUC are each 4-fold greater in patients with Childs-Pugh A disease. Cmax and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease (see CONTRAINDICATIONS).

Clinical Studies

Prevention of Cardiovascular Disease

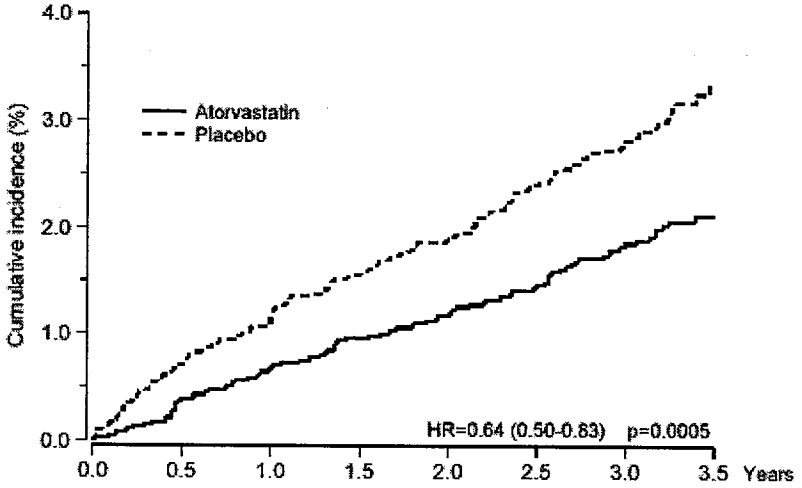
In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of LIPITOR (atorvastatin calcium) on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40-80 years of age (mean of 63 years), without a previous myocardial infarction and with TC levels ≤251 mg/dl (6.5 mmol/l). Additionally all patients had at least 3 of the following cardiovascular risk factors: male gender (81.1%), age >55 years (84.5%), smoking (33.2%), diabetes (24.3%), history of CHD in a first-degree relative (26%), TC:HDL >6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypertrophy (14.4%), prior cerebrovascular event (9.8%), specific ECG

abnormality (14.3%), proteinuria/albuminuria (62.4%)]. In this double-blind, placebo-controlled study patients were treated with anti-hypertensive therapy (Goal BP <140/90 mm Hg for non-diabetic patients, <130/80 mm Hg for diabetic patients) and allocated to either LIPITOR 10 mg daily (n=5168) or placebo (n=5137), using a covariate adaptive method which took into account the distribution of fourteen baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients were followed for a median duration of 3.3 years.

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

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

Figure 1: Effect of LIPITOR 10 mg/day on Cumulative Incidence of Nonfatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT-LLA)



LIPITOR also significantly decreased the relative risk for revascularization procedures by 42%. Although the reduction of fatal and non-fatal strokes did not reach a pre-defined significance level (p 0.01), a favorable trend was observed with a 26% relative risk reduction (incidences of 1.7% for LIPITOR and 2.3% for placebo). There was no significant difference between the treatment groups for death due to cardiovascular causes (p=0.51) or noncardiovascular causes (p=0.17).

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)[a]

Dose	N	TC	LDL-C	Apo B	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

[a] 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^{th} and 75^{th} 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	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Study 1							
Atorvastatin 10 mg	707	-27[a]	-36[a]	-28[a]	-17[a]	+7	-37[a]
Lovastatin 20 mg	191	-19	-27	-20	- 6	+7	-28
95% CI for Diff[1]		-9.2, -6.5	-10.7, -7.1	-10.0, -6.5	-15.2, -7.1	-1.7, 2.0	-11.1, -7.1
Study 2							
Atorvastatin 10 mg	222	-25[b]	-35[b]	-27[b]	-17[b]	+6	-36[b]
Pravastatin 20 mg	77	-17	-23	-17	- 9	+8	-28
95% CI for Diff[1]		-10.8, -6.1	-14.5, -8.2	-13.4, -7.4	-14.1, -0.7	-4.9, 1.6	-11.5, -4.1
Study 3							
Atorvastatin 10 mg	132	-29[c]	-37[c]	-34[c]	-23[c]	+7	-39[c]
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff[1]		-8.7, -2.7	-10.1, -2.6	-8.0, -1.1	-15.1, -0.7	-4.3, 3.9	-9.6, -1.9

[1] 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.

[a] Significantly different from lovastatin, ANCOVA, $p \leq 0.05$

[b] Significantly different from pravastatin, ANCOVA, $p \leq 0.05$

[c] 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.

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%.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients

In a double-blind, placebo-controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (FH) or severe hypercholesterolemia were randomized to Lipitor (n=140) or placebo (n=47) for 26 weeks and then all received Lipitor for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level ≥ 190 mg/dL or 2) a baseline LDL-C ≥ 160 mg/dL and positive family history of FH or documented premature cardiovascular disease in a first- or second-degree relative. The mean baseline LDL-C value was 218.6 mg/dL (range: 138.5-385.0 mg/dL) in the Lipitor group compared to 230.0 mg/dL (range: 160.0-324.5 mg/dL) in the placebo group. The dosage of Lipitor (once daily) was 10 mg for the first 4 weeks and up-titrated to 20 mg if the LDL-C level was > 130 mg/dL. The number of Lipitor-treated patients who required up-titration to 20 mg after Week 4 during the double-blind phase was 80 (57.1%).

Lipitor significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26 week double-blind phase (see Table 5).

TABLE 5
Lipid-altering Effects of Lipitor in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia
(Mean Percent Change from Baseline at Endpoint in Intention-to-Treat Population)

DOSAGE	N	Total-C	LDL-C	HDL-C	TG	Apolipoprotein B
Placebo	47	-1.5	-0.4	-1.9	1.0	0.7
Lipitor	140	-31.4	-39.6	2.8	-12.0	-34.0

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

The safety and efficacy of doses above 20 mg have not been studied in controlled trials in children. The long-term efficacy of Lipitor therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

INDICATIONS AND USAGE

Prevention of Cardiovascular Disease
In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age ≥ 55 years, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, Lipitor is indicated to:

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

Hypercholesterolemia
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;

5. as an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial

hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:

a. LDL-C remains ≥ 190 mg/dL or
b. LDL-C remains ≥ 160 mg/dL and:
   - there is a positive family history of premature cardiovascular disease or
   - two or more other CVD risk factors are present in the pediatric patient

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 6).

TABLE 6. NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD [a] or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional) [b]
2+ Risk Factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥ 160
0-1 Risk factor [c]	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

[a] CHD, coronary heart disease

[b] Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of < 100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.

[c] Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dL, non HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

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).

The NCEP classification of cholesterol levels in pediatric patients with a familial history of hypercholesterolemia or premature cardiovascular disease is summarized below:

Category	Total-C (mg/dL)	LDL-C (mg/dL)
Acceptable	<170	<110
Borderline	170-199	110-129
High	≥200	≥130

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^2).

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

Safety and effectiveness in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial of 6 months duration in adolescent boys and postmenarchal girls. Patients treated with Lipitor had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups, regardless of causality assessment, were infections. **Doses greater than 20 mg have not been studied in this patient population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in boys or on menstrual cycle length in girls (see CLINICAL PHARMACOLOGY, Clinical Studies section; ADVERSE REACTIONS, Pediatric Patients (ages 10-17 years); and DOSAGE AND ADMINISTRATION, Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age). Adolescent females should be counseled on appropriate contraceptive methods while on Lipitor therapy (see CONTRAINDICATIONS and PRECAUTIONS, Pregnancy). **Lipitor has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.**

Clinical efficacy with doses up to 80 mg/day for 1 year have been evaluated in an uncontrolled study of patients with homozygous FH including 8 pediatric patients (see CLINICAL PHARMACOLOGY, Clinical Studies: Homozygous Familial Hypercholesterolemia).

Geriatric Use

The safety and efficacy of atorvastatin (10-80 mg) in the geriatric population (≥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 (≥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 ≥2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment, are shown in Table 7.

TABLE 7. 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
BODY AS A WHOLE					
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
DIGESTIVE SYSTEM					
Constipation	1.8	2.1	0.0	2.5	1.1
Diarrhea	1.5	2.7	0.0	3.8	5.3
Dyspepsia	4.1	2.3	2.8	1.3	2.1
Flatulence	3.3	2.1	2.8	1.3	1.1
RESPIRATORY SYSTEM					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
SKIN AND APPENDAGES					
Rash	0.7	3.9	2.8	3.8	1.1
MUSCULOSKELETAL SYSTEM					
Arthralgia	1.5	2.0	0.0	5.1	0.0
Myalgia	1.1	3.2	5.6	1.3	0.0

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)
In ASCOT (see CLINICAL PHARMACOLOGY, *Clinical Studies*) involving 10,305 participants treated with Lipitor 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with Lipitor was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.

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.

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.

Pediatric Patients (ages 10-17 years)
In a 26-week controlled study in boys and postmenarchal girls (n=140), the safety and tolerability profile of Lipitor 10 to 20 mg daily was generally similar to that of placebo

(see CLINICAL PHARMACOLOGY, Clinical Studies section and PRECAUTIONS, Pediatric Use).

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 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of Lipitor is 10 to 80 mg once daily. Lipitor can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of Lipitor should be individualized according to patient characteristics such as goal of therapy and response (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.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age)

The recommended starting dose of Lipitor is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy (see NCEP Pediatric Panel Guidelines[1], CLINICAL PHARMACOLOGY, and INDICATIONS AND USAGE). Adjustments should be made at intervals of 4 weeks or more.

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

[1] National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children Adolescents, *Pediatrics.* 89(3):495-501. 1992.

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.
NDC 0071-0155-23 bottles of 90
NDC 0071-0155-34 bottles of 5000
NDC 0071-0155-40 10 x 10 unit dose blisters

20 mg tablets: coded "PD 156" on one side and "20" on the other.
NDC 0071-0156-23 bottles of 90
NDC 0071-0156-40 10 x 10 unit dose blisters
NDC 0071-0156-94 bottles of 5000

40 mg tablets: coded "PD 157" on one side and "40" on the other.
NDC 0071-0157-23 bottles of 90
NDC 0071-0157-73 bottles of 500

80 mg tablets: coded "PD 158" on one side and "80" on the other.
NDC 0071-0158-23 bottles of 90
NDC 0071-0158-73 bottles of 500
Storage
Store at controlled room temperature 20 - 25°C (68 - 77°F) [see USP].

Rx Only

Manufactured by:

Pfizer Ireland Pharmaceuticals
Dublin, Ireland

Distributed by:

Parke-Davis
Division of Pfizer Inc, NY, NY 10017

69-5884-00-4.1

Revised July 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-702/S039

MEDICAL REVIEW(S)

MEDICAL TEAM LEADER MEMO

NDA #:	20-702/SE1/supplement 039
Sponsor:	Pfizer
Drug product:	Lipitor® (atorvastatin)
Date of Submission:	September 30, 2003
Primary Medical Reviewer:	Karen M. Mahoney, MD
Statistical Reviewer:	Joy Mele, MS

EXECUTIVE SUMMARY

The Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) is a large, placebo-controlled study evaluating the effects of atorvastatin 10 mg daily treatment in a population of treated hypertensive patients who have not manifested clinical cardiovascular disease but are, however, at high risk for an event due to the presence of multiple risk factors for CVD. ASCOT-LLA is a substudy of a larger trial designed to evaluate the effects of two different antihypertensive regimens. The larger study is still ongoing; however, the lipid-lowering portion was terminated by the Data Safety Monitoring Board after 3.3 years of treatment identified a significant difference in the treatment between atorvastatin and placebo.

The study enrolled 10,305 patients who had nonfasting total cholesterol levels below 251 mg/dL and at least 3 risk factors described in the clinical study design. The primary efficacy analysis was the time to first event of either a nonfatal myocardial infarction or coronary heart disease death. Other clinical events related to atherosclerosis were evaluated as secondary measures. After 3.3 years, treatment with atorvastatin 10 mg daily reduced the relative risk of experiencing a NFMI or CHD by 36% (atorvastatin 1.9% vs placebo 3.0%; p=0.0005) with NFMIs being the predominant event in this composite measure. This effect was consistent regardless of age, smoking status, obesity, renal function, and baseline LDL-C. There were too few events in women to allow for any conclusive statement on the effect of atorvastatin in women (36 out of 254 primary endpoint events).

Significant risk reductions associated with atorvastatin therapy were also observed for rate of revascularization procedures and incidence of angina. While the incidence rate for fatal and nonfatal strokes was lower in the atorvastatin group than placebo, the relative risk reduction did not reach a pre-defined criterion of statistical significance ($p<0.01$).

ASCOT-LLA adds further to the substantial controlled-trials database for statins. There were no safety findings revealed in this trial that has not already been described in the approved package insert for atorvastatin.

To date, the Agency has reviewed 7 statin clinical outcomes trial that have each demonstrated a clinical benefit with cholesterol lowering in patients who have varied risks for heart disease and whose baseline LDL-C levels average between 130 and 190

mg/dL (see Table 1). ASCOT-LLA now extends the benefit of cholesterol-lowering to the hypertensive patient population without clinically evident heart disease but who have multiple risk factors for CHD. Despite these risk factors, it is notable that the placebo event rate in ASCOT is only 3% compared to studies involving higher risk patients where placebo event rates are 2-3 times of that observed in ASCOT.

Table 1. Statin Clinical Outcomes Trials

CLINICAL TRIAL AND PRIMARY ENDPOINT MEASURED	MEAN BASELINE LIPIDS (MG/DL)	STATIN EVENT RATE	PLACEBO EVENT RATE	RELATIVE RISK
Primary Prevention Trials				
WOSCOPS (n=6,595) NF-MI/fatal CHD	LDL-C 192 TC 272	174/3302 (5.3%)	248/3293 (7.5%)	0.69
AFCAPS/TexCAPS (n=6,605) NF-MI/fatal CHD/UAP	LDL-C 150 TC 221	116/3304 (3.5%)	183/3301 (5.5%)	0.63
ASCOT (n=10,240) NF-MI/fatal CHD	LDL-C 133	100/5134 (1.9%)	154/5106 (3.0%)	0.64
Secondary Prevention Trials				
4S (n=4,444) Total Mortality	LDL-C 189 TC 260	182/2221 (8.2%)	256/2223 (11.5%)	0.70
CARE (n=4,159) NF-MI/fatal CHD	LDL-C 139 TC 209	212/2081 (10.2%)	274/2078 (13.2%)	0.76
LIPID (n=9,014) Total CHD Mortality	LDL-C 150 TC 219	287/4512 (6.4%)	373/4502 (8.3%)	0.76
HPS (n=20,536) Total Mortality	LDL-C 131 TC 226	1328/10,269 (12.9%)	1507/10,267 (14.7%)	0.87
CHD Death		587/10,269 (5.7%)	707/10,267 (6.9%)	0.82

INTRODUCTION AND BACKGROUND

Lipitor (atorvastatin) is a lipid-altering drug belonging to a class of drugs known as HMG-CoA reductase inhibitors or statins. It was approved in 1996 at dosage strengths of 10, 20, 40, and 80 mg for the following indications:

- as an adjunct to diet to reduce elevated total-C, LDL-C, apoB, 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)
- as an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV)
- 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) or if such treatments are unavailable

An indication for pediatric heterozygous familial hypercholesterolemia was approved in 2002.

This application includes the results of a clinical outcomes study submitted in support of the following under INDICATIONS AND USAGE:

Prevention of Cardiovascular Disease

without clinically evident coronary heart disease, Lipitor is indicated to:

- Reduce the risk myocardial infarction
-
-

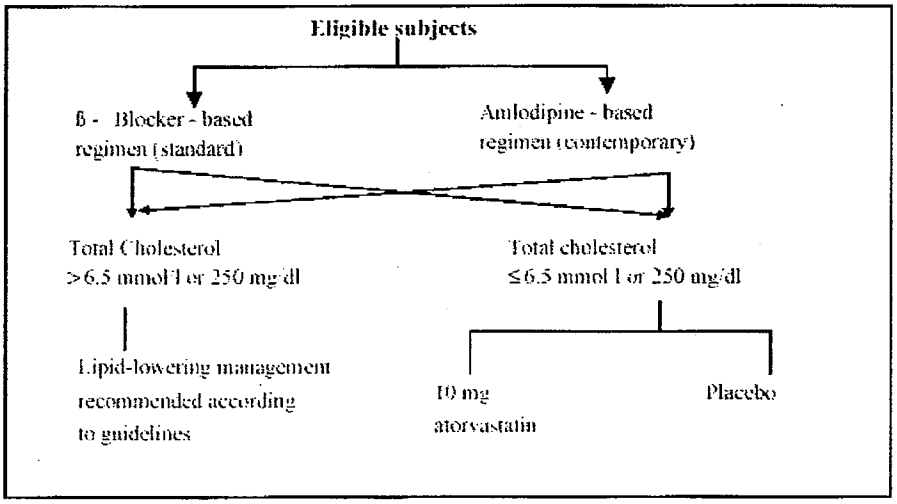
While other studies involving atorvastatin at higher doses have been submitted to support claims of clinical benefit, efficacy findings of these other studies have either been uninterpretable due to poor study design or not robust enough to support labeling changes.

DESCRIPTION OF CLINICAL TRIAL

Study Design

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) is a 2x2 factorial, placebo-controlled study designed to evaluate the separate and combined effects of blood pressure-lowering and lipid-lowering in patients with hypertension, 3 or more CV risk factors, and normal or slightly elevated cholesterol levels. The study aimed to enroll 18,000 hypertensive patients who would then be assigned to receive either amlodipine or a beta-blocker. It was estimated that approximately half of the cohort would have a total-C $\leq$ 250 mg/dL, and these patients would further be allocated to receive treatment with either atorvastatin 10 mg daily or placebo. The study design of ASCOT and ASCOT-LLA is depicted in the following figure submitted by the sponsor.

Figure 1 Trial Profile for ASCOT-LLA study



Patient Selection

Male or female patients aged 40 to 79 years of age were eligible if they were hypertensive by study definitions and had at least three of the following:

- smoking
- LVH
- specific ECG abnormalities
- h/o early CHD in first degree relative
- age ≥ 55 years
- microalbuminuria
- Type 2 diabetes
- PVD
- h/o cerebrovascular event more than 3 months prior to recruitment
- male
- TC/HDL ratio ≥ 6 (for those entering ASCOT-LLA the TC had to be ≤ 250 mg/dL and the patient could not be currently taking a statin or fibrate)

Patients were excluded if there was a previous history of MI or angina pectoris and a recent history (≤ 3 mos) of stroke, TIA or cerebrovascular surgery.

Efficacy Endpoints

The primary endpoint for ASCOT-LLA was a composite endpoint of fatal CHD and nonfatal MI (symptomatic and silent).

Secondary endpoints included other composite endpoints discussed in Dr. Karen Mahoney's review. Some of these secondary endpoints include revascularization procedures, stroke, all-cause mortality, and heart failure.

CLINICAL EFFICACY RESULTS

Of the 19,342 patients who were allocated to the two antihypertensive treatment regimens, 10,305 were further assigned to treatment with either atorvastatin 10 mg (n=5,168) or placebo (n=5,137). This lipid-lowering trial was terminated early by the DSMB after an average treatment duration of 3.3 years.

The majority of patients were Caucasian (~94%) and male (~81%). The mean age was 63 years in both treatment groups. Although this study excluded patients with clinically evident cardiovascular disease, all patients had to have had at least 3 protocol-defined characteristics that would increase the risk of CV events. More than 99% of the cohort had 2 or more NCEP CHD risk factors and these risks were balanced between the two treatment groups (see Table 6.1.3.12.2 from Dr. Mahoney's review).

Mean baseline lipid values were similar in both treatment groups. Mean LDL-C level at baseline was 133 mg/dL in both the atorvastatin and placebo groups. During the trial, more patients in the placebo group (12.8% vs. 4.4%) had lipid-lowering therapy initiated. A slightly higher percentage of patients in the placebo group also received anti-hypertensive therapy and aspirin. This difference, however, would more likely attenuate any clinical benefit observed within the atorvastatin group.

Primary Endpoint

The primary efficacy analysis was a time-to-first event of non-fatal MI or CHD death in 10,240 patients (two centers were excluded due to an independent audit which could not verify blood pressure readings). The following table summarizes the incidence of primary endpoint events as a composite measure and by the individual components.

Table 2. Primary Endpoint (Composite and Individually)

	Atorvastatin N=5,134	Placebo N=5,106	Unadjusted HR (95% CI)
Primary (composite of nonfatal MI and CHD death)	100 (1.9%)	154 (3.0%)	0.64 (0.50-0.83)
Nonfatal MI	60 (1.2%)	108 (2.1%)	0.55 (0.40-0.75)
Fatal CHD	41 (0.8%)	46 (0.9%)	0.89 (0.58-1.35)

Atorvastatin treatment significantly reduced the relative risk of experiencing a nonfatal MI or CHD death by 36% (p=0.00053) compared to placebo, with nonfatal MIs comprising the majority of events.

Subgroup analyses were performed on the primary efficacy measure as summarized in the FDA statistical review. The effect of atorvastatin was consistent across the following subgroups analyzed: age, smoking status, obesity, renal dysfunction, and baseline LDL-C. An analysis by gender did not reveal consistent effects of atorvastatin therapy between men and women. For the primary efficacy measure, the event rate in females was higher in the atorvastatin group (1.97%) compared to placebo (1.78%); however, the small number of events (36 total) in this trial precluded any conclusive statement regarding the effect of atorvastatin in women.

Secondary Endpoints of Note

The occurrence of clinical cardiovascular events other than those comprising the primary efficacy measure was also evaluated. Treatment with atorvastatin significantly reduced the risk of having a revascularization procedure (RR 0.58; 95% CI 0.43 – 0.77) and the risk of angina (RR 0.59; CI 0.38 – 0.90).

The risk of fatal and non-fatal stroke was reduced with atorvastatin therapy (RR 0.74; 95% CI 0.56 – 0.98); however, the results did not meet the pre-specified criterion for statistical significance ($p \leq 0.01$).

CLINICAL SAFETY RESULTS

ASCOT-LLA included safety data on more than 5,000 patients treated with atorvastatin 10 mg daily for an median duration of 3.08 years. In this placebo-controlled study, known safety concerns associated with statin therapy were summarized by Dr. Mahoney in her review. In addition, due to recent interests in the effects of statins on neurologic/cognitive function, Dr. Mahoney specifically addressed safety findings within this body system.

Two cases of rhabdomyolysis were reported in this trial; both were in the atorvastatin group (0.04%). These 2 cases are summarized in Dr. Mahoney's review. One patient was taking concomitant simvastatin and the other patient had a history of heavy alcohol use. Both patients recovered after hospitalization for IVF hydration.

The incidence of liver AEs was similar between the two treatment groups. There were 11 (0.21%) cases in the atorvastatin treatment group compared to 10 (0.2%) in the placebo group.

Dr. Mahoney summarized the incidence of dementia and related-AE terms under Table 7.1.2.4.5 of her review. There were 5 cases within the category, "Total All Specific Dementia Terms" (2 in atorvastatin and 3 in placebo). The incidence of "total all possibly dementia-related AEs" was 0.2% in the atorvastatin group versus 0.4% in the placebo. These results do no support a conclusion that there is an association between atorvastatin and cognitive impairment, as has been suggested in recent post-marketing safety reports. While the patient population did include 6,556 patients who were older than 60 years of age, ASCOT-LLA, however, was not designed to specifically evaluate cognitive function using standardized measures. Prospective studies specifically designed to evaluate neurologic function associated with statin use will need to be conducted to address this concern.

Overall, the safety profile of atorvastatin 10 mg based on the results of ASCOT-LLA is similar to the current package insert.

PROPOSED LABELING CHANGES AND FDA COMMENTS

The applicant has proposed changes to the CLINICAL PHARMACOLOGY; Clinical Studies section to describe the design, conduct, and results of ASCOT. In addition, the proposed indications based on the results of ASCOT include a reduction in risk of:

- [redacted] myocardial infarction
- [redacted]
- [redacted]

Based on the reviews of Dr. Mahoney and Ms. Mele, the Division recommends the Indications and Usage section to be modified to include the following:

Prevention of Cardiovascular Disease
In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age ≥ 55 years, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, Lipitor is indicated to:

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

Labeling negotiations were completed on July 19, 2004 during a teleconference between members of the FDA review team and the applicant. The sponsor accepted the above revisions to the INDICATIONS and USAGE section of the label.

CONCLUSIONS AND RECOMMENDATIONS

ASCOT-LLA is another placebo-controlled clinical cardiac outcomes study that, again, demonstrates the clinical benefit of cholesterol lowering through the inhibition of the rate-limiting enzyme in cholesterol synthesis with the statin, atorvastatin. This study extends the benefit of cholesterol lowering to hypertensive patients without clinical evidence of heart disease or hypercholesterolemia but who had multiple other CHD risk factors. No new safety signals were identified in this trial that offset the benefits observed. Consequently, this efficacy supplement should be approved pending changes to labeling as recommended by the Division.

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/s/

Mary Parks
7/23/04 04:44:52 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	sNDA 20702
Submission Number	039
Submission Code	SE1
Letter Date	30 Sep 03
Stamp Date	1 Oct 03
PDUFA Goal Date	30 Jul 04
Clinical Reviewer	Karen Murry Mahoney, MD
Statistical Reviewer	Joy Mele, MS
Review Completion Date	28 Jul 04
Established Name	Atorvastatin calcium
Trade Name	Lipitor®
Therapeutic Class	Lipid-altering drugs
Applicant	Pfizer Pharmaceuticals Group
Priority Designation	S
Formulation	Oral tablet
Dosing Regimen	Once daily
Proposed Indication	
Intended Population	Patients without clinically evident coronary heart disease

Table of Contents

1 EXECUTIVE SUMMARY

THE ANGLO-SCANDINAVIAN CARDIOVASCULAR OUTCOMES TRIAL, LIPID-LOWERING ARM
EFFICACY SUPPLEMENT FOR ATORVASTATIN CALCIUM FOR REDUCTION IN RISK OF CARDIOVASCULAR EVENTS

1.1 Recommendation on Regulatory Action

The clinical reviewer recommends that new indications be granted for atorvastatin for reduction in risk for myocardial infarction, revascularization procedures and angina. [redacted] The clinical reviewer does not recommend the granting of the sponsor's [redacted]

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Not applicable

1.2.2 Required Phase 4 Commitments

The sponsor is to submit the complete study report of the parent trial, after that trial is completed and unblinded. The lipid-lowering trial reviewed for this supplemental New Drug Application (sNDA) was the Anglo-Scandinavian Cardiovascular Outcomes Trial Lipid-Lowering Arm (ASCOT-LLA), which is part of a larger trial (ASCOT) examining the effect of different blood pressure medications on cardiovascular outcomes. ASCOT is still ongoing and blinded. The [redacted]

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The Anglo-Scandinavian Cardiovascular Outcomes Trial Lipid Lowering Arm (ASCOT-LLA) was a lipid-lowering subtrial of a still-ongoing parent hypertension treatment trial (ASCOT). ASCOT-LLA was intended to be the first large-scale long-term study to evaluate the benefits of cholesterol lowering in the primary prevention of coronary heart disease in hypertensive patients with normal to mildly elevated lipid levels and a number of additional cardiovascular risk factors. ASCOT continues, and is examining the effect of specific antihypertensive treatments on primary prevention of cardiovascular events. ASCOT-LLA was terminated early (at a median follow-up of 3.3 years rather than the planned five years) due to a conclusion by the trial's Data Safety Monitoring Committee that atorvastatin had resulted in a highly significant reduction in the composite primary endpoint (described below), compared to placebo. The degree of statistical significance necessary for early trial termination had been decided *a priori*.

A total of 19,342 hypertensive adult male and female patients were first randomized to one of two antihypertensive regimens. All patients had at least three specified cardiovascular risk factors [male gender, age >55 years, smoking, diabetes, history of coronary heart disease in a first degree relative, ratio of total cholesterol to high density lipoprotein cholesterol (TC:HDL-C) >6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific electrocardiographic (ECG) abnormalities, or proteinuria/albuminuria]. Inclusion of patients with multiple risk factors was intended to allow targeting of a population with a ten-year risk for CHD of >20%.

After allocation to one of the two antihypertensive regimens, nonfasting serum cholesterol levels were used to identify candidates for ASCOT-LLA. Patients with baseline total serum cholesterol levels ≤ 6.5 mmol/L (251 mg/dL) were eligible for ASCOT-LLA. Patients with higher cholesterol levels were not eligible for ASCOT-LLA, but continued in the antihypertensive portion of ASCOT and had their lipids managed by their primary care physician.

The 10,305 patients with baseline nonfasting serum cholesterol levels ≤ 6.5 mmol/L were assigned by statistical minimisation to receive either atorvastatin (n = 5,134 patients) 10 mg by mouth (po) each (q) day, or a matching placebo (n = 5,106 patients). Atorvastatin was not titrated. Unless some clear indication for study cessation developed, study treatments were to continue until 1,150 primary endpoint events had occurred, or for an average of five years per subject, whichever was longer.

The primary endpoint was a composite of nonfatal myocardial infarction (symptomatic and silent) + fatal coronary heart disease. *A priori*, the Data Safety Monitoring Committee (DSMC) decided to use a Haybittle-Peto statistical boundary as a guideline for whether or not to recommend early termination. A critical value Z1 = ±3 was used for interim analyses. Attainment of this criterion for the primary endpoint led the DSMC to terminate ASCOT-LLA

after a median followup of 3.3 years. Numerous secondary (composite and individual) and tertiary endpoints were also evaluated.

1.3.2 Efficacy

For the composite primary endpoint [nonfatal myocardial infarction (symptomatic and silent) + coronary heart disease death], there were 100 events (1.9% of treatment arm) in the atorvastatin group and 154 (3.0% of treatment arm) in the placebo group [hazard ratio (HR) 0.64, 95% confidence interval (CI) 0.5-0.83, p 0.0005]. Examination of the individual components revealed that only nonfatal symptomatic myocardial infarction was significantly reduced in the atorvastatin group compared to placebo. The sponsor seeks an indication for reduction of risk of myocardial infarction.

Stroke risk was reduced in the atorvastatin group [89 (1.7%) vs 119 (2.3%) events HR 0.74, 95% CI 0.56-0.98], but the p-value attained (0.033) did not meet the sponsor's predefined criterion for significance. The sponsor had chosen a p-value of 0.01 for significance , the only individual component (other than nonfatal symptomatic myocardial infarction) that achieved predefined statistical significance favoring atorvastatin was reduction in number of revascularization procedures [74 (1.4%) vs 127 (2.5%) events, HR 0.58, 95% CI 0.43-0.77, p 0.00016], although the reduction in risk of chronic stable angina came very close to significance [33 (0.6%) vs 56 (1.1%) events, HR 0.59, 95% CI 0.38-0.90, p 0.01354].

The clinical reviewer recommends additions to the Lipitor® label of indications for reduction in risk for myocardial infarction, revascularization procedures and angina.

1.3.3 Safety

The safety profile in ASCOT-LLA was similar to that seen for atorvastatin in prior trials. Two cases of rhabdomyolysis occurred in patients taking atorvastatin; one patient was also taking simvastatin and the other patient was an alcoholic. No significant increase in the incidence of events of special interest for atorvastatin (hepatic, other muscle, neuropathic, dementia, dyspnea) was seen for atorvastatin vs placebo.

1.3.4 Dosing Regimen and Administration

ASCOT-LLA used 10 mg atorvastatin po q day, the lowest approved dose. It is likely that the benefits of cardiovascular risk reduction will also be seen in patients who require higher doses to attain National Cholesterol Education Program low-density lipoprotein cholesterol goals.

1.3.5 Drug-Drug Interactions

No new information regarding drug-drug interactions was obtained through this trial.

1.3.6 Special Populations

Risk reduction was comparable between subjects older and younger than age 60 years. Because 95% of study subjects were White/Europid; no meaningful analysis was possible for other racial groups. Males comprised 81% of study subjects. No significant effect of atorvastatin on the primary endpoint was seen for women, but the very low event rates preclude definite statements regarding the effect in women.

2 INTRODUCTION AND BACKGROUND

Atorvastatin is a synthetic hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor used in the treatment of several dyslipidemias.

Prior to submission of this NDA efficacy supplement, trials conducted thus far had not shown convincing evidence of a reduction [redacted] associated with atorvastatin administration. The sponsor now seeks such an efficacy claim based on the results of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), a large, multinational study involving atorvastatin or placebo treatment of hypertensive patients with cholesterol levels below the level at which European guidelines would ordinarily recommend drug treatment.

Effects of Atorvastatin on Lipid Metabolism

HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate, the first step in cholesterol synthesis. Inhibition of this enzyme causes reduction in hepatocyte cholesterol content which leads to upregulation of low-density lipoprotein (LDL) receptor expression, increased LDL clearance from plasma and, hence, a reduction in plasma cholesterol (12). Atorvastatin and other statin drugs act via HMG-CoA reductase inhibition, but also have actions on other intermediates in cholesterol synthesis, including farnesyl-pyrophosphate and geranyl-pyrophosphate. Statins affect the peroxisomal proliferating activator receptor alpha (PPAR alpha) pathways and modulate inflammation via interleukin-6 (Il-6) (11,12). They modestly affect high density lipoprotein (HDL) metabolism through effects on apolipoprotein A1 (Apo-A1) and apolipoprotein A2 (Apo-A2) synthesis (12). Small reductions in triglycerides appear to occur because of decreased very-low-density-lipoprotein (VLDL) production related to inhibition of cholesterol synthesis, and perhaps because of increased production and binding capacity of LDL receptors with enhanced binding of VLDL particles (11).

In humans with hyperlipoproteinemias, atorvastatin has a dose-dependent effect on LDL levels, with reductions of 35 to 60% in LDL in published randomized clinical trials (11, 13-18). In major trials, a reduction of 50% in LDL is typically achieved on an intention-to-treat basis of analysis (19).

Atorvastatin has also been shown to modestly lower triglycerides (TGs) in patients with primary hypertriglyceridemia and mixed hyperlipoproteinemia, with reductions of 17 to 45% in published studies (11, 20-22). The triglyceride reduction achieved is proportionate to the degree of LDL reduction, and is proportionately related to initial triglyceride levels (23, 24). Atorvastatin is less effective than fibrates (53,54) and nicotinic acid (55) in TG reduction.

Atorvastatin promotes some degree of reduction in levels of the small, dense, highly atherogenic form of LDL; and promotes formation of large buoyant LDL particles, which are less atherogenic (23, 24, 38, 39).

Atorvastatin's effect on high density lipoprotein (HDL) levels is somewhat variable. Lower doses are efficacious in raising HDL when administered to patients with lower initial levels of HDL (25). However, higher doses appear less effective in raising HDL, and may result in some HDL lowering (26-28). Atorvastatin has little effect on lipoprotein (a) [Lp(a)] (12). Overall, HDL increases of 5-9% occurred with atorvastatin in most comparative trials.

Apolipoprotein-B (Apo-B) reductions of 17-50% have been reported in published trials (11).

Atorvastatin Trials of Efficacy in Clinical Endpoints Prior to this Supplemental New Drug Application (sNDA) Submission

Two trials of the effects of aggressive lipid-lowering with atorvastatin on clinical endpoints have been conducted. However, neither of these trials showed robust results, and neither has resulted in label changes for Lipitor®.

The MIRACL (Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering) trial was designed to examine the effect of atorvastatin (compared with placebo) on outcomes in acute coronary syndromes. After 16 weeks of study, 80 mg of atorvastatin daily resulted in a reduction in the risk for the combined primary endpoint of death, nonfatal myocardial infarction, cardiac arrest or recurrent symptomatic ischemia. Symptomatic ischemia comprised the majority of events. Although the risk of recurrent symptomatic ischemia was reduced in the atorvastatin group, this finding conflicted with a finding of an increased risk for revascularization procedures. There was no significant reduction in the individual endpoints of death, nonfatal myocardial infarction or cardiac arrest.

The AVERT (Atorvastatin VErsus Revascularization Treatment) trial compared 80 mg daily atorvastatin to angioplasty in the management of stable angina. The atorvastatin group did not meet the predefined criteria for statistically significant superiority over angioplasty for reduction of time to first ischemic event. Atorvastatin reduced the risk of ischemic events with only marginal significance; the individual component of "angina requiring hospitalization" was the predominant component of the composite endpoint showing significance. Furthermore, the selection of an angioplasty comparator group introduced a question of bias; it was unclear whether drug therapy improved outcomes, or whether the common procedural outcomes of angioplasty resulted in more angina events in the comparator group.

Overview of Adverse Effects Noted Prior to Submission of this Supplemental NDA

The adverse event profile of atorvastatin is similar to that of other statins.

The most common adverse effects associated with atorvastatin are gastrointestinal in nature, and include nausea, bloating, diarrhea and constipation. These are generally transient, resolving within 2-3 weeks. Elevations in serum transaminases occur in about 1% of patients, and are usually reversible on discontinuation of the drug (29). Hepatitis occurs in 0.01-0.02% of patients taking the drug (29,30).

Myalgia occurs in 1-5% of patients taking atorvastatin, sometimes accompanied by serum creatine phosphokinase (CPK) elevations. Myopathy and/or myositis occur in about 0.1% of statin-treated patients, and are more likely to occur when atorvastatin is concomitantly administered with another drug metabolized via CYP3A4. Rhabdomyolysis with renal failure has been reported; particularly notable is the occurrence with concomitant administration of cyclosporine (44).

Also rare, but notable, is the occurrence of a peripheral neuropathy (32). Anecdotal reports have led to some concern for an increased risk of dementia, but no clear association has been established.

An excess of any adverse event has not been demonstrated when atorvastatin is compared to other statins (31,37). Less than 2% of 2,502 patients in larger published clinical trials to date withdrew due to treatment-related adverse events.

2.1 Product Information

Atorvastatin (Lipitor®) is a synthetic hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor used in the treatment of several dyslipidemias.

2.2 Currently Available Treatment for Indications

The following sections contain the current (as of 29 Mar 04) information from the INDICATIONS AND USAGE sections of the labels of drugs which have indications for reduction of cardiovascular events:

2.2.1 Lipid Altering Agents

2.2.1.1 HMG-CoA Reductase Inhibitors

2.2.1.1.1 Simvastatin

"*Reductions in Risk of CHD Mortality and Cardiovascular Events*

In patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, [redacted]. is indicated to:

- Reduce the risk of total mortality by reducing CHD deaths
- Reduce the risk of nonfatal myocardial infarction and stroke
- Reduce the need for coronary and non-coronary revascularization procedures."

2.2.1.1.2 Pravastatin

"Primary Prevention of Coronary Events

In hypercholesterolemic patients without clinically evident coronary heart disease, [redacted] is indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of undergoing myocardial revascularization procedures
- Reduce the risk of cardiovascular mortality with no increase in death from non-cardiovascular causes.

Secondary Prevention of Cardiovascular Events
In patients with clinically evident coronary heart disease, [redacted] is indicated to:

- Reduce the risk of total mortality by reducing coronary death
- Reduce the risk of myocardial infarction
- Reduce the risk of undergoing myocardial revascularization procedures
- Reduce the risk of stroke and stroke/transient ischemic attack (TIA)
- Slow the progression of coronary atherosclerosis."

2.2.1.1.3 Lovastatin

"Primary Prevention of Coronary Heart Disease
In individuals without symptomatic cardiovascular disease, average to moderately elevated total-C and LDL-C, and below average HDL-C [redacted] is indicated to reduce the risk of:

- Myocardial infarction
- Unstable angina
- Coronary revascularization procedures"

2.2.1.1.4 Fluvastatin

"In patients with coronary heart disease [redacted] and [redacted] are indicated to reduce the risk of undergoing coronary revascularization procedures."

2.2.1.1.5 Rosuvastatin does not currently have an indication for prevention of cardiovascular events.

2.2.1.2 Fibric Acid Derivative

Gemfibrozil

[redacted] is indicated as adjunctive therapy to diet for...
2. Reducing the risk of developing coronary heart disease only in Type IIb patients without history of or symptoms of heart disease who have had an inadequate response to weight loss, dietary therapy, exercise, and other pharmacologic agents (such as bile acid sequestrants and nicotinic acid, known to reduce LDL- and raise HDL- cholesterol) and who have the following triad of lipid abnormalities: low HDL-cholesterol levels in addition to elevated LDL-cholesterol and elevated triglycerides.... BECAUSE OF POTENTIAL TOXICITY SUCH AS MALIGNANCY, GALLBLADDER DISEASE, ABDOMINAL PAIN LEADING TO

APPENDECTOMY AND OTHER ABDOMINAL SURGERIES, AN INCREASED INCIDENCE IN NON-CORONARY MORTALITY, AND THE 44% RELATIVE INCREASE DURING THE TRIAL PERIOD IN AGE-ADJUSTED ALL-CAUSE MORTALITY SEEN WITH THE CHEMICALLY AND PHARMACOLOGICALLY RELATED DRUG, CLOFIBRATE, THE POTENTIAL BENEFIT OF GEMFIBROZIL IN TREATING TYPE IIA PATIENTS WITH ELEVATIONS OF LDL-CHOLESTEROL ONLY IS NOT LIKELY TO OUTWEIGH THE RISKS."

2.2.1.3 Niacin

(From /——/ label)

"In patients with a history of myocardial infarction and hypercholesterolemia, niacin is indicated to reduce the risk of recurrent nonfatal myocardial infarction."

2.2.2 Angiotensin Converting Enzyme (ACE) Inhibitors and Angiotensin II Receptor Blockers

2.2.2.1 ACE Inhibitor: Ramipril

/——/ is indicated in patients 55 years or older at high risk of developing a major cardiovascular event because of a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes that is accompanied by at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low HDL levels, cigarette smoking, or documented microalbuminuria), to reduce the risk of myocardial infarction, stroke, or death from cardiovascular causes. /——/ can be used in addition to other needed treatment (such as antihypertensive, antiplatelet or lipid-lowering therapy)." (sic)

2.2.2.2 ACE Inhibitor: Captopril

"Captopril tablets, USP are indicated to improve survival following myocardial infarction in clinically stable patients with left ventricular dysfunction manifested as an ejection fraction $\leq 40\%$ and to reduce the incidence of overt heart failure and subsequent hospitalizations for congestive heart failure in these patients." (sic)

2.2.2.3 ACE Inhibitor: Lisinopril

/——/ is indicated for the treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction, to improve survival."

2.2.2.4 Angiotensin II Receptor Blocker: Losartan potassium

/——/ is indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy, but there is evidence that this benefit does not apply to Black patients."

2.2.3 Beta Blockers

2.2.3.1 Atenolol

[redacted] is indicated in the management of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment can be initiated as soon as the patient's clinical condition allows. ... In general, there is no basis for treating patients like those who were excluded from the ISIS-1 trial (blood pressure less than 100 mm Hg systolic, heart rate less than 50 bpm) or have other reasons to avoid beta blockade. As noted above, some subgroups (e.g. elderly patients with systolic blood pressure below 120 mm Hg) seemed less likely to benefit." (sic)

2.2.3.2 Timolol maleate

[redacted] is indicated in patients who have survived the acute phase of a myocardial infarction, and are clinically stable, to reduce cardiovascular mortality and the risk of reinfarction."

2.2.3.3 Carvedilol

[redacted] is indicated to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of $\leq 40\%$ (with or without symptomatic heart failure)."

2.2.4 Anticoagulant and Antiplatelet Agents

2.2.4.1 Anticoagulant: Warfarin

[redacted] is indicated to reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction."

2.2.4.2 Anticoagulant: Low Molecular Weight Heparins

2.2.4.2.1 Dalteparin sodium

[redacted] injection is indicated for the prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin therapy... ." (sic)

2.2.4.2.2 Enoxaparin sodium

[redacted] injection is indicated for the prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin." (sic)

2.2.4.3 Antiplatelet Agent: Aspirin

(From [redacted] aspirin professional label)

"Aspirin is indicated to
(1) reduce the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli,
(2) reduce the risk of vascular mortality in patients with a suspected acute MI
(3) reduce the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris, and
(4) reduce the combined risk of MI and sudden death in patients with chronic stable angina pectoris." (sic)

2.2.4.4 Antiplatelet Agent: Ticlopidine hydrochloride

[redacted] is indicated to reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke. Because [redacted] is associated with a risk of life-threatening blood dyscrasias including thrombotic thrombocytopenic purpura (TTP), neutropenia/agranulocytosis and aplastic anemia (see BOXED WARNING and WARNINGS) [redacted] should be reserved for patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy."

2.2.4.5 Antiplatelet Agent: Eptifibatide

[redacted] is indicated:

- For the treatment of patients with acute coronary syndrome (unstable angina/ non-ST-segment elevation myocardial infarction) including patients who are to be managed medically and those undergoing percutaneous coronary intervention (PCI). In this setting, [redacted] has been shown to decrease the rate of a combined endpoint of death or new myocardial infarction.
- For the treatment of patients undergoing PCI, including those undergoing intracoronary stenting. In this setting, [redacted] has been shown to decrease the rate of a combined endpoint of death, new myocardial infarction, or need for urgent intervention."

2.2.4.6 Antiplatelet Agent: Tirofiban hydrochloride

[redacted], in combination with heparin, is indicated for the treatment of acute coronary syndrome, including patients who are to be managed medically and those undergoing PTCA or atherectomy. In this setting, [redacted] has been shown to decrease the rate of a combined endpoint of death, new myocardial infarction or refractory ischemia/ repeat cardiac procedure... ." (sic)

2.2.4.7 Combination Antiplatelet Agent: [redacted] (aspirin/extended-release dipyridamole)

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

No new information was submitted with this sNDA.

3.2 Animal Pharmacology/Toxicology

No new information was submitted with this sNDA

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The source of data for this review was ASCOT, a large multinational trial designed to examine the effects of two different types of antihypertensives on primary prevention of cardiovascular events in subjects with multiple cardiovascular risk factors. The sNDA and study report may be found in the FDA electronic document room via the path \\CDSESUB1\N20702\S_039\2003-09-30. ASCOT-LLA was a lipid-lowering arm of the study conducted in patients whose serum cholesterol levels were either normal or mildly elevated. In this arm, atorvastatin 10 mg and placebo were compared for effect on cardiovascular event risk. The trial was a collaborative study conducted by a study group comprised of university and government researchers. The sponsor of this application, Pfizer, provided financial support to the trial but did not conduct the research.

A literature review was also conducted (see section 10.4 for references). Adverse event data in the Adverse Event Reporting System (AERS) database was also reviewed for evidence of adverse events not currently listed in the atorvastatin label.

4.2 Tables of Clinical Studies

The application reviewed here contained the results of one large study, ASCOT-LLA, which is summarized briefly in the table below.

Table 4.2: ASCOT-LLA Trial Description

Study Region (centers)	Design	Treatment groups (N)	Duration of treatment
UK (33) Scandinavia (635)	DB, parallel, multicenter, clinical endpoints	Atorvastatin (5168) Placebo (5137	Median of 3.3 years

4.3 Review Strategy

The clinical and biostatistical reviewers initially conducted independent reviews, and then collaborated regarding individual questions and areas of controversy. The statistical reviewer's results and comments are integrated into this clinical review.

4.4 Data Quality and Integrity

4.4.1 Provisions to Enhance Data Integrity

A number of provisions were included to enhance data integrity:

- An independent external quality assurance group (retained by the sponsor) performed quality assurance audits at 41 sites. ASCOT was also inspected by regulatory authorities in Norway and Sweden.
- Although Pfizer had representatives on the International Steering Committee, they were not voting members.
- An independent Data Safety Monitoring Committee was used. The DSMC was comprised of clinicians, epidemiologists and statisticians who were not involved in the study itself. The DSMC members were not selected by the sponsor. The DSMC members were the only individuals unblinded to the treatment arms during the study.
- An independent blinded endpoint evaluation committee and an independent blinded ECG review center were used.
- The statistical analysis plan was finalized prior to unblinding of data.
- External audits were conducted for good clinical practice.

4.4.2 Potential Risks to Data Integrity

- The sponsor reported that two investigators (investigator numbers 10244 and 10247) had for-cause audits performed due to irregularities found in some of the data from the investigators' sites. The sponsor reported that some of the data, namely blood pressure and physical examination data, could not be validated. Data from these sites were not included in the efficacy analyses. The sponsor reports that a total of one primary endpoint event and three secondary endpoint events occurred at these sites, and concluded that information from these sites would not have altered study conclusions.
- In Scandinavia, clinical administration was managed by Pfizer; in the United Kingdom (UK) and Ireland, it was managed by the Imperial College.
- Different rules for assignment of patients to treatment were used in the Scandinavian sites compared to the UK sites.
- One laboratory was used for all tests in the UK; a different single laboratory was used for Scandinavia.

Efficacy was analyzed by country (by Ms. Mele, FDA biostatistician) to determine if the above differences had an impact on the results. No important differences were observed and therefore the results by country are not presented in this review.

4.4.3 The Division of Scientific Investigations did not conduct an audit or site visit for ASCOT-LLA.

4.5 Compliance with Good Clinical Practices

4.5.1 Informed Consent

For each country (Denmark, Finland, Norway, Sweden and the United Kingdom), a separate prototype informed consent was developed. Each individual study site Ethics Committee then reviewed the informed consent and sometimes required modifications. Review of the model consent forms showed them to be in compliance with the relevant Declarations of Helsinki, and to contain adequate explanation of the risks of study participation.

4.5.2 Protocol Violations

In the clinical study report (p 58), the sponsor states that because this is an endpoint trial and all subjects are included in the analysis, there is no listing of protocol deviations.

4.5.3 Site-specific Issues

The sponsor reported that two investigators (investigator numbers 10244 and 10247) had for-cause audits performed due to irregularities found in some of the data from the investigators' sites. The sponsor reported that some of the data, namely blood pressure and physical examination data, could not be validated. Data from these sites were not included in the efficacy analyses. The sponsor reports that a total of one primary endpoint event and three secondary endpoint events occurred at these sites, and concluded that information from these sites would not have altered study conclusions.

4.6 Financial Disclosures

ASCOT-LLA was not funded via variable compensation and none of the investigators held any form of proprietary interest in atorvastatin. The sponsor documented due diligence in pursuing financial disclosure from all 1216 investigators. Through multiple mailings and telephone contacts, the sponsor obtained financial disclosure forms for 950/1216 investigators. A total of eight investigators had financial information to disclose, all "significant payments of other sorts" (SPOOS). The following table provides details regarding these investigators' financial disclosures:

Table 4.6: Investigators with Financial Disclosure Information of Significance

Investigator Name	Investigator Position	Total Value of SPOOS*	Number of Patients Enrolled at Investigator's Center	% of Total Study Cohort	% of Total Patients with any Cardiovascular Endpoint
	Lead Investigator, on behalf of 15 subinvestigators	$143,724	617	6.0%	3.4%
	Study Coordinator	$36,248	0	0	0
	Lead Investigator, on behalf of 16 subinvestigators	$136,299	192	1.9%	2.2%
	Lead Investigator on behalf of 8 subinvestigators	$385,038	113	1.1%	1.3%
		$122,512	0	0	0
	Lead Investigator on behalf of 13 subinvestigators	$67,047	137	1.3%	1.6%
	Study Coordinator	$59,316	0	0	0
	Lead Investigator behalf of 12 subinvestigators	$351,989	236	2.3%	1.8%

*"Significant payments of other sorts"

Because SPOOS to subinvestigators were paid through the lead investigator for each site, and because none of the sites for the above lead investigators contributed a disproportionate number to the cardiovascular endpoints, it appears unlikely that the results of these investigators and their subinvestigators would have biased the overall results.

Center was the largest center in ASCOT; analyses (by Ms. Mele) excluding this center did not appreciably affect the primary endpoint results.

5 CLINICAL PHARMACOLOGY

ASCOT-LLA used the approved form of Lipitor®, and no new pharmacokinetic or pharmacodynamic information is included with this Supplemental New Drug Application (sNDA).

Atorvastatin acts through selective and competitive inhibition of the HMG-CoA reductase enzyme. This enzyme catalyzes the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate. This conversion is the rate-limiting step in the cholesterol synthetic pathway. Atorvastatin also increases the uptake and catabolism of low-density lipoprotein cholesterol (LDL) by increasing the number of hepatic LDL receptors.

Atorvastatin has the longest half-life of any currently marketed statin, approximately 14 hours, and has active metabolites that prolong its action. Because of its long half-life, it may be given at any time of day. About 30% of an oral dose is absorbed, and undergoes extensive first-pass metabolism (33). Bioavailability is about 14% (34), and the drug is highly (95-98%) protein-bound (11). It is metabolized via cytochrome P450 3A4, and perhaps to a lesser extent by other cytochromes (34,35). Its metabolites are excreted into bile, and peak plasma concentration is significantly increased in patients with hepatic failure; atorvastatin use is contraindicated in patients with severe liver disease. Renal impairment does not appear to have a significant effect on the pharmacokinetics of the drug. All statins are contraindicated in pregnancy and lactation.

5.1 Pharmacokinetics

No new pharmacokinetic data were presented with this sNDA.

5.2 Pharmacodynamics

No new pharmacodynamic data were presented with this sNDA.

5.3 Exposure-Response Relationships

No new exposure-response data were presented with this sNDA.

6 INTEGRATED REVIEW OF EFFICACY

The sponsor has presented the results of one study, the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA) to support the following indications:

"*Prevention of Cardiovascular Disease*
In [redacted] without clinically evident coronary heart disease.
- Reduce the risk of [redacted] myocardial infarction
- [redacted]
- [redacted]

All these indications proposed by the sponsor [redacted] The overall indication then may be characterized as prevention of cardiovascular disease.

ASCOT-LLA was intended to be the first large-scale long-term study to evaluate the benefits of cholesterol lowering in the primary prevention of CHD in hypertensive patients with normal to mildly elevated lipid levels and a number of additional cardiovascular (CV) risk factors.

Several large clinical endpoint trials (2-7) have demonstrated the efficacy of certain statins for prevention of major fatal and nonfatal cardiovascular events. Prior to this trial, trials of atorvastatin had not robustly demonstrated efficacy in this area.

Statin cardiac endpoint trials to date have varied in their design, and have examined cardiac event reduction in various target groups. Both primary and secondary prevention of cardiac events have been demonstrated. Some trials looked at clearly hypercholesterolemic patients, and others looked at patients with normal or near-normal cholesterol levels. Statin intervention has been attempted in groups where all patients were hypertensive. Interest has continued in lipid-lowering treatment of patients with normal or near-normal cholesterol levels, and also of near-normotensive patients, because most cardiovascular events and deaths attributable to hypertension and dyslipidemia occur among patients who are considered near-normotensive and nonhyperlipidemic at the time of the events (8). ASCOT-LLA targeted such a population.

ASCOT-LLA was a lipid-lowering subtrial of a still-ongoing parent trial (ASCOT). ASCOT continues, and is examining the effect of specific antihypertensive treatments on primary prevention of cardiac events. ASCOT-LLA was terminated early (at a median follow-up of 3.3 years rather than the planned five years) due to a conclusion by the trial's Data Safety Monitoring Committee that atorvastatin had resulted in a highly significant reduction in the primary endpoint compared with placebo. The ASCOT-LLA patients remain in the main ASCOT antihypertensive therapy trial.

6.1 Indication: "Prevention of Cardiovascular Disease"

6.1.1 Methods

All efficacy data for this review were obtained from the sponsor's submitted supplemental NDA, which may be accessed through the FDA Electronic Document Room path \\CDSESUB1\N20702\S_039\2003-09-30 . The information in this sNDA had been compiled by the sponsor after the sponsor obtained the data from the ASCOT Study Group. The FDA did not have direct access to the Study Group data. The sponsor's efficacy conclusions are quite similar to the Study Group's conclusions as published in the Lancet (1).

FDA performed statistical re-analyses as necessary.

6.1.2 General Discussion of Endpoints

The endpoints for this trial were devised by the ASCOT trial group, comprised of university and government investigators from the United Kingdom and Scandinavian Countries, rather than by the Pfizer.

The question of interpretation of the results of composite endpoint trials has engendered much discussion in the medical literature. As has become common in large cardiovascular endpoint trials, the primary endpoint and several of the secondary endpoints of ASCOT -LLA were "composite" endpoints, composed of groups of particular cardiovascular events. In ASCOT-LLA, a study subject was considered to have reached an endpoint when he or she experienced any one of several types of cardiovascular events contained within a composite endpoint. The primary endpoint for ASCOT-LLA was the occurrence of nonfatal MI (symptomatic or silent) or fatal CHD.

For cardiovascular outcome studies, mortality is usually the endpoint of most interest. However, because of the large trial size required to evaluate the effect of a regimen on mortality, composite endpoints are often used to increase the likely event rate and reduce the number of study subjects needed for a trial. This approach is valid only if the nonfatal components of the composite endpoint are clinically meaningful and likely to be related to a significantly adverse prognosis. In the case of the components of the primary endpoint used in ASCOT-LLA, an adverse prognosis is predictable from the medical literature for the component of nonfatal symptomatic myocardial infarction, but perhaps less so for asymptomatic nonfatal myocardial infarction. In the published medical literature, prior nonfatal symptomatic myocardial infarction is clearly associated with an increased mortality risk. The mortality risk associated with prior nonfatal asymptomatic myocardial infarction detected on electrocardiogram is less clear than that for symptomatic MI, but the overall body of evidence now supports an increased mortality risk, particularly among certain subgroups, such as diabetics and the elderly (56-59). Therefore, the components of the primary composite endpoint for this study are likely to have some predictive value for mortality risk. The disadvantage of use of the composite endpoints, however, is that the power of the study may not permit analyses of individual components of the composites.

6.1.3 Study Design For ASCOT-LLA

ASCOT-LLA was a Phase IV, multicenter, 2x2 factorial, double-blind study conducted by two coordinating centers; the Imperial College School of Medicine at St. Mary's (London) and the Clinical Research Institute (Göteborg). A total of 1,216 investigators participated.
The primary objective of the ASCOT-LLA was to compare the effect on nonfatal MI (symptomatic and silent MI) and fatal CHD of combination therapy (10 mg atorvastatin + antihypertensive therapy) to the effect of antihypertensive therapy alone.

Hypertensive patients were allocated to one of two antihypertensive regimens in the parent study, ASCOT. Hypertension was defined in untreated patients as a systolic blood pressure (SBP) of $\geq$ 160 mm Hg or a diastolic blood pressure (DBP) of $\geq$ 100 mm Hg. Hypertension in treated patients was defined as SBP $\geq$ 140 or DBP $\geq$ 90. The two antihypertensive regimens were:

- Beta blocker ± diuretic (atenolol ± bendroflumethiazide-K); if third-line drug needed, doxazosin GITS; if further therapy needed for control, cross-over to drugs from other arm only as *ultimum refugium.*

- Calcium channel blocker ± angiotensin converting enzyme inhibitor (amlodipine ± perindopril); if third-line agent needed, doxazosin GITS; if further therapy needed for control, cross-over to drugs from other arm only as *ultimum refugium*. Angiotensin receptor blockers were not permitted in this arm.

Antihypertensives are administered at specified doses, with rules for dose titration and addition of other antihypertensive agents (see study report pages 33-35). Antihypertensives are given in an open-label fashion, but the endpoint evaluation is blinded.

After allocation to one of the two antihypertensive regimens, nonfasting serum total cholesterol levels were used to identify candidates for ASCOT-LLA. Patients with baseline total serum cholesterol levels ≤ 6.5 mmol/L (251 mg/dL) were eligible for ASCOT-LLA and were allocated to either atorvastatin 10 mg or placebo.

A complex minimisation procedure was used to assign patients to the antihypertensive arm and the lipid arm. This procedure is described in detail in Appendix 10.2.

All patients had at least three of the following cardiovascular risk factors:

- smoking (regular smoking within the past year of ≥ 20 cigarettes or cigars per week)
- left ventricular hypertrophy (LVH). Noted on echocardiography within two months prior to study, or on ECG using either Cornell voltage duration product (>2440) or Sokolow Lyon criteria (>38)
- specific electrocardiographic (ECG) abnormalities (LV strain pattern, abnormal Q waves, left bundle branch block, ST-T changes compatible with ischemic heart disease)
- history of early CHD in a first degree relative (male age <55 years; female age <60 years)
- age ≥ 55 years (yrs)
- microalbuminuria or proteinuria by dipstick
- non-insulin-dependent diabetes mellitus defined by WHO criteria (NIDDM)
- peripheral vascular disease (standard questionnaire) or recent surgery for peripheral vascular disease
- history of cerebrovascular event
- male gender
- plasma TC:HDL ratio ≥ 6

Inclusion of patients with multiple risk factors was intended to allow targeting of a population with a ten-year risk for CHD of >20%. Please see section 6.1.6 for discussion of how the risk factors used in ASCOT-LLA compare to those used in the US National Cholesterol Education Program.

In addition to the required minimum of three risk factors, inclusion criteria included the following:

- male or female
- age ≥ 40 and <80
- untreated SBP ≥ 160 mmHg and/or DBP ≥ 90 mmHg; or treated hypertension on one or more antihypertensives with SBP ≥ 140 or DBP ≥ 90
- baseline plasma cholesterol ≤ 6.5 mmol/L (251.4 mg/dL)

In order to "mimic real life", few exclusion criteria were specified. A full listing may be found on pages 32-33 of the sponsor's sNDA summary. Notable exclusion criteria were the following:

- secondary or malignant hypertension
- prior MI
- current angina pectoris
- clinical congestive heart failure (NYHA class II-IV)
- uncontrolled arrhythmia
- second or third degree atrioventricular block
- recent stroke (<3 months prior to study)
- recent TIA (<3 months prior to study)
- recent cerebrovascular surgery (<3 months prior to study)
- concomitant disease which required treatment with a drug that could also be prescribed for hypertension
- fasting serum TG >4.5 mmol/L
- ALT >3x upper limit of normal (uln)
- serum Cr >200 µmol/L (2.3 mg/dL)
- current treatment, or intention of treatment by primary physician, with a statin or fibrate

Patients were seen at 6 weeks, 3 months, 6 months, and then every 6 months. Unless some clear indication for study cessation developed, study treatments were to continue until 1,150 primary endpoint events had occurred, or for an average of five years, whichever was longer.

6.1.4 Efficacy Endpoints

6.1.4.1 Primary

Composite of fatal CHD and nonfatal MI (symptomatic and silent)

6.1.4.2 Secondary

- [redacted] [CV mortality + nonfatal MI (silent and symptomatic) + unstable angina + chronic stable angina + life-threatening arrhythmias + nonfatal congestive heart failure (CHF) + nonfatal stroke + peripheral arterial disease + revascularization procedures + retinal vascular thromboses]
- [redacted] fatal CHD + nonfatal MI (silent and symptomatic) + chronic stable angina + unstable angina + CHF (fatal and nonfatal)]

- nonfatal MI (symptomatic only) + fatal CHD
- all-cause mortality
- CV mortality
- fatal and nonfatal stroke
- fatal and nonfatal heart failure

6.1.4.3 Tertiary

- silent MI
- unstable angina
- chronic stable angina
- peripheral arterial disease
- life-threatening arrhythmias [ventricular fibrillation (VF)or sustained ventricular tachycardia (VT) or complete heart block]
- development of diabetes mellitus
- development of renal impairment
- health care costs (no analysis provided in this sNDA)
- change in BP
- change in lipids
- change in blood sugar
- change in creatinine

6.1.4.4 Prespecified Subgroup Analyses

- diabetic status
- smoking status
- obesity
- LVH
- age
- gender
- previous vascular disease
- renal dysfunction
- previous vascular disease (by history or ECG)
- renal dysfunction (by serum creatinine or urinalysis)
- metabolic syndrome ["defined according to NCEP III except for replacing waist-hip ratio with BMI>30 kg/m² as subjects with triglycerides ≥ 1.69 mmol/L (150 mg/dL), HDL for males <1.03 mmol/L (40 mg/dL), for women <1.29 mmol/L (50 mg/dL), BP ≥ 130/85 mmHg, fasting glucose ≥ 6.1 mmol/L (110 mg/dL)"].

It should be noted that metabolic syndrome was not included in the original ASCOT protocol:

- Original protocol date: 23 May 97
- Trial termination date: 4 Oct 02

- Protocol amendment # 6 date: 10 Dec 02. Added "with and without metabolic syndrome" and the modified definition above
- Statistical analysis plan revision date: 13 Jan 03. Added metabolic syndrome to the subgroups

Therefore, addition of metabolic syndrome to the subgroup analyses was clearly *post hoc*, occurring over five years after the original protocol. Also, the substitution of BMI for waist-hip ratio is probably not an acceptable change to the definition; the presence of central obesity is a key feature of the evolving concept of the "metabolic syndrome".

6.1.4.5 Study Measurements other than Clinical Endpoints

The following abbreviated table lists measurements other than the clinical endpoints; full listing study report pages 26-31 of the sponsor's sNDA summary.

Table 6.1.4.5: Abbreviated Table of Non-Endpoint Study Measurements

	Scrn	Run-in	Rand	6 wks	6 mos	q yrs 1-5	Lipid Close-out visit
ECG	x		x			x (yr 2 only)	x
Blood for TC and HDL	x		x		x	x	x
Blood for TG	x	x	x		x	x	x
Blood for glucose	x	x	x		x	x	x
Blood ALT	x				x	x	x
Blood for Cr and electrolytes	x			x	x	x	x
Blood for hemoglobin	x					x	x
Urine dipstick for protein, blood, glucose, microalbumin	x					x	x

6.1.5 Study Subject Disposition

For ASCOT, about 28,240 subjects were screened. Of a total of 19,342 allocated to antihypertensive treatment, 10,305 patients with baseline nonfasting serum cholesterol levels ≤ 6.5 mmol/L were assigned to receive either atorvastatin 10 mg po q day (n = 5,168 patients), or a matching placebo (n = 5137 patients) (Table 6.1.5.1).

Table 6.1.5.1: Subject Disposition by Treatment Group for Lipid Lowering Arms of ASCOT-LLA

		Atorvastatin (# of subjects/%)	Placebo (# of subjects/%)	Total (# of subjects/%)
Randomized		5168 (100)	5137 (100)	10305 (100)
	Treated	5123 (99.1)	5087 (99)	10210 (99.1)
	Completed study*	4292 (83)	4043 (78.7)	8335 (80.9)
	Discontinued study treatment	831 (16.1)	1044 (20.3)	1875 (18.2)
Analyzed for safety				
	Adverse events	5158 (99.8)	5124 (99.7)	10282 (99.8)
	Laboratory data	5056 (97.8)	4997 (97.3)	10053 (97.6)

*on lipid-lowering medication Oct 2002 or when they died

About half the patients were recruited in the United Kingdom and half in Scandinavia (Table 6.1.5.2). The median number of patients per center was 6 patients; 90% of the centers had 25 or fewer patients with a range of 1 to 617 patients.

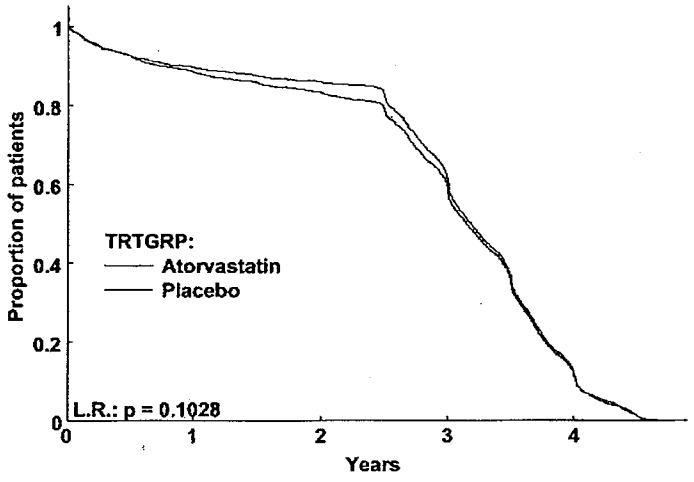
Table 6.1.5.2: Assignment of Patients to Treatment by Country

Country (# centers)	Atorvastatin (n=5168)	Placebo (n=5137)
United Kingdom (33)	2445 (47%)	2408 (47%)
Scandinavia		
Sweden (245)	1104 (21%)	1124 (22%)
Finland (94)	653 (13%)	661 (13%)
Norway (161)	521 (10%)	511 (10%)
Denmark (126)	407 (8%)	395 (8%)
Iceland (9)	38 (1%)	38 (1%)

Note that this table includes Swedish centers 10244 (39 patients) and 10247 (26 patients) which were excluded from the analyses.

All of the 1,875 subjects who were discontinued from study treatment were included in the efficacy analysis based on last known information. At the time the DSMC decided to stop the trial, vital status was available on all but 17 subjects. Time on study was similar for the two treatment groups as illustrated in the graph below.

Figure 6.1.5.1: Time on Study by Treatment in ASCOT-LLA



6.1.6 Demographics

As shown in the following table, the proportions of patients with individual cardiovascular risk factors was essentially the same for the groups, as would be expected given the "statistical minimisation" technique used for patient allocation

Table 6.1.6.1: Distribution of Cardiovascular Risk Factors (Sponsor's Table 2.3)

	Atorvastatin	Placebo	Total
Number of Subjects	5168	5137	10305
Cardiovascular Risk Factors			
Male Gender	4189 (81.1%)	4174 (81.3%)	8363 (81.2%)
Age >= 55 Years	4366 (84.5%)	4335 (84.4%)	8701 (84.4%)
Current Smoker	1718 (33.2%)	1656 (32.2%)	3374 (32.7%)
Diabetes	1258 (24.3%)	1274 (24.8%)	2532 (24.6%)
History of CHD in a first degree relative	1345 (26.0%)	1374 (26.7%)	2719 (26.4%)
Total Cholesterol / HDL >=6	738 (14.3%)	703 (13.7%)	1441 (14.0%)
Peripheral Vascular Disease	261 (5.1%)	253 (4.9%)	514 (5.0%)
LVH according to ECG or ECCO	744 (14.4%)	729 (14.2%)	1473 (14.3%)
Prior Cerebrovascular Event	508 (9.8%)	529 (10.3%)	1037 (10.1%)
ECG abnormalities other than LVH	741 (14.3%)	729 (14.2%)	1470 (14.3%)
Proteinuria / Albuminuria	3225 (62.4%)	3202 (62.3%)	6427 (62.4%)

Demographic characteristics of the full study population, and of the efficacy population excluding the two Scandinavian centers with for-cause audit concerns (the 65 patients in these 2 centers were excluded from all efficacy analyses) are presented in the following two tables. Ninety-five percent of patients were white and 81% were male; mean age was 63 yrs.

Table 6.1.6.2: Demographic Characteristics, all Centers (Sponsor's Table C1)

Table C1 Demographic Characteristics by Gender and Treatment Group

	Atorvastatin			Placebo		
	Male	Female	Total	Male	Female	Total
Number of Subjects	4189	979	5168	4174	963	5137
Age (years):						
≤60 (N,%)	1537 (36.7)	345 (35.2)	1882 (36.4)	1555 (37.3)	298 (30.9)	1853 (36.1)
>60 (N,%)	2652 (63.3)	634 (64.8)	3286 (63.6)	2619 (62.7)	665 (69.1)	3284 (63.9)
Mean ± SD	63.0 ± 8.6	63.5 ± 8.3	63.1 ± 8.5	63.0 ± 8.6	64.3 ± 8.2	63.2 ± 8.6
Range	40.1-80.0	40.1-80.0	40.1-80.0	40.1-79.9	40.9-79.8	40.1-79.9
Race: n (%)						
African	119 (2.8)	27 (2.8)	146 (2.8)	99 (2.4)	26 (2.7)	125 (2.4)
Mixed/Other	41 (1.0)	18 (1.8)	59 (1.1)	54 (1.3)	12 (1.2)	66 (1.3)
Oriental	3 (0.1)	1 (0.1)	4 (0.1)	3 (0.1)	0	3 (0.1)
South Asian	64 (1.5)	6 (0.6)	70 (1.4)	70 (1.7)	10 (1.0)	80 (1.6)
White/Europid	3962 (94.6)	927 (94.7)	4889 (94.6)	3948 (94.6)	915 (95.0)	4863 (94.7)
Weight (kg):						
Mean ± SD	87.3 ± 14.8	76.0 ±15.1		87.2 ± 14.6	75.8 ± 15.3	
Range	44.0-162.5	35.5-150.6		45.0-160.0	43.0-131.9	
Height (cm):						
Mean ± SD	174.7 ± 7.0	162.1 ± 6.7		174.6 ± 7.2	161.4 ± 6.5	
Range	130-198	108-185		100-200	133-179	
Age leaving full-time education; n (%):						
12-14 years	1246 (29.8)	347 (35.4)	1593 (30.8)	1264 (30.3)	358 (37.2)	1622 (31.6)
15-16 years	1506 (36.0)	332 (33.9)	1838 (35.6)	1524 (36.5)	336 (34.9)	1860 (36.2)
17-18 years	548 (13.1)	137 (14.0)	685 (13.3)	531 (12.7)	128 (13.3)	659 (12.8)
19+ years	888 (21.2)	163 (16.6)	1051 (20.3)	855 (20.5)	140 (14.6)	995 (19.4)

Source: Table 2.1 and Section 13, Listing 2.1

Sponsor's Table C2 below describes demographic characteristics when excluding Centers 10244 , and 10247. The medical officer's comparison of this table to sponsor's Table C1, which included all study subjects, did not reveal any significant differences associated with exclusion of the two study centers.

Table 6.1.6.3: Demography Excluding Centers 10244 and 10247 (Sponsor's Table C2)

Table C2 Demographic Characteristics by Gender and Treatment Group, Excluding Centers 10244 and 10247

	Atorvastatin			Placebo		
	Male	Female	Total	Male	Female	Total
Number of Subjects	4169	965	5134	4152	954	5106
Age (years):						
≤60 (N,%)	1519 (36.4)	334 (34.6)	1853 (36.1)	1540 (37.1)	291 (30.5)	1831 (35.9)
>60 (N,%)	2650 (63.6)	631 (65.4)	3281 (63.9)	2612 (62.9)	663 (69.5)	3275 (64.1)
Mean ± SD	63.0 ± 8.5	63.7 ± 8.2	63.2 ± 8.5	63.0 ± 8.6	64.3 ± 8.2	63.2 ± 8.6
Range	40.1-80.0	40.1-80.0	40.1-80.0	40.1-79.9	40.9-79.8	40.1-79.9
Race: n (%)						
African	119 (2.9)	27 (2.8)	146 (2.8)	99 (2.4)	26 (2.7)	125 (2.4)
Mixed/Other	41 (1.0)	18 (1.9)	59 (1.1)	54 (1.3)	12 (1.3)	66 (1.3)
Oriental	3 (0.1)	1 (0.1)	4 (0.1)	3 (0.1)	0	3 (0.1)
South Asian	64 (1.5)	6 (0.6)	70 (1.4)	70 (1.7)	10 (1.0)	80 (1.6)
White/Europid	3942 (94.6)	913 (94.6)	4855 (94.6)	3926 (94.6)	906 (95.0)	4832 (94.6)
Weight (kg):						
Mean ± SD	87.3 ± 14.8	76.0 ± 15.1		87.1 ± 14.6	75.8 ± 15.3	
Range	44.0-162.5	35.5-150.6		45.0-160.0	43.0-131.9	
Height (cm):						
Mean ± SD	174.7 ± 7.0	162.1 ± 6.7		174.6 ± 7.2	161.4 ± 6.5	
Range	130-198	108-185		100-200	133-178	
Age leaving full-time education; n (%):						
12-14 years	1235 (29.6)	338 (35.0)	1573 (30.6)	1254 (30.2)	351 (36.8)	1605 (31.4)
15-16 years	1501 (36.0)	329 (34.1)	1830 (35.7)	1515 (36.5)	335 (35.2)	1850 (36.2)
17-18 years	546 (13.1)	135 (14.0)	681 (13.3)	528 (12.7)	127 (13.3)	655 (12.8)
19+ years	886 (21.3)	163 (16.9)	1049 (20.4)	855 (20.6)	140 (14.7)	995 (19.5)

Source: Table 2.1a

Further discussion of the differences between the specified ASCOT risk factors, and those used in the US National Cholesterol Education Program (NCEP), is needed. When considering the applicability of the ASCOT study results to management of patients within the US, one must consider the NCEP guidelines which US physicians are encouraged to use in decision-making regarding initiation of lipid-lowering therapy for reduction of coronary heart disease risk. Some, but not all, of the *ASCOT* risk factors correlate with the *NCEP* major risk factors used in calculation of coronary heart disease risk in the NCEP guidelines. *NCEP* major risk factors include:

- cigarette smoking
- hypertension (blood pressure ≥ 140/90 mm Hg or on an antihypertensive medication) (sic)

- low HDL cholesterol (<40 mg/dL)
- family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years) (sic from ref 63)
- age (men ≥ 45 years; women ≥ 55 years)

In the current NCEP guidelines, persons with two or more of these major risk factors have a lower LDL goal than the general population (LDL <130 mg/dL vs <160), and undergo further risk scoring in order to determine which individuals have sufficient short-term risk to warrant intensive LDL-lowering. Diabetes and the presence of peripheral vascular disease are considered "coronary heart disease equivalents" in NCEP guidelines, i.e. subjects with these disorders are considered to have a risk equal to that of subjects with known coronary heart disease, and automatically warrant intensive LDL-lowering.

Some of the ASCOT risk factors correlate well with NCEP risk factors. However, some of the ASCOT risk factors (such as LVH, ECG abnormalities or proteinuria/ microalbuminuria) are currently considered minor or emerging risk factors for coronary artery disease. The NCEP does not consider obesity a CHD risk factor that is independent of other risk factors.

Because of the differences between ASCOT and NCEP risk factors, the question arose of how to apply the ASCOT-LLA results to US patients whose cholesterol is managed as recommended within NCEP guidelines. This was necessary because wording in the Indications and Usage section of all LDL-lowering agents approved in the US has emphasized the NCEP guidelines. Concern was expressed about the possibility that ASCOT-LLA subjects could be eligible for the trial on the basis of minor risk factors, rather than risk factors similar to those used for the NCEP. Therefore, the clinical and statistical reviewers looked at how many subjects had given numbers of ASCOT risk factors, and how many had given numbers of NCEP risk factors. This information is useful both in deciding on the relevance of the ASCOT population to US practice, and, as will be seen later, in deciding how to craft the language describing patients for whom the new indications for Lipitor® will apply.

Table 6.1.6.4 describes the numbers of risk factors among the ASCOT-LLA subjects, looking at both ASCOT and NCEP major risk factors.

Table 6.1.6.4: Comparison of Numbers of ASCOT CHD Risk Factors vs Numbers of NCEP Major Risk Factors in the ASCOT-LLA Population

Number of Risk Factors	Number of Subjects with Given Number of ASCOT RFs n (%) n = 10305	Number of Subjects with Given Number of NCEP Major or "CHD Equivalent" RFs n (%) n = 10305
1	0	19 (0.2%)
2	50 (0.5%)	2222 (21.6%)
3	5435 (52.7%)	4727 (45.9%)
4	3225 (31.3%)	2674 (26.0%)
5	1231 (11.9%)	600 (5.9%)
6	293 (2.8%)	58 (0.6%)
7	60 (0.6%)	5 (<0.1%)
8	11 (0.1%)	0

Even though ASCOT-LLA included some minor coronary heart disease risk factors, >99% of subjects had ≥ 2 NCEP major risk factors, and 78% had ≥ 3. Thus, in the US, most patients in the ASCOT population would have an LDL goal lower than that for the general population (<130 mg/dL vs <160), and would undergo further risk assessment for need for intensive lipid-lowering (LDL goal <100). Furthermore, one can comfortably describe the ASCOT patient population in terms of NCEP risk factors, and thus can use these risk factors when describing the indicated population likely to experience reduction of cardiovascular event risk. The inclusion of minor risk factors in this trial did not result in a large percentage of patients with these minor risk factors but few major risk factors.

The sponsor examined baseline lipid levels to assess for differences between treatment groups; proportions of patients with total cholesterol and LDL in set ranges were also examined. There was no significant difference between the atorvastatin and placebo groups for the proportions of patients with total cholesterol or LDL in any given range (source sponsor's table 2.4).

6.1.7 Prior and Concomitant Drug Treatments

Primary care physicians were advised of their patients' lipid profiles and of local recommendations for lipid-lowering therapy. Patients could be included only if the patient was not currently taking a statin or fibrate, and their primary care physician did not intend to treat the patient with a statin or fibrate. Other lipid-lowering agents in use prior to treatment allocation were continued. During the study, the patient's primary care physician could add other lipid-lowering therapy if the physician felt the patient required it.

The percentages of patients receiving some type of antihypertensive medication, lipid-lowering medication, or aspirin prior to the study were similar for the atorvastatin and placebo groups as illustrated in the sponsor's table below.

Table 6.1.7.1: Drug Treatments Prior to Study (Sponsor's Table D)

Table D Drug Treatments Prior to the Start of Study

	Atorvastatin (N=5168)	Placebo (N=5137)
	number (%) of subjects	
Number of subjects with drug treatment prior to the start of study[a]	4237(82.0)	4233 (82.4)
Lipid-Lowering Treatment	40 (0.8)	51 (1.0)
Statins	29 (0.6)	38 (0.7)
Fibrates	4 (0.1)	6 (0.1)
Other	8 (0.2)	9 (0.2)
Previous Antihypertensive Treatment		
None	1021 (19.8)	996 (19.4)
1	2314 (44.8)	2279 (44.4)
≥2	1833 (35.5)	1862 (36.2)
Aspirin Treatment	888 (17.2)	865 (16.8)

Source: Table 2.2
[a]only antihypertensive, lipid-lowering medications and aspirin are reported

During the trial period, a higher percentage of patients in the placebo group had lipid-lowering therapies added than did patients in the atorvastatin group. The sponsor concludes that use of concomitant antihypertensive medications and aspirin were similar for the atorvastatin and placebo groups in the trial. However, the medical officer notes that use of any given antihypertensive and aspirin was higher in the placebo groups than in the atorvastatin group. The sponsor's table below illustrates these differences and similarities.

Table 6.1.7.2: Concomitant Drug Treatments During Trial (Sponsor's Table E)

Table E Concomitant Drug Treatments

	Atorvastatin (N=5168)	Placebo (N=5137)
	number (%) of subjects	
Number of subjects with concomitant drug treatment[a]	2899 (56.1)	3127 (60.9)
Lipid-Lowering Treatment	225 (4.4)	655 (12.8)
Statin	201 (3.9)	630 (12.3)
Fibrates	13 (0.3)	24 (0.5)
Other	16 (0.3)	16 (0.3)
Antihypertensive Treatment	1969 (38.1)	2138 (41.6)
Diuretics	823 (15.9)	929 (18.1)
Beta-blockers	467 (9.0)	515 (10.0)
Calcium antagonists	442 (8.6)	514 (10.0)
Angiotensin II antagonists	345 (6.7)	398 (7.7)
ACE inhibitors	305 (5.9)	355 (6.9)
Anti-adrenergic	934 (18.1)	977 (19.0)
Other Vasodilators	43 (0.8)	38 (0.7)
Aspirin Treatment	1643 (31.8)	1757 (34.2)

Source: Table 3.2
[a]only antihypertensive, lipid-lowering medications and aspirin are reported

Because of the demonstrated efficacy of antihypertensive treatment and aspirin in lowering of risk of cardiovascular events, a slight excess of these treatments in the placebo group is unlikely to have contributed to better efficacy for atorvastatin in lowering risk of cardiovascular events.

6.1.8 Statistical Methods

6.1.8.1 Study Subject Allocation Methods

Rather than using traditional randomization, ASCOT-LLA used a combination of block randomization and an "optimal allocation procedure", sometimes referred to as "statistical minimisation". For full description of these procedures, see pages 37-38 of the study report.

Subjects were allocated separately by each of the two major coordinating centers, using slightly different methods. These methods are described in Appendix 10.2 of this review.

Allocation for the antihypertensive portion of the study occurred first. If the number of allocated subjects for a given center was ≤ 8, the current subject was randomized using standard block randomization. If the number of allocated subjects for a given center was >8, the current subject was allocated using the "optimal allocation procedure" (study report pages 37-38).

Allocation of study subjects for ASCOT-LLA then occurred among those patients who met entry criteria for the lipid-lowering portion of the trial. Again, block randomization was used for the

first eight subjects at a given study center; subsequent subjects were allocated using the "optimal allocation procedure".

This procedure was designed to minimize the differences between subgroups by "balancing" certain study subject characteristics. This complex procedure has not yet been validated in large study populations, and at this time is not considered "true" randomization.

6.1.8.2 Blinding

The main antihypertensive study (ASCOT) was open label and the lipid-lowering arm (ASCOT-LLA) was double-blind. For both the antihypertensive and lipid-lowering arm, the endpoint committee was blinded to treatment assignment. The endpoint committee analyzed all cases suspected of fulfilling criteria for endpoint events.

6.1.8.3 Efficacy Analyses

The null hypothesis for the primary efficacy parameter was that the incidence of the primary composite endpoint [nonfatal MI (symptomatic and silent MI) + fatal CHD] would be the same in the lipid-lowering group as the non-lipid-lowering group. The time to first event was compared for combination therapy (antihypertensive therapy + lipid-lowering therapy) and antihypertensive therapy alone using a log rank test. This analysis was performed without adjusting for baseline factors. Secondary and tertiary efficacy parameters were analyzed in the same manner. A Cox proportional hazards model was used to obtain the confidence intervals. A two-sample T-test was used to compare the treatment effect on change in blood pressure, lipids, blood sugar and creatinine over time.

All hypothesis tests were two-sided. Results were considered statistically significant if a p-value of <0.05 (including adjustment for interim analyses) was obtained for primary hypothesis and <0.01 for secondary and tertiary hypotheses. The sponsor states that the choice of 0.01 was due to the fact that a large number of secondary and tertiary hypotheses were planned, and that choice of 0.01 acted as a "crude" way of guarding against the multiple testing problem.

For ASCOT-LLA, the sponsor hypothesized a relative effect of 30% (equivalent to a hazard ratio of 0.7) on the primary endpoint, when comparing atorvastatin 10 mg vs placebo. Using an intention-to-treat (ITT) principle for analysis, power was calculated to be >90% for the primary endpoint with a sample size of 9,000 patients. Assumptions included a significance level of 1% and a yearly endpoint rate in the placebo group of 6.35% for 5 years of treatment.

The initial study plan called for all randomized patients to be included in the intent-to-treat (ITT) population. However, the sponsor reports that irregularities of follow-up were detected by site-audit at two centers. At these centers, vital signs information on patients could not be verified. This audit data "came to light" after publication of the data. For this sNDA submission, the Steering Committee recommended that efficacy data from these two sites be excluded from the primary efficacy analyses. Safety data from these sites were included in the analyses. The sponsor reports that exclusion of the data did not change the significance of any of the endpoints.

When the sponsor uses the term "ITT analyses", they refer to the population excluding efficacy data for the 65 patients from these two sites.

Data were analyzed according to allocated treatment groups, regardless of study subject compliance with study medication.

A priori, the Data Safety Monitoring Committee decided to use a Haybittle-Peto statistical boundary as a guideline for whether or not to recommend early termination. A critical value $Z_I = \pm 3$ was used for interim analyses. The sponsor states that there was a "negligible" adjustment of the p-value for the final test because of repeated testing.

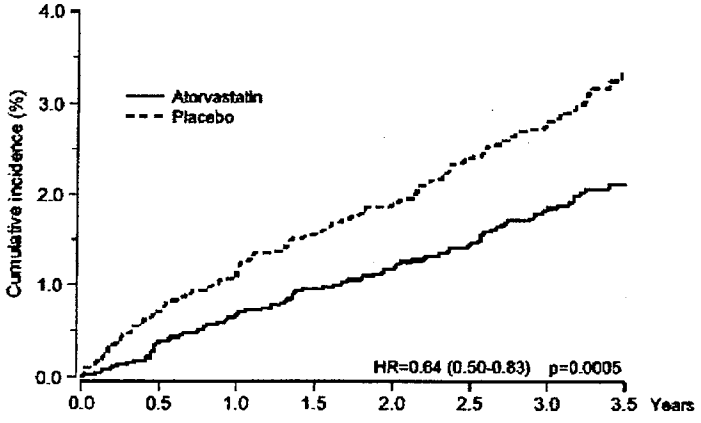
Because the hypertensive portion of ASCOT is still ongoing, analyses for the lipid-lowering portion of the trial will not be performed using the 2x2 factorial structure until the hypertensive portion of the trial has ended.

6.1.9 Efficacy Findings

6.1.9.1 Primary endpoint: nonfatal myocardial infarction (symptomatic and silent) + fatal coronary heart disease

A total of 100 patients (1.9%) in the atorvastatin group and 154 patients (3.0%) in the placebo group experienced a primary event. This difference was statistically significant with a p-value of 0.0005 and a hazard ratio of 0.64 (95% confidence interval 0.5-0.83 for the hazard ratio). The sponsor's Kaplan-Meier plot below illustrates their findings.

Figure 6.1.9.1: Kaplan-Meier Plot, Incidence of Primary Endpoint



The following table summarizes the outcomes for the primary endpoint and its components:

Table 6.1.9.1: Incidence of the Composite Primary Endpoint and its Components

Endpoint	Atorva (N = 5134) n	Pbo (N = 5106) n	Atorva %	Pbo %	Atorva Rate[1]	Pbo Rate[1]	HR (95% CI)	p-value
Primary[2]	100	154	1.9%	3.0%	6.1	9.4	0.64 (0.50-0.83)	0.00053
Nonfatal Symptomatic MI	46	91	0.9%	1.8%	2.8	5.6	0.50 (0.35-0.71)	0.00010
Silent MI	14	17	0.3%	0.3%	0.8	1.0	0.82 (0.40-1.66)	0.58236
Fatal CHD	41	46	0.8%	0.9%	2.5	2.8	0.89 (0.58-1.35)	0.57653

[1] Rate per 1,000 patient years
[2] Composite of nonfatal myocardial infarction (symptomatic and silent) and fatal coronary heart disease

that treatment with atorvastatin 10 mg po q day (compared to placebo) was associated with a 36% reduction (HR 0.64) in the composite primary endpoint of nonfatal myocardial infarction (MI) plus fatal coronary heart disease (CHD).

There was a 50% reduction in risk for symptomatic nonfatal MI (p = 0.0001). Incidences of fatal CHD and of silent MI were similar for the atorvastatin and placebo groups. Mortality endpoints did not trend in the wrong direction, i.e. did not favor placebo over atorvastatin. The difference between the atorvastatin and placebo groups for the primary endpoint may be largely attributable to a reduction in risk for symptomatic nonfatal MI. It should be noted that the sponsor was not responsible for the decision regarding early cessation of the trial; an independent data safety monitoring committee made that decision based on *a priori* rules.

The primary concern for the medical reviewer regarding the possible granting of an indication

The sponsor proposes inclusion of reduction of risk of myocardial infarction". This concern led the medical reviewer to examine the prior approval of other agents currently carrying

Please see the armamentarium section (2.2) for a full listing of the agents. At this time, simvastatin, pravastatin and lovastatin have such claims. however, except for ramipril, their indications primarily address administration of the agent in the immediate post-infarction period.

In the Heart Protection Study (simvastatin), reveals highly significant reductions in mortality risks (p-values of 0.0003 for total mortality and

0.0005 for coronary heart disease mortality). In the Longterm Intervention with Pravastatin in Ischemic Disease trial (pravastatin), reveals highly significant reductions in risk for CHD mortality (p 0.0004), total mortality (p <0.0001), and cardiovascular mortality (p <0.0001). For lovastatin, although the included myocardial infarction, unstable angina, and sudden cardiac death, In that trial, there were eight cases of sudden cardiac death in patients taking lovastatin and nine among placebo patients. were independently statistically significant (unstable angina p = 0.023. myocardial infarction p = 0.002). While the lovastatin label does not include an indication

In the Heart Outcomes Protection Evaluation (ramipril), reveals significant reduction in risk of cardiovascular death (p = 0.0002) and total mortality (p = 0.005).

Thus, other lipid-lowering agents (and ramipril), demonstrated strong evidence As a contrasting argument, however, particularly among certain subgroups, such as diabetics and the elderly (56-59).

In the medical reviewer's opinion, an indication for reduction in risk of myocardial infarction is warranted for atorvastatin based on the ASCOT-LLA result. It is reasonable to simply word this as reduction of risk for myocardial infarction, rather than requiring the word in the sponsor's draft label) is not appropriate.

6.1.9.1.1 Incidence of Primary Endpoint By Prespecified Subgroups

The following table summarizes for the primary endpoint results for prespecified subgroups.

Table 6.1.9.1.1.1 Incidence of the Primary Endpoint in Prespecified Subgroups (Sponsor's Table J)

Table J Incidence of the Primary Endpoint[a] in Prespecified Subgroups, All Subjects Excluding Centers 10244 and 10247

		Atorvastatin		Placebo		Unadjusted hazard ratio (95% CI)
Subgroup	N	n (%)	Rate[b]	n (%)	Rate[b]	
Diabetes	2526	38 (3.0)	9.6	46 (3.6)	11.4	0.84 (0.55-1.29)
Non-Diabetes	7714	62 (1.6)	4.9	108 (2.8)	8.8	0.56 (0.41-0.77)
Current Smoker	3359	35 (2.0)	6.3	60 (3.6)	11.3	0.56 (0.37-0.85)
Non-Current Smoker	6881	65 (1.9)	6.0	94 (2.7)	8.5	0.70 (0.51-0.96)
Obese[c]	3407	35 (2.1)	6.5	59 (3.5)	10.9	0.59 (0.39-0.90)
Non Obese	6833	65 (1.9)	5.9	95 (2.8)	8.7	0.67 (0.49-0.92)
LVH according to ECG or ECCO	1466	15 (2.0)	6.2	22 (3.0)	9.4	0.66 (0.34-1.28)
No LVH according to ECG or ECCO	8774	85 (1.9)	6.0	132 (3.0)	9.4	0.64 (0.49-0.84)
Older (>60)	6556	71 (2.2)	6.8	111 (3.4)	10.7	0.64 (0.47-0.86)
Younger (≤60)	3684	29 (1.6)	4.8	43 (2.3)	7.2	0.67 (0.42-1.07)
Female	1919	19 (2.0)	6.0	17 (1.8)	5.4	1.11 (0.58-2.13)
Male	8321	81 (1.9)	6.1	137 (3.3)	10.4	0.59 (0.44-0.77)
Previous Vascular Disease	1469	21 (2.9)	9.0	26 (3.5)	11.2	0.80 (0.45-1.42)
No Previous Vascular Disease	8771	79 (1.8)	5.6	128 (2.9)	9.1	0.61 (0.46-0.81)
Renal Dysfunction	6454	60 (1.9)	5.7	97 (3.0)	9.4	0.61 (0.44-0.84)
No Renal Dysfunction	3786	40 (2.1)	6.6	57 (3.0)	9.5	0.70 (0.46-1.04)
With Metabolic Syndrome	3913	47 (2.4)	7.6	61 (3.1)	9.9	0.77 (0.52-1.12)
Without Metabolic Syndrome	6327	53 (1.7)	5.1	93 (3.0)	9.1	0.56 (0.40-0.79)

Source: Table 5.4
N=total number of subjects in subgroup; n=number with primary endpoint
[a] Non-Fatal MI (symptomatic and silent MI) + Fatal CHD
[b] per 1000 patient-years
[c] BMI >30 kg/m^2

The sponsor reported no significant interactions with treatment for any of the subgroups, however FDA analyses revealed a significant interaction for gender by treatment with a p-value of 0.078 and borderline significant results (p=0.14) for diabetics/non-diabetics.

The gender differences in treatment effects are clearly illustrated in the following two figures.

Figure 6.1.9.1.1.1: Kaplan Meier Plot of Primary Endpoint For Females

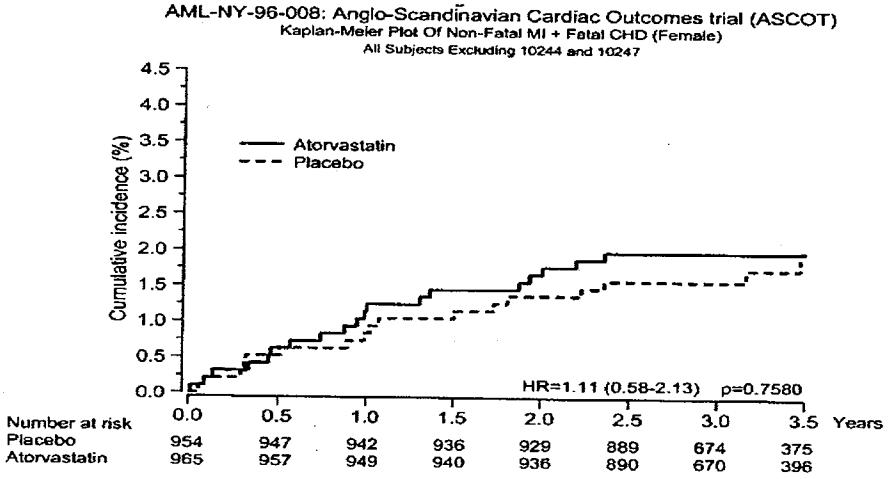
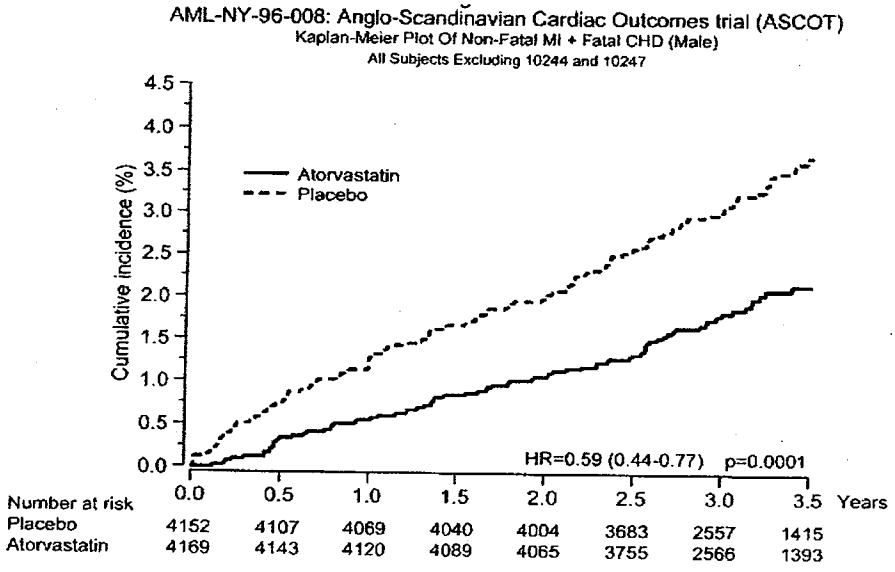


Figure 6.1.9.1.1.2: Kaplan-Meier Plot of Primary Endpoint for Males



For men, the incidence of the primary endpoint appears lower in the atorvastatin group (compared to placebo) almost throughout the study period, with very significant separation nearing the end of the study. For women, however, the incidence of the primary endpoint actually appears lower in the placebo group throughout most of the study until study cessation (at 3.3 yrs), when the incidence lines appear to suddenly converge.

The overall small number of events seen for females may explain the lack of a treatment effect. To examine the gender issue further, the results for secondary endpoints by gender are summarized below. Only the results for cardiovascular procedures show a strong effect for atorvastatin in females; these results drive the results seen for the composite endpoint; total cardiovascular events plus procedures. Overall the results for females are not strong and suggest that a comment in the labeling is warranted.

Table 6.1.9.1.1.2 Secondary Endpoint Results for Males and Females

	Atorva	Placebo	HR (CI)	Int. p-value
NFMI+Fatal CHD				
Males	1.94% (81/4169)	3.30% (137/4152)	0.59 (0.44, 0.77)	
Females	1.97% (19/965)	1.78% (17/954)	1.11 (0.58, 2.13)	0.078
Total CV+Proc				
Males	7.68% (320/4169)	9.61% (399/4152)	0.79 (0.69, 0.92)	
Females	7.15% (69/965)	8.81% (84/954)	0.81 (0.59, 1.11)	0.30
Total Coronary				
Males	3.60% (150/4169)	5.18% (215/4152)	0.69 (0.56, 0.85)	
Females	2.90% (28/965)	3.35% (32/954)	0.87 (0.52, 1.44)	0.42
CV Mortality				
Males	1.37% (57/4169)	1.69% (70/4152)	0.81 (0.57, 1.15)	
Females	1.76% (17/965)	1.26% (12/954)	1.41 (0.67, 2.94)	0.19
All Cause Mortality				
Males	3.53% (147/4169)	4.38% (182/4152)	0.81 (0.65, 1.00)	
Females	3.94% (38/965)	3.14% (30/954)	1.26 (0.78, 2.03)	0.10
CV Procedures				
Males	1.63% (68/4169)	2.58% (107/4152)	0.63 (0.47, 0.86)	
Females	0.62% (6/965)	2.10% (20/954)	0.30 (0.12, 0.74)	0.12

6.1.9.2 Secondary and Tertiary endpoints.

The following table summarizes the outcomes for the prespecified secondary and tertiary endpoints.

Table 6.1.9.2.1: Summary of Endpoint Outcomes (Sponsor's Table 5.1)

	Atorvastatin		Placebo		Unadjusted hazard ratio	
Endpoint	n (%)	Rate*	n (%)	Rate*	(95% CI)	p-value
Non-Fatal MI (includes Silent MI) + Fatal CHD	100 (1.9%)	6.1	154 (3.0%)	9.4	0.64 (0.50-0.83)	0.00053
Total Cardiovascular Events and Procedures†	389 (7.6%)	24.3	483 (9.6%)	30.6	0.80 (0.70-0.91)	0.00078
Total Coronary Events‡	178 (3.5%)	10.9	247 (4.8%)	15.3	0.71 (0.59-0.86)	0.00056
Non-Fatal MI (excludes Silent MI) + Fatal CHD	88 (1.7%)	5.2	137 (2.7%)	8.4	0.62 (0.47-0.81)	0.00049
All Cause Mortality	185 (3.6%)	11.1	212 (4.2%)	12.8	0.87 (0.71-1.08)	0.16048
Cardiovascular Mortality	74 (1.4%)	4.5	82 (1.6%)	5.0	0.90 (0.66-1.23)	0.50858
Fatal and Non-Fatal Stroke	86 (1.7%)	5.4	119 (2.3%)	7.3	0.74 (0.56-0.98)	0.03320
Fatal and Non-Fatal Heart Failure	41 (0.8%)	2.5	36 (0.7%)	2.2	1.14 (0.73-1.78)	0.57774
Silent MI	74 (0.3%)	0.8	17 (0.3%)	1.0	0.82 (0.40-1.68)	0.58236
Unstable Angina	21 (0.4%)	1.3	24 (0.5%)	1.5	0.87 (0.49-1.57)	0.64588
Chronic Stable Angina	33 (0.6%)	2.0	56 (1.1%)	3.4	0.59 (0.38-0.90)	0.01354
Peripheral Arterial Disease	42 (0.8%)	2.5	41 (0.8%)	2.5	1.02 (0.66-1.57)	0.92372
Life Threatening Arrythmias	10 (0.2%)	0.6	3 (0.1%)	0.2	3.31 (0.91-12.02)	0.05387
Development of Diabetes Mellitus	154 (3.0%)	9.4	133 (2.6%)	8.2	1.15 (0.92-1.46)	0.22317
Development of Renal Impairment	31 (0.6%)	1.9	24 (0.5%)	1.5	1.29 (0.76-2.19)	0.35044

†cardiovascular mortality + non-fatal MI (symptomatic and silent) + unstable angina + chronic stable angina + life-threatening arrhythmias + non-fatal heart failure + non-fatal stroke + peripheral arterial disease + revascularization procedures + retinal vascular thromboses
‡fatal CHD + non-fatal MI (symptomatic and silent) + chronic stable angina + unstable angina + fatal and non-fatal heart failure
*per 1000 patient years.

Endpoints meeting the prespecified criteria for statistical significance ($p \leq 0.01$) include nonfatal myocardial infarction, total cardiovascular events and procedures, total coronary events, and nonfatal MI (excluding silent MI) + fatal CHD. All-cause mortality and cardiovascular mortality were not statistically significantly different between the atorvastatin and placebo groups, but these mortality endpoints did trend in a favorable direction.

The following table breaks down the composite cardiovascular endpoints into their individual components.

Table 6.1.9.2.2: Decomposition of Composite Cardiovascular Endpoints (Sponsor's Table 5.1a)

AML-NY-96-008: Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)
Decomposition of Composite Cardiovascular Endpoints
All Subjects Excluding Centers 10244 and 10247

Endpoint	Atorvastatin n (%)	Atorvastatin Rate*	Placebo n (%)	Placebo Rate*	Unadjusted Hazard ratio (95% CI)	p-value
Non-Fatal MI (includes Silent MI) + Fatal CHD	100 (1.9%)	6.1	154 (3.0%)	9.4	0.64 (0.50-0.83)	0.00053
Non-Fatal MI (Symptomatic)	46 (0.9%)	2.8	91 (1.8%)	5.6	0.50 (0.35-0.71)	0.00010
Silent MI	14 (0.3%)	0.8	17 (0.3%)	1.0	0.82 (0.40-1.66)	0.58236
Fatal CHD	41 (0.8%)	2.5	46 (0.9%)	2.8	0.89 (0.58-1.35)	0.57653
Total Cardiovascular Events and Procedures	389 (7.6%)	24.3	483 (9.5%)	30.6	0.80 (0.70-0.91)	0.00078
Cardiovascular Mortality	74 (1.4%)	4.5	82 (1.6%)	5.0	0.90 (0.66-1.23)	0.50859
Non-Fatal MI (Symptomatic and Silent)	60 (1.2%)	3.6	108 (2.1%)	6.6	0.55 (0.40-0.75)	0.00017
Unstable Angina	21 (0.4%)	1.3	24 (0.5%)	1.5	0.87 (0.49-1.57)	0.64588
Chronic Stable Angina	33 (0.6%)	2.0	56 (1.1%)	3.4	0.59 (0.38-0.90)	0.01354
Life Threatening Arrythmias	10 (0.2%)	0.6	3 (0.1%)	0.2	3.31 (0.91-12.02)	0.05387
Non-Fatal Heart Failure	37 (0.7%)	2.2	34 (0.7%)	2.1	1.09 (0.68-1.73)	0.73072
Non-Fatal Stroke	78 (1.5%)	4.7	98 (1.9%)	6.0	0.79 (0.59-1.06)	0.11998
Transient Ischaemic Attack (TIA)	31 (0.6%)	1.9	43 (0.8%)	2.6	0.72 (0.45-1.14)	0.15994
Reversible Ischaemic Neurological Deficit (RIND)	15 (0.3%)	0.9	11 (0.2%)	0.7	1.36 (0.62-2.95)	0.44158
Retinal Vascular Thromboses	4 (0.1%)	0.2	2 (0.0%)	0.1	1.99 (0.36-10.88)	0.41674
Peripheral Arterial Disease	42 (0.8%)	2.5	41 (0.8%)	2.5	1.02 (0.66-1.57)	0.92372
Revascularization Procedures	74 (1.4%)	4.5	127 (2.5%)	7.6	0.58 (0.43-0.77)	0.00016
Total Coronary Events	178 (3.5%)	10.9	247 (4.8%)	15.3	0.71 (0.59-0.86)	0.00055
Fatal CHD	41 (0.8%)	2.5	46 (0.9%)	2.8	0.89 (0.58-1.35)	0.57653
Non-Fatal MI (Symptomatic and Silent)	60 (1.2%)	3.6	108 (2.1%)	6.6	0.55 (0.40-0.75)	0.00017
Unstable Angina	21 (0.4%)	1.3	24 (0.5%)	1.5	0.87 (0.49-1.57)	0.64588
Chronic Stable Angina	33 (0.6%)	2.0	56 (1.1%)	3.4	0.59 (0.38-0.90)	0.01354
Fatal and Non-Fatal Heart Failure	41 (0.8%)	2.5	36 (0.7%)	2.2	1.14 (0.73-1.78)	0.57774
Cardiovascular Mortality	74 (1.4%)	4.5	82 (1.6%)	5.0	0.90 (0.66-1.23)	0.50859
Fatal CHD	41 (0.8%)	2.5	46 (0.9%)	2.8	0.89 (0.58-1.35)	0.57653
Fatal Stroke	15 (0.3%)	0.9	22 (0.4%)	1.3	0.68 (0.35-1.31)	0.24818
Other Fatal Cardiovascular Events	18 (0.4%)	1.1	14 (0.3%)	0.8	1.28 (0.64-2.58)	0.48203

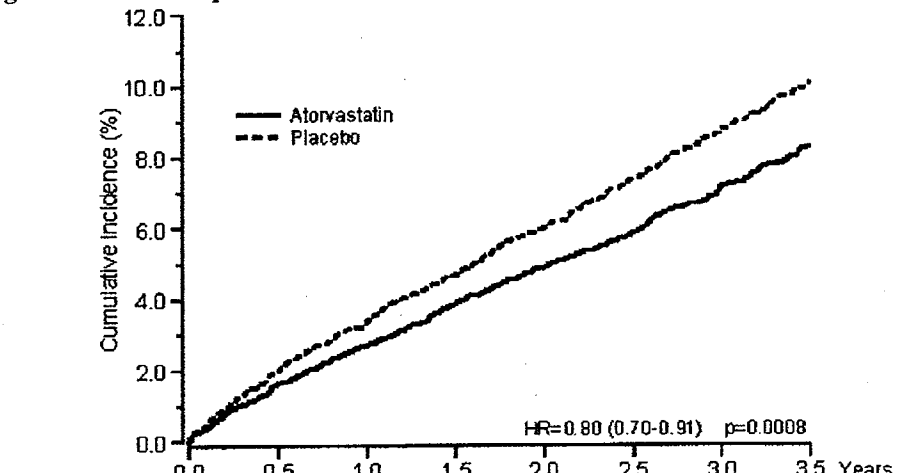
*per 1000 patient years.

6.1.9.2.1 Secondary Endpoint Results: Total Cardiovascular Events and Procedures

"Total Cardiovascular Events and Procedures" was a composite endpoint with the following components: cardiovascular mortality, nonfatal (symptomatic and silent) MI, unstable angina, chronic stable angina, life-threatening arrhythmias, nonfatal heart failure, nonfatal stroke, peripheral arterial disease, revascularization procedures and retinal vascular thromboses. Comparison of the risk for this composite for the atorvastatin group vs the placebo group reveals an unadjusted hazard ratio favoring atorvastatin [389 events (7.6%) vs 483 events (9.5%), HR 0.80, CI for HR 0.70-0.91, p= 0.00078].

The following Kaplan-Meier Plot illustrates the difference between groups for this endpoint.

Figure 6.1.9.2.1: Kaplan-Meier Plot of Total Cardiovascular Events and Procedures



Number at risk								
Placebo	5106	4992	4909	4832	4746	4362	3041	1677
Atorvastatin	5134	5041	4973	4894	4827	4453	3063	1690

The sponsor asserts that this demonstrates early separation between atorvastatin and placebo. There is a large drop-off of number of patients at risk between 3.0 and 3.5 years due to early termination of the lipid-lowering portion of the study.

When examining the individual components of the Total Cardiovascular Events and Procedures endpoint, only the differences in nonfatal symptomatic MI and revascularization procedures appear to be statistically significant for the atorvastatin group compared to the placebo group, as shown in Table 6.1.9.2.2. Chronic stable angina occurred less frequently in the atorvastatin group; while not meeting the sponsor's predefined criterion ($p < 0.01$) for statistical significance, it came very close (p 0.01354). Some components were associated with hazard ratios >1 (nonfatal heart failure, reversible ischemic neurologic deficit, retinal vascular thrombosis and peripheral arterial disease), but all confidence intervals fell on either side of 1, and numbers of events were too small for meaningful conclusions. Some components (life-threatening arrhythmia, retinal vascular thrombosis) had wide confidence intervals.

[redacted] reductions in risk for nonfatal myocardial infarction and revascularization procedures, with some contribution from reduction in risk for chronic stable angina. The sponsor is seeking an indication stating that Lipitor® has been shown to "reduce the risk of [redacted]". In order to give the prescribing clinician the most accurate and specific information about what is known about atorvastatin efficacy, the medical officer recommends that the revised "Indications and Usage" section add only reduction of risk for revascularization procedures and angina from this

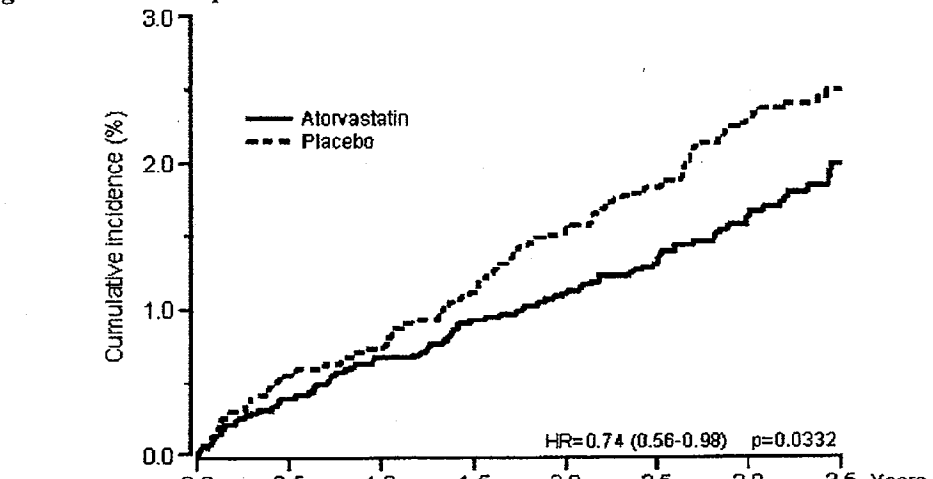
composite endpoint. (The reviewer has already recommended inclusion of myocardial infarction risk reduction.)

6.1.9.2.2 Secondary Endpoint Results: Stroke

For this composite secondary endpoint, there was some risk reduction in the atorvastatin group compared to placebo [89 events (1.7%) vs 89 events (2.3%), HR 0.74, CI for HR 0.56-0.98]. P-value was 0.033, which did not meet the prespecified criterion for statistical significance of ≤ 0.01.

In the following Kaplan-Meier plot, the sponsor notes that the cumulative incidence curves continue to diverge beyond the three-year follow-up point.

Figure 6.1.9.2.2: Kaplan-Meier Plot for Incidence of Stroke



There is a large drop-off in number of patients at risk between 3.0 and 3.5 years because of early termination of the study.

As shown in table 6.1.9.2.2, neither of the individual components of the combined stroke endpoint achieved statistical significance for a difference between atorvastatin and placebo. Nonfatal stroke occurred in 78 atorvastatin patients (1.5%) and 98 placebo patients (1.9%) (HR 0.79, CI for HR 0.59-1.06, p-value 0.11998). Fatal stroke occurred in 15 atorvastatin patients (0.3%) and 22 placebo patients (0.4%) (HR 0.68, CI for HR 0.35-1.31, p-value 0.24818).

Information on hemorrhagic vs ischemic stroke was available only for those study subjects who died. The following table presents this information:

Table 6.1.9.2.2.1: Stroke Type Among Study Subjects who Died

	Atorvastatin Grp (total n = 5134) n (% of arm)	Placebo Grp (total n = 5106) n (% of arm)
Hemorrhagic	5 (0.09%)	10 (0.20%)
Ischemic	7 (0.14%)	8 (0.16%)
Unknown	4 (0.07%)	6 (0.12%)

The total numbers of strokes in this table exceed the total number of fatal strokes listed above; this is because the data used to construct the table included all mortal endpoints, and some patients who had a stroke were considered to have a different endpoint as their cause of death. Thus, this table includes both patients who died from stroke, and some who had a stroke, but died from another cardiovascular event. Because the event rates for all three classifications of stroke are very low, little can be said about the relationship between atorvastatin and risk of any subset of stroke. However, in each subtype, slightly fewer atorvastatin patients had that type of stroke, when compared to placebo.

Two questions arise for the medical officer regarding the

1.

2. When considered independently of question 1, is the degree comparable to that seen with other large trials

Regarding the first question, the medical officer considered the fact that there were a large number of secondary and tertiary hypotheses, and thus a problem with multiple testing that does necessitate more stringency in determination of significance.

Therefore, the question returns to the Table 6.1.9.2.2.2 summarizes agents At present, there are seven approved agents; within the context of their clinical trials, six of these agents achieved The seventh agent, pravastatin, significance as that demonstrated for atorvastatin.

Table 6.1.9.2.2.2:

Agent		Comparator	P-Value for Stroke Risk Reduction
Simvastatin	Heart Protection Study (HPS)	Placebo	<0.0001
Pravastatin	Cholesterol and Recurrent Events (CARE)	Placebo	0.029
	Longterm Intervention with Pravastatin in Ischemic Disease (LIPID)	Placebo	all-cause stroke = 0.0477 non-hemorrhagic stroke = 0.0154
Losartan	Losartan Intervention for Endpoint Reduction in Hypertension (LIFE)	Atenolol	0.001
Warfarin	Atrial Fibrillation, Aspirin and Anticoagulation (AFASAK)	Aspirin	0.027
	Stroke Prevention in Atrial Fibrillation (SPAF)	Aspirin	0.01
	Boston Area Anticoagulation for Atrial Fibrillation (BAATAF)	Control population could include aspirin	<0.05
	Stroke Prevention in Non-rheumatic Atrial Fibrillation (SPINAF)	Placebo	0.001
Aggrenox (dipyridamole aspirin combination)	European Stroke Prevention Study 2 (ESPS2)	Placebo	<0.001
	ESPS2	Aspirin	0.008
	ESPS2	Dipyridamole	0.002
Ticlodipine	Ticlopidine Aspirin Stroke Study (TASS)	Aspirin	0.011
	Canadian American Ticlopidine Study (CATS)	Placebo	0.017
Ramipril	Heart Outcomes Protection Evaluation (HOPE)	Placebo	0.0002

Naturally, one must keep in mind that all of these trials had different designs and study populations, and thus the p-values are not strictly comparable.

ASCOT-LLA, since a p-value of 0.033 is greater than the prespecified alpha level of 0.01.

inclusion of the stroke information in the "Clinical Studies" section of the label

6.1.9.2.3 Secondary Endpoint Results: Total Coronary Events

The composite endpoint, total coronary events, was composed of fatal CHD, nonfatal MI (silent and symptomatic), chronic stable angina, unstable angina, and fatal and nonfatal heart failure.

There was some risk reduction with atorvastatin [178 events (3.5%) vs 247 events (4.8%), HR 0.71, CI for HR 0.59-0.86, p value 0.0006)]. The individual components of the endpoint for which the confidence intervals for the unadjusted hazard ratio for atorvastatin vs. placebo did not include 1 were nonfatal MI (symptomatic and silent), and chronic stable angina. The reduction in risk for chronic stable angina did not meet the sponsor's predefined criterion for statistical significance, but came very close, as previously discussed. The confidence interval for the unadjusted hazard ratio for the atorvastatin group compared to the placebo group did include 1 for the other three individual components of this composite endpoint.

this composite endpoint was driven almost entirely by reduction in risk for nonfatal MI, with some contribution of reduction in risk for chronic stable angina.

previously discussed, the reduction in risk for the overall composite was driven by the reduction in the risk for symptomatic nonfatal myocardial infarction.

6.1.9.2.4 Additional Secondary Endpoint Results

There was no significant difference between groups for either all-cause mortality or cardiovascular mortality. However, the study was powered for the primary composite endpoint, and not for mortality. Neither of these mortality endpoints trended in an unfavorable direction.

For the composite of nonfatal MI (excluding silent MI) plus fatal CHD, the hazard ratio of 0.62 (p-value 0.0005, CI for the HR 0.47-0.81) favored atorvastatin over placebo. However, as above, individual component predefined statistical significance was achieved only for nonfatal symptomatic MI.

The difference between groups for development of fatal and nonfatal heart failure was not statistically significant by predefined criteria. Numerically, this endpoint slightly favored the placebo group, and is discussed in the safety review.

6.1.9.2.5 Tertiary Endpoint Results

ASCOT-LLA also predefined statistical significance for all tertiary endpoints as a p-value of <0.01.

As illustrated in the following table, no tertiary endpoints met the predefined criteria for statistical significance for a difference between atorvastatin and placebo. However, some degree of favorable risk reduction was noted for chronic stable angina (p = 0.014, CI 0.38-0.9, risk reduction 41%). Some degree of unfavorable risk increase was noted for life-threatening arrhythmias, with a higher rate among atorvastatin-treated patients than among placebo-treated patients, but this was not a statistically significant difference.

Table 6.1.9.2.5: Incidence of Tertiary Efficacy Endpoints

3° Efficacy Endpoints	Atorvastatin n (%)	Rate[a]	Placebo n (%)	Rate[a]	Unadjusted hazard ratio (95% CI)	p value
Silent MI	14 (0.3)	0.8	17 (0.3)	1.0	0.82 (0.40-1.66)	0.58236
Unstable Angina	21 (0.4)	1.3	24 (0.5)	1.5	0.87 (0.49-1.57)	0.64588
Chronic Stable Angina	33 (0.6)	2.0	56 (1.1)	3.4	0.59 (0.38-0.90)	0.01354
Peripheral Arterial Disease	42 (0.8)	2.5	41 (0.8)	2.5	1.02 (0.66-1.57)	0.92372
Life Threatening Arrhythmias	10 (0.2)	0.6	3 (0.1)	0.2	3.31 (0.91-12.02)	0.05387
Development of Diabetes Mellitus	154 (3.0)	9.4	133 (2.6)	8.2	1.15 (0.92-1.46)	0.22317
Development of Renal Impairment	31 (0.6)	1.9	24 (0.5)	1.5	1.29 (0.76-2.19)	0.35044

Source: Table 5.1, Section 13, Listing 5.1
[a]per 1000 patient-years

6.1.9.2.6 Lipid-altering Efficacy

The following sponsor's table compares the mean changes in TC, HDL, LDL and TG over time.

Table 6.1.9.2.6.: Change in Lipid Parameters over Time (from Sponsor's Table 5.3)

		Atorvastatin	Placebo
Lipid Parameter	Time Period	Number of Subjects (baseline mean or mean change)	
Total Cholesterol	Baseline	5134 (5.48)	5106 (5.48)
	6 months – baseline	4771 (-1.36)	4715 (-0.02)
	Year 1 – baseline	4705 (-1.32)	4642 (-0.03)
	Year 2 – baseline	4631 (-1.34)	4562 (-0.13)
	Year 3 – baseline	3891 (-1.31)	3875 (-0.22)
	Year 4 – baseline	1205 (-1.20)	1200 (-0.24)
HDL	Baseline	5134 (1.31)	5106 (1.31)
	6 months – baseline	4768 (-0.00)	4715 (-0.02)
	Year 1 – baseline	4705 (-0.01)	4642 (-0.03)
	Year 2 – baseline	4631 (-0.01)	4561 (-0.03)
	Year 3 – baseline	3891 (-0.01)	3875 (-0.03)
	Year 4 – baseline	1205 (0.02)	1200 (-0.00)
LDL-C	Baseline	4650 (3.44)	4619 (3.44)
	6 months – baseline	4128 (-1.24)	4053 (-0.01)
	Year 1 – baseline	4110 (-1.20)	4010 (-0.01)
	Year 2 – baseline	4071 (-1.21)	3980 (-0.08)
	Year 3 – baseline	3422 (-1.17)	3385 (-0.15)
	Year 4 – baseline	1059 (-1.07)	1052 (-0.17)
Triglycerides	Baseline	4713 (1.66)	4679 (1.65)
	6 months – baseline	4203 (-0.30)	4169 (0.03)
	Year 1 – baseline	4192 (-0.28)	4132 (0.00)
	Year 2 – baseline	4148 (-0.29)	4077 (-0.05)
	Year 3 – baseline	3486 (-0.34)	3468 (-0.11)
	Year 4 – baseline	1069 (-0.39)	1072 (-0.19)

Source: Table 5.3
Note: All laboratory measurements in mmol/l

Median changes in mg/dL, with 25th and 75th percentiles, from baseline after one year of atorvastatin, were as follows: Total cholesterol -54.05 mg/dL (-69.50, -34.75); LDL-C -49.03 mg/dL (-64.09, -32.43); TG -17.70 mg/dL (-53.10, +8.85); and HDL-C 0.00 mg/dL (-3.86, +3.86). Changes in all lipid parameters were statistically significantly more favorable for the atorvastatin group versus the placebo group at 6, 12 and 24, 36 and 48 months. The changes

(decreases) from baseline in total cholesterol, LDL-C and triglycerides in the atorvastatin compared to the placebo treatment group were significant from six months through four years ($p<0.0001$). Small, but statistically significant decreases in HDL occurred in both groups from six months to three years. This decline was slightly more marked in the placebo group than in the atorvastatin group. The degree of change in lipid parameters is similar to that previously described for Lipitor® 10 mg/day.

The following graphs illustrate the mean differences in lipid parameters between the atorvastatin and placebo groups, over the course of the study.

Figure 6.1.9.2.6.1: Mean LDL-C Over Time

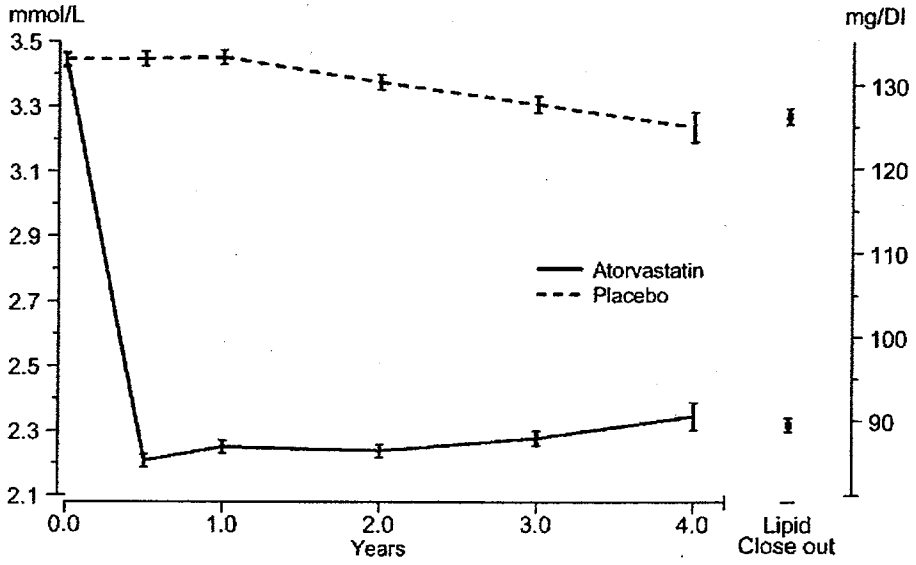


Figure 6.1.9.2.6.2: Mean Total Cholesterol Over Time

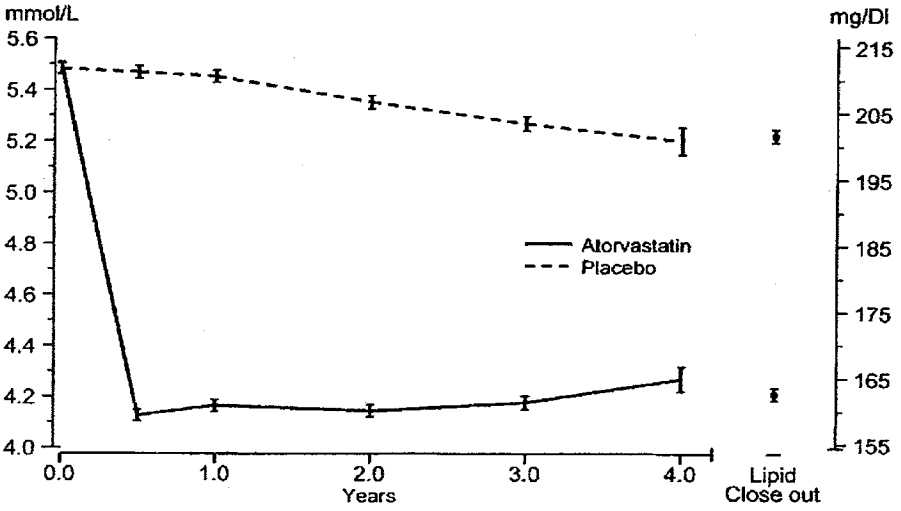


Figure 6.1.9.2.6.3: Mean Triglycerides Over Time

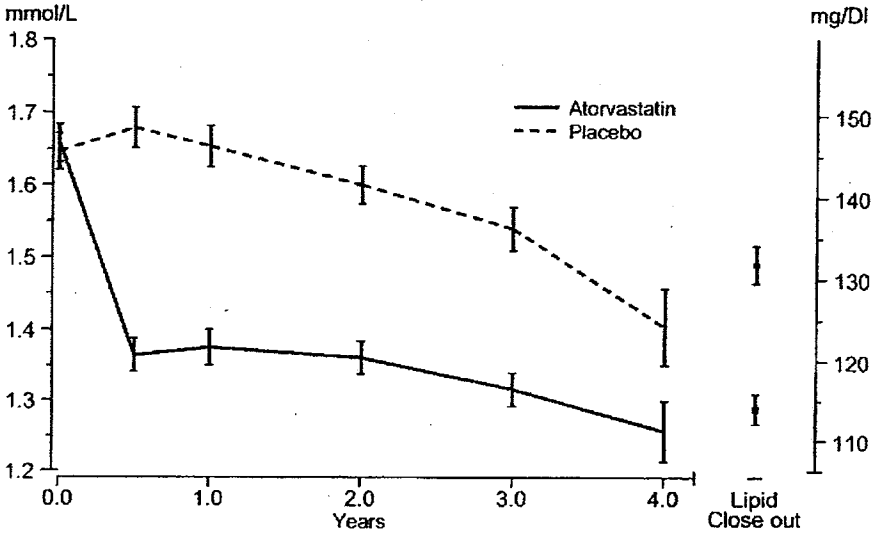
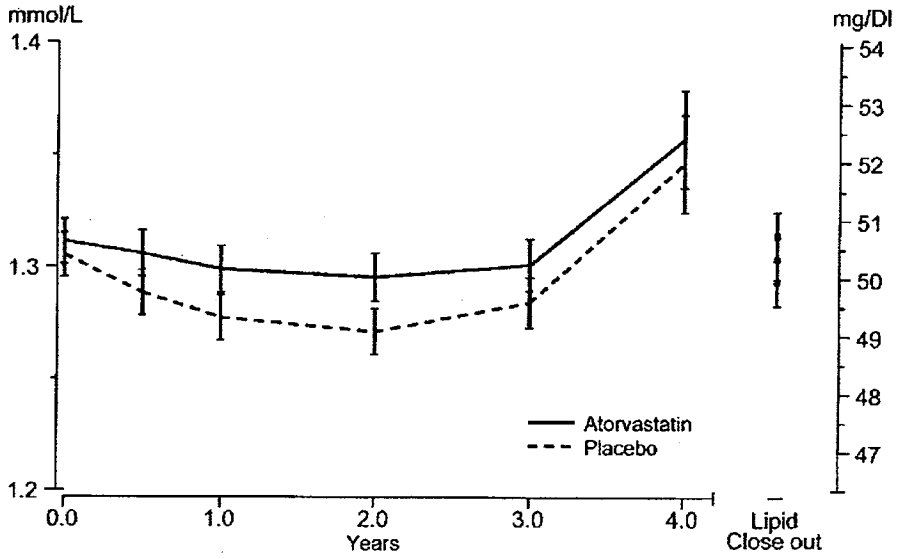


Figure 6.1.9.2.6.4: Mean HDL Over Time



6.1.10 Potentially Confounding Efficacy Factors

6.1.10.1 Blood Pressure Control

The sponsor reports that blood pressure was well-controlled and similar between treatment groups throughout the study. Blood pressure control, both systolic and diastolic, is illustrated in the following two graphs:

Figure 6.1.10.1.1: Systolic Blood Pressure Over Time

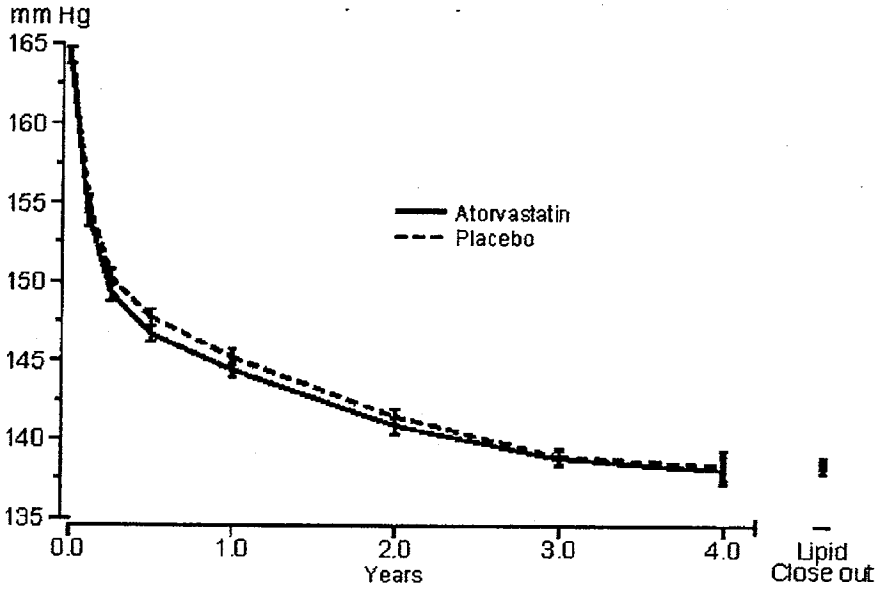
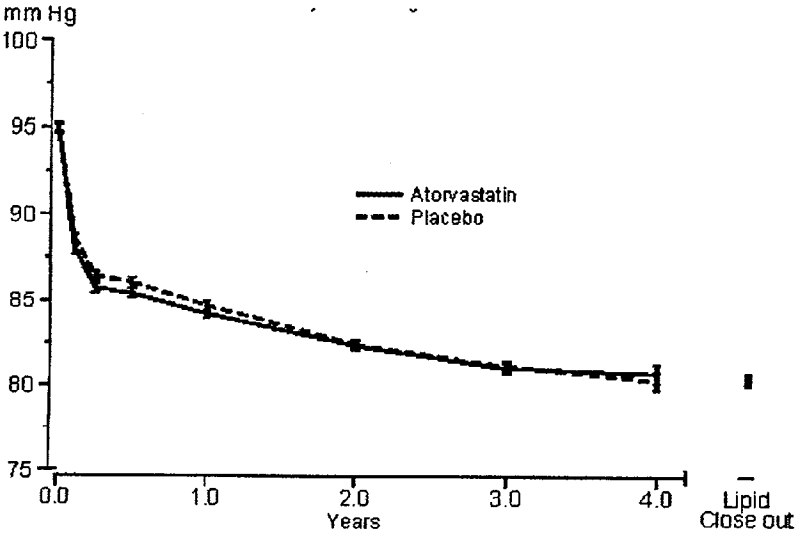


Figure 6.1.10.1.2: Change in Diastolic Blood Pressure Over Time



The following table shows the changes in blood pressure and heart rate observed over time.

Table 6.1.10.1.1: Mean Office Blood Pressure and Heart Rate (Sponsor's Table 5.2)

		Atorvastatin			Placebo			
Period	Variable	N	Mean	SD	N	Mean	SD	p-value*
Baseline	Sitting SBP	5134	164.24	17.74	5106	164.24	17.99	0.9990
	Sitting DBP	5134	94.93	10.31	5106	94.97	10.28	0.8285
	Heart Rate	5134	71.26	12.73	5106	71.81	12.61	0.0278
6 Months - Baseline	Sitting SBP	4967	-17.59	19.74	4902	-16.44	19.61	0.0037
	Sitting DBP	4967	-9.52	10.58	4902	-8.95	10.64	0.0080
	Heart Rate	4966	-5.00	14.06	4893	-5.05	13.84	0.8513
Year 1 - Baseline	Sitting SBP	4887	-19.71	19.63	4812	-19.02	20.20	0.0861
	Sitting DBP	4887	-10.73	10.44	4812	-10.31	10.73	0.0509
	Heart Rate	4880	-4.87	13.91	4799	-5.00	13.81	0.6372
Year 2 - Baseline	Sitting SBP	4758	-23.19	20.33	4692	-22.64	20.44	0.1923
	Sitting DBP	4758	-12.60	10.63	4692	-12.63	10.88	0.9165
	Heart Rate	4750	-5.17	13.86	4680	-5.53	13.75	0.1967
Year 3 - Baseline	Sitting SBP	4038	-25.34	20.41	3993	-25.35	20.45	0.9761
	Sitting DBP	4038	-14.19	10.89	3993	-14.26	10.85	0.7907
	Heart Rate	4029	-5.32	14.00	3984	-5.35	14.12	0.9136
Year 4 - Baseline	Sitting SBP	1258	-26.84	20.69	1271	-26.70	22.08	0.8688
	Sitting DBP	1258	-15.42	11.21	1271	-15.66	11.69	0.6040
	Heart Rate	1257	-5.14	14.28	1263	-5.11	14.51	0.9661

* p-value comes from two-sample t-tests

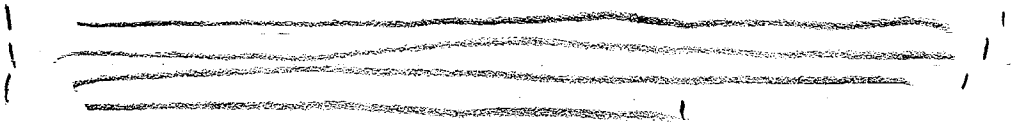
At six months, there was a small but statistically significantly greater reduction in mean systolic and diastolic blood pressures for the atorvastatin group vs. the placebo group. To a lesser degree, systolic blood pressure remained slightly lower in the atorvastatin group at years 1 and 2. It is possible that atorvastatin has some independent effect on blood pressure that may have contributed in part to the effect seen on cardiovascular events, or that there is an interaction between atorvastatin and one of the blood pressure regimens under study. However, the main ASCOT trial is still ongoing and blinded, and thus the contributions of the assigned antihypertensive agents cannot be analyzed.

6.1.11 Numbers Needed to Treat to Avoid Events

As illustrated in the following table, the number of patients needed to treat (NNTT) to prevent a single primary endpoint event is 89 for 3.3 years of treatment with atorvastatin.

Table 6.1.11: Numbers Needed to Treat to Prevent a Single Event

	At One Year	At 3.3 Years
Primary Endpoint	294	89
Total Cardiovascular Events and Procedures	154	47
Total Coronary Events	227	69



7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

Deaths that were classified by the DSMC as efficacy endpoints were not reported as serious adverse events (SAEs) by the sponsor. Because cardiovascular deaths were endpoints in the study, this analysis will focus on noncardiovascular deaths. Cardiovascular deaths were addressed in the efficacy analysis.

The sponsor reports that there was no increase in death from noncardiovascular causes or incidence of cancer with atorvastatin.

Reanalysis by the medical officer confirms this conclusion. Noncardiovascular deaths were coded as being due to cancer, respiratory, other noncardiovascular, or unknown causes. The following table by the medical officer summarizes these data:

Table 7.1.1: Noncardiovascular Causes of Death

Cause of Death	Atorvastatin (total n = 5134) n (% of arm)	Placebo (total n = 5106) n (% of arm)
Cancer	86 (1.7%)	90 (1.8%)
Respiratory	3 (0.06%)	3 (0.06%)
Other Noncardiovascular	25 (0.49%)	15 (0.29%)
Unknown	9 (0.18%)	11 (0.21%)
Total Noncardiovascular Deaths	123 (2.4%)	119 (2.3%)

The numbers of cancer and total noncardiovascular deaths were very similar between groups. A few more patients in the atorvastatin group (compared to the placebo group) died of "other noncardiovascular" causes. Review of these case report forms revealed a variety of etiologies of death, and no preponderance of any given cause of death in the atorvastatin group. On review of the case report forms, the medical officer found no evidence of miscoding of cause of death. However, most case report forms had little narrative due to the simplified remote data entry system used for the trial.

In conclusion, no evidence of a difference between the atorvastatin and placebo groups was identified in either numbers or causes of noncardiovascular deaths.

7.1.2 Other Serious Adverse Events

7.1.2.1 "Large Simple Trial" with Simplified Adverse Event Reporting

Per protocol, only serious adverse events (SAEs) were reported. SAEs included any experience, which was not a study endpoint, and which suggested a significant hazard. A significant hazard was defined as including events which:

- were life-threatening
- resulted in a persistent or significant disability/incapacity
- required inpatient hospitalization or prolongation of a hospital stay
- resulted in a congenital anomaly/birth defect, or
- required medical intervention to prevent any one of the above.

Significant hazards also included any additional adverse experience which the investigator considered serious.

SAEs were recorded in the ASCOT project database and were also reported to the Pfizer early alert safety database. The Pfizer database, which was used for this sNDA, contains cases of adverse events reported spontaneously to Pfizer, cases reported from health authorities, cases published in the medical literature and cases of serious adverse events reported from clinical

studies and Pfizer-sponsored marketing programs (solicited cases), regardless of causality. Events in the ASCOT project database were coded using the MEDRA coding dictionary, whereas events in the Pfizer early alert safety database were coded using WHOART. The ASCOT project database recorded only minimal data on the SAEs. Pfizer states that SAEs were followed in more detail in their database, and that these data were used to provide information for SAE narratives. Because of these differences in SAE database recording, some differences exist between the Pfizer sNDA safety report and the ASCOT publication for terminology and numbers of reported events.

Pfizer selected all cases with the following WHO Preferred Terms for special review:

- coma hepatic
- hepatic cirrhosis
- hepatic enzymes increased
- hepatic failure
- hepatic function abnormal
- hepatic necrosis
- hepatitis
- hepatocellular damage
- jaundice
- neuropathy
- muscle weakness
- myalgia
- myopathy
- myositis
- dyspnea

7.1.2.2 Total Numbers of Serious Adverse Events

A total of 21.3% of atorvastatin-treated patients and 23.2% of placebo-treated patients experienced serious adverse events (SAEs).

7.1.2.3 Serious Adverse Events of Greatest Frequency

Complete review of the sponsor's comprehensive SAE reporting did not reveal significant differences in reported adverse event rates between the atorvastatin and placebo groups. Adverse events occurring in the atorvastatin group did not differ from those seen in previous trials using atorvastatin.

The following two tables address SAEs occurring in >0.5% and >0.2% of study subjects, respectively.

Table 7.1.2.3.1: SAEs occurring in >0.5% of Patients

Event	Atorvastatin (%)	Placebo (%)
Chest Pain	0.8	1.2
Atrial fibrillation	0.7	0.9
Dyspnea NOS	0.4	0.6
Prostate cancer NOS	0.6	0.6
Arthralgia	0.5	0.7
Pneumonia NOS	0.5	0.6

Table 7.1.2.3.2: Serious Adverse Events Occurring in >0.2% of Subjects in Either Treatment Group

Body System/AE	Atorvastatin (N=5158)	Placebo (N=5124)
	number (%) of subjects	
Number (%) with SAEs	1099 (21.3)	1190 (23.2)
Blood and lymphatic system disorders	14 (0.3)	22 (0.4)
Anemia NOS	9 (0.2)	16 (0.3)
Cardiac disorders	95 (1.8)	95 (1.9)
Atrial fibrillation	35 (0.7)	44 (0.9)
Ear and labyrinth disorders	24 (0.5)	27 (0.5)
Vertigo	18 (0.3)	17 (0.3)
Eye disorders	22 (0.4)	21 (0.4)
Gastrointestinal disorders	181 (3.5)	170 (3.3)
Abdominal pain NOS	26 (0.5)	17 (0.3)
Diarrhea NOS	13 (0.3)	14 (0.3)
Inguinal hernia NOS	19 (0.4)	19 (0.4)
General disorders and administration site conditions	109 (2.1)	123 (2.4)
Chest pain	41 (0.8)	59 (1.2)
Fatigue	15 (0.3)	11 (0.2)
Hepatobiliary disorders	25 (0.5)	28 (0.5)
Infections and infestations	113 (2.2)	127 (2.5)
Pneumonia NOS	24 (0.5)	29 (0.6)
Urinary tract infection NOS	18 (0.3)	9 (0.2)
Injury, poisoning and procedural complications	75 (1.5)	107 (2.1)
Investigations	31 (0.6)	29 (0.6)

(Table continued on next page)

Table 7.1.2.3.2 (cont): Serious Adverse Events Occurring in >0.2% of Subjects in Either Treatment Group (Continuation of Table from Previous Page)

Body System/ AE	Atorvastatin (N = 5158)	Placebo (N = 5124)
Metabolism and nutrition disorders	15 (0.3)	23 (0.4)
Musculoskeletal and connective tissue disorders	145 (2.8)	166 (3.2)
Arthralgia	27 (0.5)	35 (0.7)
Back pain	20 (0.4)	18 (0.4)
Joint swelling	7 (0.1)	13 (0.3)
Localized osteoarthritis	19 (0.4)	22 (0.4)
Osteoarthritis NOS	7 (0.1)	18 (0.4)
Pain in limb	12 (0.2)	15 (0.3)
Neoplasms benign, malignant and unspecified	141 (2.7)	146 (2.8)
Prostate cancer NOS	29 (0.6)	31 (0.6)
Nervous system disorders	119 (2.3)	127 (2.5)
Dizziness	15 (0.3)	15 (0.3)
Syncope	19 (0.4)	20 (0.4)
Psychiatric disorders	11 (0.2)	32 (0.6)
Renal and urinary disorders	61 (1.2)	72 (1.4)
Hematuria	10 (0.2)	21 (0.4)
Reproductive system and breast disorders	38 (0.7)	37 (0.7)
Respiratory, thoracic and mediastinal disorders	78 (1.5)	96 (1.9)
Dyspnea NOS	19 (0.4)	31 (0.6)
Skin and subcutaneous tissue disorders	26 (0.5)	26 (0.5)
Surgical and medical procedures	79 (1.5)	83 (1.6)
Uncoded	3 (0.1)	14 (0.3)
Vascular disorders	56 (1.1)	70 (1.4)
Circulatory collapse	16 (0.3)	11 (0.2)

Source: Table 6.1
NOS=not otherwise specified

The table below summarizes SAEs by frequency.

Table 7.1.2.3.3: Serious Adverse Events by Frequency Occurring in >0.2% of Subjects in Either Treatment Group

Adverse Event	Atorvastatin (N=5158)		Placebo (N=5124)	
	number (%) of subjects			
Chest pain	41	(0.8)	59	(1.2)
Atrial fibrillation	35	(0.7)	44	(0.9)
Prostate cancer NOS	29	(0.6)	31	(0.6)
Arthralgia	27	(0.5)	35	(0.7)
Abdominal pain NOS	26	(0.5)	17	(0.3)
Pneumonia NOS	24	(0.5)	29	(0.6)
Back pain	20	(0.4)	18	(0.4)
Dyspnea NOS	19	(0.4)	31	(0.6)
Syncope	19	(0.4)	20	(0.4)
Localized osteoarthritis	19	(0.4)	22	(0.4)
Inguinal hernia NOS	19	(0.4)	19	(0.4)
Urinary tract infection NOS	18	(0.3)	9	(0.2)
Vertigo	18	(0.3)	17	(0.3)
Circulatory collapse	16	(0.3)	11	(0.2)
Dizziness	15	(0.3)	15	(0.3)
Fatigue	15	(0.3)	11	(0.2)
Diarrhea NOS	13	(0.3)	14	(0.3)
Pain in limb	12	(0.2)	15	(0.3)
Hematuria	10	(0.2)	21	(0.4)
Anemia NOS	9	(0.2)	16	(0.3)
Joint swelling	7	(0.1)	13	(0.3)
Osteoarthritis NOS	7	(0.1)	18	(0.4)
Deep vein thrombosis	6	(0.1)	15	(0.3)

Source: Table 6.1
NOS=not otherwise specified

Complete review of sponsor's comprehensive SAE reporting in the sponsor's Table 6.1 did not reveal any further significant differences in reported adverse event rates between the atorvastatin and placebo groups. Adverse events occurring in the atorvastatin group were no different from those seen in previous trials using atorvastatin.

7.1.2.4 Serious Adverse Events of Special Interest

Pfizer chose 5 categories of SAEs that they considered of special relevance for a statin. The incidence of these events is illustrated in the following table:

Table 7.1.2.4.0: SAEs of Special Interest for Statins (from Pfizer AEM Database)

	Atorvastatin (N=5158)		Placebo (N=5124)	
	N	(%)	N	(%)
Liver-related events	11	(0.21)	10	(0.20)
Rhabdomyolysis	2	(0.04)	0	(0.00)
Other muscle-related events	3	(0.06)	11	(0.21)
Neuropathy	10	(0.19)	4	(0.08)
Dyspnea	8	(0.14)	16	(0.31)

Source: Table 6.2

7.1.2.4.1 Liver-related Events

A total of 0.21% of atorvastatin-treated patients and 0.2% of placebo-treated patients experienced liver function test elevations. Pfizer reports that historically, 1.3% of patients treated with Lipitor have some type of liver function test abnormality, and 0.8% develop "clinically important" [>3x the upper limit of normal (uln)] liver function test elevations. These data are for patients receiving Lipitor® at doses under 80 mg/day.

For liver-related events, 8/11 atorvastatin group cases and 8/10 placebo group cases were considered not causally related to study drug by either the sponsor or the investigator. A history of alcohol abuse was the most common factor contributing to the development of liver abnormalities. History of alcohol abuse was not an exclusion criterion. The sponsor reports that in those cases where atorvastatin could not be excluded with certainty, liver function tests were <3x uln (where provided) and prodromal symptoms of hepatitis (e.g. malaise and loss of appetite) were present.

Brief details of the medical officer's review of the liver event cases are as follows:

Case [redacted]: 79 year old woman developed jaundice after >3 years on study drug. After drainage of a bile duct obstruction, jaundice resolved.

Case [redacted]: 59 year old man who developed jaundice after four years of study drug therapy. No other information was provided.

Case [redacted]: 76 year old man admitted with abdominal pain and "perturbated" liver enzymes on study day 1503. Patient had a 29 year history of recurring gallstones. Outcome not reported.

Case [redacted]: 73 year old man hospitalized after three months of study drug with jaundice; diagnosed with acute alcoholic steatohepatitis. Study drug held briefly, then resumed.

Case [redacted]: 62 year old woman admitted with urinary tract infection after four months on study drug. Found to have cirrhosis and history of chronic alcohol abuse. Died from anastomotic bleeding at site of iliac graft.

Case [redacted]: 66 year old man hospitalized for atrial fibrillation after two years on study drug. Developed alcohol withdrawal symptoms and elevated liver function tests (LFTs) (peak AST 263 U/L) while in hospital. Blinded therapy continued.

Case [redacted]: 48 year old man with twenty-year history of ulcerative colitis developed nausea, vomiting and jaundice on study day 672. Found to have bowel obstruction.

Case [redacted]: 75 year old man admitted for miliary tuberculosis after two years on study drug. Started pyrazinamide, and then developed elevated LFTs. Pyrazinamide stopped; study drug continued.

Case [redacted]: 74 year old man developed malaise and elevated liver function tests on Day 63 of study medication. ALT was 242 IU/L [normal (nl) <31], alkaline phosphatase was 156 IU/L and GGT was 440 IU/L (nl 7-32). The study was unblinded and atorvastatin was stopped. Concomitant medications included aspirin and azapropazone.

Case [redacted]: 76 year old woman hospitalized for pneumonia and abdominal pain on Day 542 of study medication. ALT was 139 IU/L, AST was 223 mmol/L (nl <40) and GGT was 120 mmol/l. She had a history of cholecystectomy prior to randomization. Abdominal sonogram during this hospitalization revealed a normal liver, pancreas and bile duct. The blind was broken and atorvastatin was discontinued. The day after admission, ALT was 77, AST was 39, and GGT was 72.

In the medical officer's review, most of these cases appeared to have a history of alcohol abuse or other significant additional reason for liver dysfunction. Three cases described above might be attributable to atorvastatin, but the incidence of clinical liver events in this trial did not exceed that seen with atorvastatin in prior studies.

7.1.2.4.2 Muscle-related Events

In this study, rhabdomyolysis was defined as muscle symptoms with markedly elevated (>10x uln) CPK level, and with elevated serum creatinine. The definition further added that brown urine and urinary myoglobin usually occur. Two cases of rhabdomyolysis were reported, both in the atorvastatin group. The sponsor reports that both patients recovered after "a few days" of hydration, and that both had contributing factors (excessive alcohol intake and concomitant simvastatin therapy). The patient on concomitant simvastatin therapy was not reported in the original publication of the ASCOT-LLA results, because the Data Safety Monitoring Committee

(DSMC) did not feel that this patient met the criteria for the diagnosis of rhabdomyolysis. However, Pfizer does include this patient in their adverse event reporting.

Brief details of the two cases of rhabdomyolysis are as follows:

Case [redacted] was a 67 year old woman who developed symptoms of gastroenteritis on day 1,152 of study medication. She was also receiving simvastatin, prescribed by her primary care physician. The simvastatin had been started about one year prior to the event, and about two years after she entered the study and was randomized to atorvastatin. She was admitted to the hospital and developed "symptoms of rhabdomyolysis", renal failure and myoglobinemia. Atorvastatin was stopped and her study antihypertensive therapy was temporarily stopped. Simvastatin was also stopped. With intravenous hydration, she recovered in four to five days.

Case [redacted] was a 56 year old man who was admitted to the hospital with weakness and fainting on Day 1,155 of study medication. He was a heavy drinker of alcohol. He was found to have elevated myoglobin and liver function tests, a CPK of 1,765 U/L, and acute renal failure. He was discharged after four days.

Both these cases have additional predisposing factors for rhabdomyolysis. The incidence of rhabdomyolysis did not exceed that seen with statin therapy in general.

Other muscle-related SAEs occurred in 4 atorvastatin-treated and 11 placebo patients. Pfizer reports that contributing etiologies included angina, embolism, pneumonia, disc disease, and anemia. In the medical officer's review of these additional "muscle-related" adverse event cases, none appear attributable to atorvastatin.

There were no cases of increased CPK reported as SAEs in either the placebo or atorvastatin group.

7.1.2.4.3 Neuropathy

Ten atorvastatin-treated and four placebo-treated patients had SAEs coded as neuropathy. Pfizer states that none were considered related to study treatment. A total of 6/10 atorvastatin-treated patients had a prior history relevant to the neuropathic event. One patient had an "anatomic rationale" for the event and one had a normal neurologic exam. All four of the placebo patients had a pre-existing condition or alternative etiology.

On medical officer review of the atorvastatin group neuropathy cases, six patients had a prior history of the same neurologic problem; two had nerve entrapment syndromes while on atorvastatin which were treated surgically; one had a nerve entrapment syndrome with onset seven months after discontinuation from atorvastatin; and one had only vague symptoms and a normal neurologic exam.

In this study, there did not appear to be a relationship between atorvastatin and neuropathy risk.

7.1.2.4.4 Dyspnea

Eight atorvastatin-treated and 16 placebo patients had dyspnea-related SAEs. The sponsor states that 7/8 atorvastatin-treated patients had an explanatory concomitant disease such as anemia, or a concurrent event such as angina. The remaining patient was obese; the sponsor states the patient may have had heart failure. In 13/16 of placebo-treated patients with dyspnea, no causality to drug was identified. Alternative etiologies in placebo patients included pre-existing lung disease, atrial fibrillation, coronary disease and infection.

On medical officer review of the atorvastatin group dyspnea cases, six patients had clear underlying explanations for dyspnea, and no temporal evidence of exacerbation by atorvastatin. Brief details of the remaining two cases are as follows:

Case [redacted] was a 71 year old woman with a history of chronic bronchitis who developed dyspnea after five days of study medication. Both study arms were discontinued.

Case [redacted] was an 80 year old man who developed shortness of breath and abdominal pain after two years of study drug. Past medical history included left ventricular hypertrophy, renal impairment and smoking. Study drug was not discontinued.

In this study, atorvastatin did not appear to contribute to an increased risk of dyspnea.

7.1.2.4.5 Dementia and Related Disorders

Although dementia was not targeted by the sponsor as a serious adverse event of special interest, recent anecdotal reports have led to concerns about a possible association between statin use and the development of dementia. The reviewer pulled all adverse event terms possibly related to dementia; the incidence of these events is summarized in the following table:

Table 7.1.2.4.5: Incidence of Dementia and Related Adverse Event Terms

Adverse Event Term	Atorvastatin (total n = 5158) # (%)	Placebo (total n = 5,124) # (%)
Amnesia	2 (0.04%)	2 (0.04%)
Amnestic Disorder NOS	0	1 (0.02%)
Cognitive Disorder	0	1 (0.02%)
Confusional State	0	10 (0.20%)
Dementia of the Alzheimer's Type NOS	1 (0.02%)	1 (0.02%)
Encephalopathy	1 (0.02%)	0
Memory Impairment	2 (0.04%)	2 (0.04%)
Neurological Symptoms NOS	1 (0.02%)	0
Senile Dementia NOS	1 (0.02%)	0
Vascular Dementia	0	2 (0.04%)
Total All Specific Dementia Terms	2 (0.04%)	3 (0.06%)
Total All Possibly Dementia-Related Terms	8 (0.16%)	18 (0.35%)

The rate of dementia and dementia-related serious adverse events was very low in both the atorvastatin and placebo groups; there is no evidence of an association between atorvastatin use and dementia in ASCOT-LLA.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall Profile of Dropouts

A total of 924 subjects (18%) were discontinued from the atorvastatin group, and 1,147 (22.5%) were discontinued from the placebo group.

Total discontinuations from study medication, including temporary discontinuations, are illustrated in the following table:

Table 7.1.3.1: Discontinuations From Study Medication (Sponsor's Table F)

Table F Discontinuations from Study Medication

	Atorvastatin (N=5168)	Placebo (N=5137)
	number (%) of subjects	
Number of treated subjects	5123 (99.1)	5087 (99.0)
Total discontinued	924 (18.0)	1147 (22.5)
Reason for discontinuation		
Insufficient clinical response	3 (0.1)	71 (1.4)
Adverse event	302 (5.9)	299 (5.9)
Laboratory abnormality(s)	11 (0.2)	18 (0.4)
Subject died	123 (2.4)	138 (2.7)
Protocol violation	15 (0.3)	22 (0.4)
Lost to follow-up	25 (0.5)	29 (0.6)
Other	209 (4.1)	317 (6.2)
Withdrew consent	151 (2.9)	163 (3.2)
Unknown	85 (1.7)	90 (1.8)

Source: Table 4.1
Note: % discontinued is calculated from number treated

A slightly larger percentage of placebo-treated subjects (compared to atorvastatin-treated subjects) were discontinued from the lipid-lowering portion of the study. Insufficient clinical response and study subject deaths accounted for a majority of the excess discontinuations in the placebo group. There was no clinically significant difference between groups for numbers of patients in each category of reasons given for discontinuation.

A total of 2.7% of atorvastatin-treated patients and 2.6% of placebo-treated patients permanently discontinued the study due to adverse events (AEs); specific reasons for discontinuation are discussed in section 7.1.3.2 below.

In addition to those subjects removed for SAEs, subjects were to be removed if they permanently stopped taking study medication without having a primary event. The sponsor reports that these subjects were followed to the end of the study if at all possible. The sponsor includes the following typical reasons for subjects' discontinuation of study medication:

- request of the subject
- investigator concern that subject's health was compromised due to adverse events or concomitant illness that developed after entering the study
- persistent uncooperativeness or violations of protocol requirements by subject.

7.1.3.2 Adverse Events Associated with Dropouts

A total of 0.3% (n=17) of atorvastatin-treated patients and 0.2% (n=9) of placebo-treated patients discontinued the study due to myalgia. Myalgia was defined as muscle ache or weakness

without elevated creatinine kinase. Myalgia was the only individual AE that led to discontinuation with a difference in incidence between the atorvastatin and placebo groups.

Table 7.1.3.2.1: Adverse Events Leading to Permanent Discontinuation Occurring in ≥ 0.2% of Subjects in Either Treatment Group

Body System/AE	Atorvastatin (N=5158)	Placebo (N=5124)
	number (%) of subjects	
Permanently Discontinued	138 (2.7)	132 (2.6)
Cardiac disorders	4 (0.1)	9 (0.2)
Gastrointestinal disorders	38 (0.7)	38 (0.7)
Diarrhea NOS	9 (0.2)	7 (0.1)
Dyspepsia	7 (0.1)	8 (0.2)
Nausea	8 (0.2)	10 (0.2)
General disorders and administration site conditions	22 (0.4)	21 (0.4)
Fatigue	9 (0.2)	8 (0.2)
Musculoskeletal and connective tissue disorders	37 (0.7)	23 (0.4)
Myalgia	17 (0.3)	9 (0.2)
Nervous system disorders	21 (0.4)	19 (0.4)
Headache	11 (0.2)	10 (0.2)
Psychiatric disorders	9 (0.2)	10 (0.2)
Reproductive system and breast disorders	8 (0.2)	7 (0.1)
Respiratory, thoracic and mediastinal disorders	10 (0.2)	9 (0.2)
Skin and subcutaneous tissue disorders	11 (0.2)	14 (0.3)

Source: Table 4.2
NOS = no other symptoms

Medical officer examination of all specific preferred terms for adverse events leading to discontinuation revealed little difference between groups. The following table (extracted from sponsor's full table 4.2) notes those events which were somewhat different between groups.

Table 7.1.3.2.2: Selected Specific Adverse Events Leading to Permanent Discontinuation

System Organ Class	Preferred Adverse Event Term	Atorva Grp (total n = 5158) n (%)	Pbo Grp (total n = 5124) n (%)
Gastrointestinal Disorders	All	38 (0.74%)	38 (0.74%)
	Flatulence	4 (0.08%)	0
Musculoskeletal and Connective Tissue Disorders	All	37 (0.72%)	23 (0.45%)
	Muscle Cramp	5 (0.10%)	1 (0.02%)
	Myalgia	17 (0.33%)	9 (0.18%)

Extraction (by the reviewer) of all potentially muscle-related terms from the total adverse event data revealed the following:

Table 7.1.3.2.3: Rates of Muscle-related Adverse Events Leading to Permanent Discontinuation

Event	Atorvastatin (total = 5123) n (%)	Placebo (total = 5087) n (%)
Muscle Cramp	5 (0.10%)	1 (0.02%)
Myalgia	17 (0.33%)	9 (0.18%)
Muscle Weakness	1 (0.02%)	3 (0.06%)
Musculoskeletal Discomfort	0	1 (0.02%)
Musculoskeletal Stiffness	1 (0.02%)	0
Myalgia Aggravated	1 (0.02%)	0
Rhabdomyolysis	2 (0.04%)	0
All Muscle-Related Discontinuations	27 (0.53%)	15 (0.29%)

Rates of discontinuation due to any potentially muscle-related event were low in both the atorvastatin and placebo groups. Although there were slightly more muscle-related discontinuations in the atorvastatin group, this cannot be deemed significant due to the very low overall rate.

There were 11 discontinuations due to laboratory test abnormalities in the atorvastatin group and 18 in the placebo group; no atorvastatin-associated discontinuation event laboratory abnormality occurred with significant frequency.

7.1.3.3 Other Significant Adverse Events

7.1.3.3.1 Heart Failure

In the sponsor's subgroup analyses (sponsor's Table 5.4), for most of the cardiovascular efficacy endpoints, the unadjusted hazard ratio was <1 when comparing the efficacy of atorvastatin vs placebo. Please see Section 6 for details of these efficacy parameters. For one category, fatal and nonfatal heart failure, the hazard ratio exceeded 1 for most (12/18) of the subgroups, i.e. the HR did not favor atorvastatin. However, confidence intervals for all these hazard ratios crossed 1, and thus the significance of this observation is uncertain.

The following abbreviated table details the hazard ratios for fatal and nonfatal heart failure among prespecified subgroups:

Table 7.1.3.3.1: Fatal and Nonfatal Heart Failure in Subgroup Analyses (From Sponsor's Table 5.4)

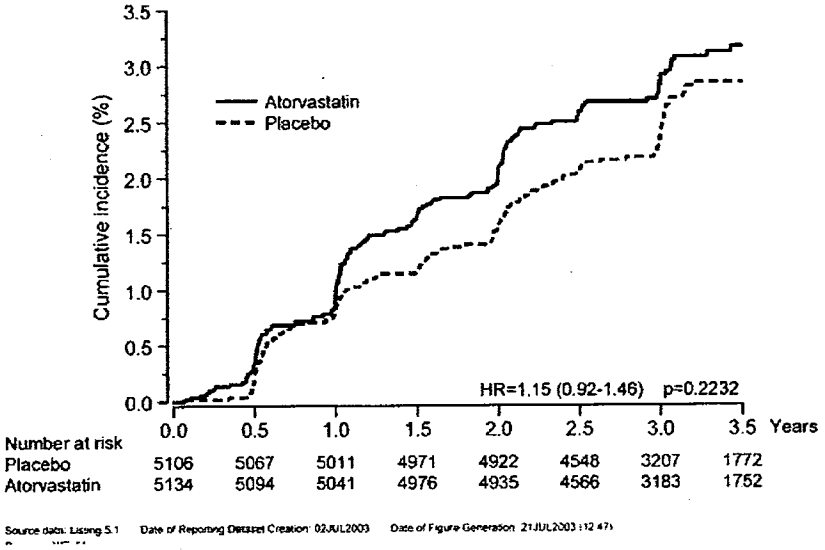
Subgroup (n in subgroup)	Atorvastatin n/(% of subgroup)	Placebo n/(% of subgroup)	Unadjusted HR	95% CI for HR	p-value
Diabetics (2526)	17 (1.4%)	14 (1.1%)	1.24	0.61-2.52	0.54690
Non-diabetics (7714)	24 (0.6%)	22 (0.6%)	1.08	0.61-1.93	0.79418
Current Smokers (3359)	12 (0.7%)	8 (0.5%)	1.45	0.59-3.55	0.41282
"Non-Current" Smokers (6881)	29 (0.8%)	28 (0.8%)	1.05	0.62-1.76	0.85830
Obese (3407)	18 (1.1%)	20 (1.2%)	0.9	0.48-1.71	0.75649
Non-obese (6833)	23 (0.7%)	16 (0.5%)	1.43	0.75-2.7	0.27139
LVH (1466)	7 (0.9%)	9 (1.2%)	0.76	0.28-2.05	0.59106
No LVH (8774)	34 (0.8%)	27 (0.6%)	1.26	0.76-2.09	0.36719
Age > 60 Years (6556)	39 (1.2%)	32 (1.0%)	1.22	0.77-1.95	0.40176
Age ≤ 60 Years (3684)	2 (0.1%)	4 (0.2%)	0.49	0.09-2.68	0.40259
Female (1919)	5 (0.5%)	6 (0.6%)	0.83	0.25-2.73	0.76192
Male (8321)	36 (0.9%)	30 (0.7%)	1.2	0.74-1.94	0.46435
Previous Vascular Disease (1469)	10 (1.4%)	10 (1.4%)	1.01	0.42-2.43	0.97642
No Previous Vascular Disease (8771)	31 (0.7%)	26 (0.6%)	1.19	0.71-2	0.51428
Renal Dysfunction (6454)	25 (0.8%)	26 (0.8%)	0.96	0.55-1.66	0.87482
No Renal Dysfunction (3786)	16 (0.8%)	10 (0.5%)	1.6	0.73-0.53	0.23717
With Metabolic Syndrome (3913)	18 (0.9%)	19 (1.0%)	0.94	0.05-1.8	0.85992
Without Metabolic Syndrome (6327)	23 (0.7%)	17 (0.5%)	1.35	0.71-2.53	0.34655

Overall, the medical officer does not feel there is significant evidence of an increased risk for the development of heart failure with atorvastatin.

7.1.3.3.2 Development of Diabetes Mellitus

A slightly larger percentage of patients in the atorvastatin group developed diabetes during the course of the study, although the difference did not achieve statistical significance.
The following Kaplan-Meier plot by the sponsor illustrates this difference:

Figure 7.1.3.3.2: Kaplan-Meier Plot of Development of Diabetes Mellitus



Number at risk								
Placebo	5106	5067	5011	4971	4922	4548	3207	1772
Atorvastatin	5134	5094	5041	4976	4935	4566	3183	1752

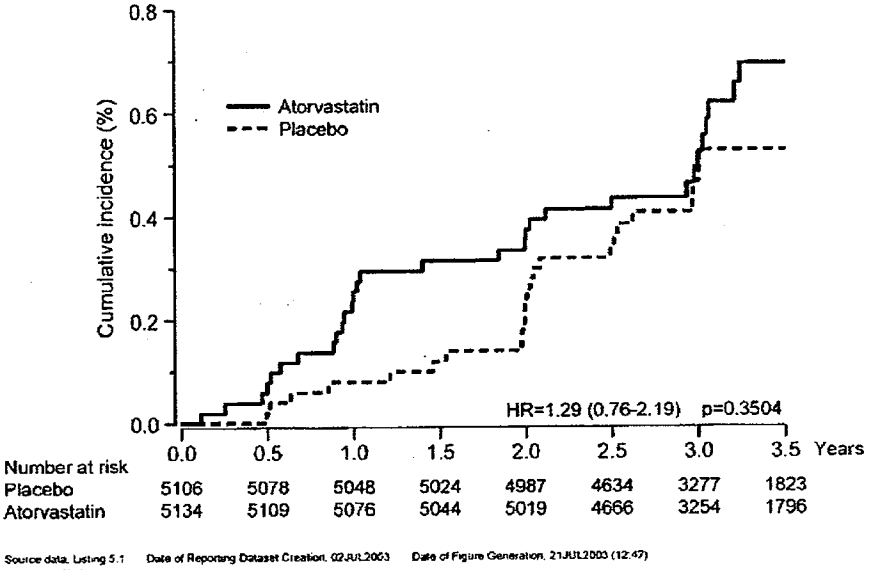
Source data: Listing 5.1 Date of Reporting Dataset Creation: 02JUL2003 Date of Figure Generation: 21JUL2003 12:47

At 12 months, there was a small statistically significant difference in mean blood sugar change, slightly favoring the placebo group. However, this difference (mean % increase of 0.26% for the atorvastatin group vs 0.16% for the placebo group) is too small to have likely clinical significance. Overall, the differences in mean blood glucose and incidence of new diabetes are unlikely to be of clinical consequence.

7.1.3.3.3 Development of Renal Impairment

A slightly larger percentage of patients in the atorvastatin group developed renal impairment when compared to the placebo group. However, this difference did not reach statistical significance. The following Kaplan-Meier plot illustrates this difference:

Figure 7.1.3.3.3: Kaplan-Meier Plot of Development of Renal Impairment



Source data, Listing 5.1 Date of Reporting Dataset Creation: 02JUL2003 Date of Figure Generation: 21JUL2003 (12:47)

The development of renal failure was a tertiary efficacy endpoint, and therefore the above analysis was conducted on the efficacy population.

Because of this finding, the clinical reviewer examined all renal and urinary adverse events. Per protocol (and supported by a waiver from FDA), efficacy endpoints were not to be doubly reported as adverse events; renal failure was a tertiary endpoint. If one includes all reported renal and urinary events, both of structure and function, 61 (1.2%) of the patients in the atorvastatin and 72 (1.4%) of those in the placebo group developed any of these events. Those events potentially related to renal failure are summarized by the clinical reviewer in the following table. As defined in the protocol, patients could enter the study with proteinuria as one of their risk factors for cardiovascular disease. Therefore, this table includes only the new development of proteinuria.

Table 7.1.3.3.3: Incidence of Renal and Urinary Events

Event Term	Atorvastatin Group (total n = 5158) n (%)	Placebo Group (total n = 5124) n (%)
Albuminuria	0	1 (0.02%)
Bladder Obstruction	0	2 (0.04%)
Bladder Stenosis	0	1 (0.02%)
Calculus Bladder	2 (0.04%)	0
Calculus Ureteric	0	3 (0.06%)
Calculus Urinary	4 (0.08%)	5 (0.10%)
Dysuria	2 (0.04%)	3 (0.06%)
Enuresis	0	1 (0.02%)
Hematuria	10 (0.19%)	21 (0.41%)
Incontinence NOS	0	1 (0.02%)
Microalbuminuria	1 (0.02%)	0
Micturition Urgency	0	1 (0.02%)
Nephritis NOS	1 (0.02%)	0
Nephrolithiasis	7 (0.14%)	4 (0.08%)
Nephropathy	0	1 (0.02%)
Nocturia	3 (0.06%)	2 (0.04%)
Proteinuria	0	2 (0.04%)
Renal Artery Stenosis	1 (0.02%)	1 (0.02%)
Renal Colic	1 (0.02%)	1 (0.02%)
Renal Disorder NOS	0	2 (0.04%)
Renal Impairment NOS	1 (0.02%)	2 (0.04%)
Urethral Hemorrhage	1 (0.02%)	0
Urethral Obstruction	2 (0.04%)	0
Urethral Stricture	0	1 (0.02%)
Urinary Incontinence	5 (0.10%)	2 (0.04%)
Urinary Retention	6 (0.12%)	11 (0.21%)
Urinary Tract Disorder NOS	0	1 (0.02%)
Urinary Tract Obstruction	1 (0.02%)	0
Urine Flow Decreased	0	1 (0.02%)
Total Urinary Events of Possible Relevance to Renal Failure	48 (0.93%)	70 (1.4%)
All Urinary Calculus Events	13 (0.25%)	12 (0.23%)
All Proteinuria Events	1 (0.02%)	3 (0.06%)
All Urinary Obstruction Events	10 (0.19%)	16 (0.31%)
All Urinary Incontinence Events	5 (0.10%)	3 (0.06%)

The degree of difference in incidence of new renal failure noted in the tertiary efficacy endpoint analysis is unlikely to be of clinical significance. Analysis of all other renal and urinary adverse event data did not reveal a concern for atorvastatin-associated renal adverse events. Overall, renal and urinary adverse events occurred numerically somewhat more frequently in the placebo group. One specific event which occurred more frequently in the placebo group was hematuria, as above, but the incidence of all individual renal and urinary adverse events was low.

7.1.4 Other Search Strategies

A review of the medical literature published since completion of ASCOT-LLA revealed no evidence of previously undescribed safety concerns for atorvastatin and drugs of the statin class.

7.1.5 Common Adverse Events

In design of ASCOT-LLA, the study group sought to simplify the trial design where possible. As part of this, the protocol specified that only serious adverse events were to be reported. Therefore, no information on common nonserious adverse events was documented. See section 7.1.2.3 for SAEs of greatest frequency.

7.1.6 Less Common Adverse Events

See section 7.1.2.4 for SAEs of special interest for atorvastatin.

7.1.7 Laboratory Findings

Per the study group's goal of a simplified trial design, the trial primarily examined liver function tests (LFTs) and glucose. Serum creatine phosphokinase levels (CPKs) were not routinely done, and were assessed only if subjects had new unexplained muscle pain or weakness. Bilirubin was tested only in the U.K. All UK study subjects' labs were analyzed by [redacted] in Dublin, and all Scandinavian subjects' labs were analyzed by [redacted]. Per protocol, quality assurance testing was routinely performed to assure comparability of results from the two labs.

A total of 1015 (21.4%) of atorvastatin-treated patients and 951 (20.3%) of placebo patients had laboratory abnormalities that met the sponsor's criteria for clinical significance during the study. The incidence of those laboratory abnormalities predefined to be of interest are summarized in the following table:

Table 7.1.7: Incidence of Laboratory Test Abnormalities (Without Regard to Baseline Abnormality)

		Atorvastatin (N=4734)	Placebo (N=4678)
Parameter	Criteria	n/N (%)	
Total bilirubin	>1.5 x ULN	121/2173 (5.6)	78/2141 (3.6)
ALT	>3.0 x ULN	39/4669 (0.8)	64/4607 (1.4)
CPK	>2.0 x ULN	1/39 (2.6)	1/31 (3.2)
Blood sugar	<0.6 x LLN	69/4700 (1.5)	60/4644 (1.3)
	>1.5.0 x ULN	822/4700 (17.5)	787/4644 (16.9)

Source: Table 7.1

For total bilirubin, 5.6% of atorvastatin-treated and 3.6% of placebo patients had levels >1.5x uln. Median bilirubin changes from baseline to last observation for the total patients in each group were 0.15 mg/dL (25^{th} and 75^{th} percentiles -0.01 and 0.314) for the atorvastatin group, and 0.09 mg/dL (25^{th} and 75^{th} percentiles -0.05 and 0.232) for the placebo group. This difference is unlikely to be of clinical significance.

For serum alanine aminotransferase, (ALT), 0.8% of atorvastatin-treated and 1.4% of placebo patients had a value >3x uln. Median ALT changes from baseline to last observation for the total patients in each group were zero for the atorvastatin group and -1.5 IU/L for the placebo group. Detailed descriptions of the discontinuation rules for ALT and CPK abnormalities may be found on page 43 of the study report. The difference between groups is unlikely to be of clinical significance. The incidence of ALT increases of >3x uln is not higher than previously described for atorvastatin.

The incidence of reported abnormalities in CPK was similar between the atorvastatin and placebo groups.

A large percentage of laboratory abnormalities were related to diabetes. A total of 24.6% of patients had diabetes at baseline; 287 developed diabetes during the study. Development of diabetes was a tertiary endpoint. At 12 months, there was a small statistically significant difference in mean blood sugar change, slightly favoring the placebo group. However, this difference (mean % increase of 0.26% for the atorvastatin group vs 0.16% for the placebo group) is too small to have likely clinical significance.

Mean serum creatinine did not change significantly, and was not different between groups.

There were 11 discontinuations due to laboratory test abnormalities in the atorvastatin group and 18 in the placebo group.

7.1.8 Vital Signs

Systolic and diastolic blood pressure, and heart rate, were the only routinely measured vital signs in ASCOT-LLA. The following table compares vital sign parameters for the atorvastatin and placebo groups from baseline to year four:

Table 7.1.8: Change in Blood Pressure and Heart Rate over Time

AML-MY-96-008: Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)
Change in Mean Office Blood Pressure & Heart Rate Over Time
All Subjects Excluding Centers 10244 and 10247.

Page 1 of 1

		Atorvastatin			Placebo			
Period	Variable	N	Mean	SD	N	Mean	SD	p-value*
Baseline	Sitting SBP	5134	164.24	17.74	5106	164.24	17.99	0.9990
	Sitting DBP	5134	94.93	10.31	5106	94.97	10.28	0.8285
	Heart Rate	5134	71.26	12.73	5106	71.81	12.61	0.0278
6 Months - Baseline	Sitting SBP	4967	-17.59	19.74	4902	-16.44	19.61	0.0037
	Sitting DBP	4967	-9.52	10.58	4902	-8.95	10.64	0.0080
	Heart Rate	4966	-5.00	14.06	4893	-5.05	13.84	0.8513
Year 1 - Baseline	Sitting SBP	4887	-19.71	19.63	4812	-19.02	20.20	0.0861
	Sitting DBP	4887	-10.73	10.44	4812	-10.31	10.73	0.0509
	Heart Rate	4886	-4.87	13.91	4799	-5.00	13.81	0.6372
Year 2 - Baseline	Sitting SBP	4758	-23.19	20.33	4692	-22.64	20.44	0.1923
	Sitting DBP	4758	-12.60	10.63	4692	-12.63	10.88	0.9165
	Heart Rate	4750	-5.17	13.86	4680	-5.53	13.75	0.1987
Year 3 - Baseline	Sitting SBP	4038	-25.34	20.41	3993	-25.35	20.45	0.9761
	Sitting DBP	4038	-14.19	10.89	3993	-14.26	10.85	0.7907
	Heart Rate	4029	-5.32	14.00	3984	-5.35	14.12	0.9136
Year 4 - Baseline	Sitting SBP	1258	-26.84	20.69	1271	-26.70	22.08	0.8688
	Sitting DBP	1258	-15.42	11.21	1271	-15.68	11.69	0.6040
	Heart Rate	1257	-5.14	14.28	1263	-5.11	14.51	0.9661

* p-value comes from two-sample t-tests
Source Data: Listing 5.2 Date of Reporting Dataset Creation: 02JUL2003 Date of Table Generation: 02JUL2003 (18:34)
Program: XTab52.sas

There is no evidence of a difference between groups that would present a safety concern for the atorvastatin group. Please see section 6.1.10 for a discussion of the possible efficacy implications of the slightly lower systolic blood pressures seen in the atorvastatin group at 6 months, one year and two years.

7.1.9 Electrocardiograms (ECGs)

Analysis of the effect of atorvastatin on specific intervals of the ECG was not conducted for ASCOT-LLA. The occurrence of life-threatening arrhythmias was an endpoint, and there was no significant difference between atorvastatin and placebo for this endpoint.

7.1.10 Immunogenicity

No new information regarding immunogenicity was included with this efficacy supplement.

7.1.11 Human Carcinogenicity

No new carcinogenicity information was included with this efficacy supplement.

7.1.12 Special Safety Studies

No special safety studies were done for this efficacy supplement.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no evidence in the medical literature or the Adverse Event Reporting System of abuse potential of atorvastatin. Physical symptoms of withdrawal have not been described. There is limited evidence of rapid occurrence of endothelial dysfunction after withdrawal of atorvastatin and other statins (60, 61).

7.1.14 Human Reproduction and Pregnancy Data

Atorvastatin is in Pregnancy Category X; no new information regarding human reproductive risk was included in this efficacy supplement.

7.1.15 Assessment of Effect on Growth

Not applicable

7.1.16 Overdose Experience

No new information regarding overdose experience was included with this efficacy supplement. There are no reports of atorvastatin overdosage in a medical literature search conducted 11 May 04. In the AERS database, there are 14 reports of non-accidental overdose of atorvastatin, usually in combination with other drugs. One of these patients developed rhabdomyolysis, and two developed hepatic failure.

7.1.17 Postmarketing Experience

After introduction of Lipitor®, the following adverse events were added to the label: rhabdomyolysis, anaphylaxis, angioneurotic edema, and bullous rashes. A review of the AERS database does not reveal substantial evidence for the need for addition of other adverse event data at this time.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

ASCOT-LLA was adequately powered for its intended composite primary efficacy endpoint. However, the early cessation of the trial for reasons other than a mortality difference led to limitations in the interpretability of the overall efficacy effect of atorvastatin on cardiovascular

events. The trial did provide a large placebo-controlled setting in which to further examine the safety of atorvastatin.

Some limitations exist on the interpretation of adverse event information. Because of the study group's efforts at simplified trial design, non-serious AEs were not recorded unless they led to study discontinuation. The sponsor obtained a waiver from the FDA that allowed the reporting of endpoints to the endpoint committee and not as adverse events. Overall, however, the trial size and design provided adequate reassurance of no new serious safety concerns for atorvastatin.

7.2.1.1 Worldwide Exposure Since Initial Approval of Atorvastatin

The sponsor reports that over / billion tablets of Lipitor had been sold worldwide as of March 31, 2002, and that over / million patient years of treatment have occurred with the drug.

7.2.1.2 Atorvastatin Exposure in ASCOT-LLA

The breakdown of subject evaluation groups is illustrated in the following table:

Table 7.2.1.2: Evaluation Groups

Evaluation Groups:

Subject Evaluation Groups

	Atorvastatin	Placebo	Total
	number of subjects (%)		
Randomized to lipid-lowering portion of study	5168 (100.0)	5137 (100.0)	10305 (100.0)
Treated	5123 (99.1)	5087 (99.0)	10210 (99.1)
Completed study[a]	4292 (83.0)	4043 (78.7)	8335 (80.9)
Discontinued study treatment	831 (16.1)	1044 (20.3)	1875 (18.2)
Analyzed for safety			
Adverse events	5158 (99.8)	5124 (99.7)	10282 (99.8)
Laboratory data	5056 (97.8)	4997 (97.3)	10053 (97.6)

Source: Table 1.1
[a]on lipid-lowering medication October 2002 or when they died

Although 1875 subjects were discontinued from study treatment, all subjects were included in the efficacy analysis based on last known information. At the time the DSMC decided to stop the trial, vital status was available on all but 17 subjects in the lipid-lowering arm. Overall, 5158/5168 (99.8%) of the atorvastatin-treated patients were evaluable for adverse events. 5124/5137 (99.9%) of the placebo-treated patients were evaluable for adverse events.

Maximum duration of treatment in the atorvastatin group was 4.6 yrs; median was 3.08 yrs. Maximum duration of treatment in the placebo group was 4.6 yrs; median was 3.05 yrs. The majority of subjects in the atorvastatin and placebo treatment groups received between two and three years of therapy [1606/5123 (31.3%) and 1553/5087 (30.5%) subjects respectively] or three

to four years of therapy [2415/5123 (47.1%) and 2307/5087 (45.4%) subjects respectively] (source sponsor's table 3.1).

The study subject exposure to atorvastatin was adequate in ASCOT-LLA for the reviewer to reach accurate conclusions regarding serious adverse event risk, with the possible exception of very rarely occurring events.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

See section 4.1

7.2.3 Adequacy of Overall Clinical Experience

ASCOT-LLA was adequately powered for its intended composite primary efficacy endpoint. However, the early cessation of the trial for reasons other than a mortality difference led to limitations in the interpretability of the overall efficacy effect of atorvastatin on cardiovascular events. The trial did provide a large placebo-controlled setting in which to further examine the safety of atorvastatin.

Some limitations exist on the interpretation of adverse event information. Because of the study group's efforts at simplified trial design, non-serious AEs were not recorded unless they led to study discontinuation. The sponsor obtained a waiver from the FDA that allowed the reporting of endpoints to the endpoint committee and not as adverse events. Overall, however, the trial size and design provided adequate reassurance of no new serious safety concerns for atorvastatin.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No new animal or in vitro data were submitted with this sNDA.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing for ASCOT-LLA is described in section 6.1.3, and was adequate for this large simple trial.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No new information in this area was submitted for this efficacy supplement.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

This efficacy supplement did not involve a new drug.

7.2.8 Assessment of Quality and Completeness of Data

The trial design was simplified by the study group in order to facilitate manageability of this very large trial population. Completeness of data was facilitated by a simplified, computerized, remote data entry system. Endpoint and adverse event information was obtained for over 99% of study participants. The study coordinators and the sponsor included multiple provisions for enhancement of data quality, completeness and integrity.

7.2.9 Additional Submissions, Including Safety Update

Not applicable

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Adverse events identified in ASCOT-LLA are expected for the drug class of statins, and are adequately covered in the current Lipitor® label. Salient safety points include the following:

- The proportion of subjects discontinuing treatment because of AEs was similar for the atorvastatin (138/5158; 2.7%) and placebo (132/5124; 2.6%) groups.
- The only individual AE that led to discontinuation with a difference between the atorvastatin and placebo groups was myalgia [17 (0.3%) and 9 (0.2%), respectively].
- The proportion of subjects experiencing SAEs was similar for the atorvastatin (21.3%) and placebo (23.2%) groups.
- The most common SAEs, with respective incidences for the atorvastatin and placebo groups, were: chest pain (0.8% vs 1.2%), atrial fibrillation (0.7% vs 0.9%), dyspnea NOS (0.4% vs 0.6%), prostate cancer NOS (0.6 % vs 0.6%), arthralgia (0.5% vs 0.7%), abdominal pain NOS (0.5% vs 0.3%), and pneumonia (0.5% vs 0.6%).
- A slightly larger proportion of study subjects in the atorvastatin group developed heart failure, diabetes, or renal impairment, but the difference between the atorvastatin and placebo groups was not statistically or clinically significant.
- The proportion of subjects with total bilirubin >1.5x uln was slightly larger in the atorvastatin (5.6%) than in the placebo (3.6%) group.
- The proportion of subjects with ALT >1.5x uln was larger in the placebo (1.4%) than in the atorvastatin (0.8%) group, but the incidence in the atorvastatin group was not higher than that described in previous studies with atorvastatin.

No new safety labeling related to ASCOT-LLA appears necessary.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Only one study was included in this efficacy supplement.

7.4.2 Explorations for Predictive Factors

No new information was revealed in ASCOT-LLA regarding factors which could be predictive of risk for adverse events related to atorvastatin.

7.4.3 Causality Determination

Causality related to atorvastatin is likely for the two reported cases of rhabdomyolysis in ASCOT-LLA, but both patients had a significant underlying predisposing factor for rhabdomyolysis. The overall incidence of rhabdomyolysis in this trial is no higher than that previously described with previous experience with atorvastatin and other statins. For other adverse events occurring in this trial, causal association to atorvastatin cannot be assigned.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

This trial used only the lowest commercially available dose of atorvastatin, 10 mg. It is likely that the beneficial effect of atorvastatin on reduction of risk for cardiac events would also be conferred upon patients who require higher doses in order to achieve National Cholesterol Education Program LDL-C goals.

8.2 Drug-Drug Interactions

No new drug-drug interaction information was submitted with this efficacy supplement.

Atorvastatin can interact negatively with other CYP3A4-metabolized drugs. Cyclosporine co-administration results in an increased risk of rhabdomyolysis (44). Other CYP3A4 drugs likely to cause adverse interactions include fibrates, erythromycin (42), ethinyl estradiol (11) and conazole antifungals (43). Grapefruit juice appears to decrease metabolism of atorvastatin (40). Digoxin levels may be increased with co-administration of 80 mg atorvastatin (41). No interaction has been demonstrated with warfarin (36).

8.3 Special Populations

ASCOT-LLA was not powered to look at differences within population subgroups.
The sponsor's heterogeneity analysis asserted that all of the population subgroups studied benefited from atorvastatin.

8.3.1 Gender

The study population was 18.7% female. A total of 14.2% of primary endpoint events occurred in females [19 (2%) in the atorvastatin group and 17 (1.8%) in the placebo group]. The

unadjusted hazard ratio for occurrence of the primary endpoint in females is 1.11 (CI 0.58-2.13, p = 0.75803).

For female study subjects (n = 1919), prespecified criteria for statistical significance for a difference between the atorvastatin and placebo groups were not met for any cardiovascular endpoint.

Among men (n = 8321), prespecified criteria for statistical significance favoring the atorvastatin group were met for nonfatal MI (excluding silent MI) + fatal CHD (HR 0.59, CI 0.44-0.77, p 0.00011), total cardiovascular events and procedures (HR 0.79, CI 0.69-0.92, p 0.00208), total coronary events (HR 0.69, CI 0.56-0.85, p 0.00047), and nonfatal MI (including silent MI) + fatal CHD (HR 0.56, CI 0.42-0.76, p = 0.00011).

Ms. Mele of Biostatistics performed a test for interaction regarding the subgroup analysis for gender, which revealed a significant interaction for the female subgroup, as discussed in section 6.1.9. However, event rates were low; the evidence for efficacy for the primary endpoint for women is inconclusive.

8.3.2 Age

For the primary endpoint, the HR for subjects older than 60 years was 0.64 (95% CI 0.47-0.86); for those age 60 years or younger, the HR was 0.67, but 95% confidence intervals ranged from 0.42-1.07.

For study subjects > age 60 years at entry (n = 6556), prespecified criteria for statistical significance favoring the atorvastatin group were met for nonfatal MI (including silent MI) + fatal CHD (HR 0.64, CI 0.47-0.86, p = 0.00264), total cardiovascular events and procedures (HR 0.79, CI 0.57-0.92, p = 0.00269), and nonfatal MI (excluding silent MI) + fatal CHD (HR 0.63, CI 0.46-0.86, p = 0.00397).

For study subjects ≤ age 60 years at entry (n = 3684), prespecified criteria for statistical significance for a difference between the study groups were not met for any cardiovascular endpoint.

ASCOT-LLA did not specifically demonstrate efficacy of atorvastatin in reduction of risk of cardiovascular events in persons ≤ age 60, but the study was not powered to look at age differences. A test for interaction was nonsignificant.

8.3.3 Race

As illustrated in the following table, the overwhelming majority of study subjects in ASCOT-LLA were classified as White/Europid. There are insufficient numbers of other racial groups to conduct a meaningful analysis for differences in safety or efficacy.

Table 8.3.3: Age and Race Demography

	Atorvastatin			Placebo		
	Male	Female	Total	Male	Female	Total
Number of Subjects	4189	979	5168	4174	963	5137
Age (years):						
≤60 (N,%)	1537 (36.7)	345 (35.2)	1882 (36.4)	1555 (37.3)	298 (30.9)	1853 (36.1)
>60 (N,%)	2652 (63.3)	634 (64.8)	3286 (63.6)	2619 (62.7)	665 (69.1)	3284 (63.9)
Mean ± SD	63.0 ± 8.6	63.5 ± 8.3	63.1 ± 8.5	63.0 ± 8.6	64.3 ± 8.2	63.2 ± 8.6
Range	40.1-80.0	40.1-80.0	40.1-80.0	40.1-79.9	40.9-79.8	40.1-79.9
Race: n (%)						
African	119 (2.8)	27 (2.8)	146 (2.8)	99 (2.4)	26 (2.7)	125 (2.4)
Mixed/Other	41 (1.0)	18 (1.8)	59 (1.1)	54 (1.3)	12 (1.2)	66 (1.3)
Oriental	3 (0.1)	1 (0.1)	4 (0.1)	3 (0.1)	0	3 (0.1)
South Asian	64 (1.5)	6 (0.6)	70 (1.4)	70 (1.7)	10 (1.0)	80 (1.6)
White/Europid	3962 (94.6)	927 (94.7)	4889 (94.6)	3948 (94.6)	915 (95.0)	4863 (94.7)

8.4 Pediatrics

ASCOT-LLA was conducted only in adults.

8.5 Advisory Committee Meeting

No Advisory Committee meeting occurred for this efficacy supplement.

8.6 Literature Review

Pfizer reports that they used different data processing algorithms than the ASCOT steering committee, and therefore the results reported in this sNDA will not exactly match those in the primary Lancet publication (1). These differences are minor and did not alter efficacy conclusions. The sponsor was actually somewhat more inclusive in its serious adverse event analysis than was the study group, thus increasing the likelihood of accurate safety conclusions. For example, the study group acknowledged only one case of rhabdomyolysis, but the sponsor felt that a second subject in the atorvastatin group met criteria for rhabdomyolysis.

Relevant portions of the literature review conducted for this application appear in appropriate sections of the review. The literature review did not reveal any new areas of safety concern for atorvastatin, and did not call into question the efficacy conclusions reached through review of this application.

8.7 Postmarketing Risk Management Plan

None submitted.

8.8 Other Relevant Materials

Labeling for all other approved lipid-lowering agents, and for all agents with indications for reduction of risk [redacted] was also reviewed. This review was conducted for historical background for the indications sought, and to seek a fair and consistent approach to this application.

9 OVERALL ASSESSMENT

9.1 Conclusions

In ASCOT-LLA, atorvastatin was associated with a 36%, statistically significant, reduction in risk for a composite primary endpoint of nonfatal myocardial infarction (symptomatic and silent) and fatal coronary heart disease. Among the components of this primary endpoint, only the reduction in risk for nonfatal symptomatic myocardial infarction was individually statistically significant.

[redacted] cardiovascular mortality, nonfatal myocardial infarction (silent and symptomatic), unstable angina, chronic stable angina, life-threatening arrhythmias, nonfatal congestive heart failure, nonfatal stroke, peripheral arterial disease, revascularization procedures and retinal vascular thromboses. [redacted] statistical significance favored the atorvastatin group were nonfatal symptomatic myocardial infarction and revascularization procedures, although chronic stable angina came very close.

[redacted] fatal coronary heart disease, nonfatal symptomatic myocardial infarction, chronic stable angina, unstable angina and congestive heart failure (fatal and nonfatal). [redacted] statistical significance was nonfatal symptomatic myocardial infarction.

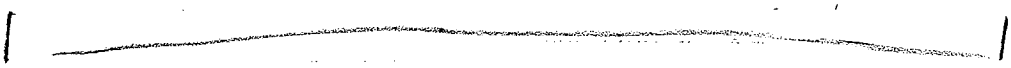
[redacted] fatal and nonfatal stroke, the predefined criterion for statistical significance (alpha 0.01) was not met for favoring atorvastatin over placebo, although there were numerically fewer strokes in the atorvastatin group with a p-value of 0.033 [redacted]

The clinical reviewer recommends additions to the Lipitor® label of indications for reduction of risk for myocardial infarction, revascularization procedures and angina. / [redacted] /

No new safety issues for atorvastatin were identified in ASCOT-LLA.

9.2 Recommendation on Regulatory Action

Add indications for reduction in risk for [redacted] myocardial infarction, revascularization procedures and [redacted] angina.



9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

None recommended in relation to ASCOT-LLA.

9.3.2 Required Phase 4 Commitments

None recommended in relation to ASCOT-LLA.

9.3.3 Other Phase 4 Requests

The sponsor is required to submit the study report for the ongoing parent hypertension trial, ASCOT, after that trial is completed. The Division wishes to review the report to look for any possible efficacy interaction between atorvastatin and either of the blood pressure treatment regimens, and to evaluate whether the results of the 2x2 factorial analysis alter the conclusions reached through ASCOT-LLA.

9.4 Labeling Review

The sponsor's proposed changes and the Medical Officer's suggested revisions are organized by the sections of the label in which proposed changes appear. The medical officers comments are in *italics*. At the time of finalization of this review, labeling negotiations were essentially complete; however, minor changes may occur, and one should refer to the final label attached to the approval letter.

A. Changes in CLINICAL PHARMACOLOGY Section

1. Mechanism of Action Section

Although discussion occurred regarding the possibility of removing only

2. Clinical Studies Section

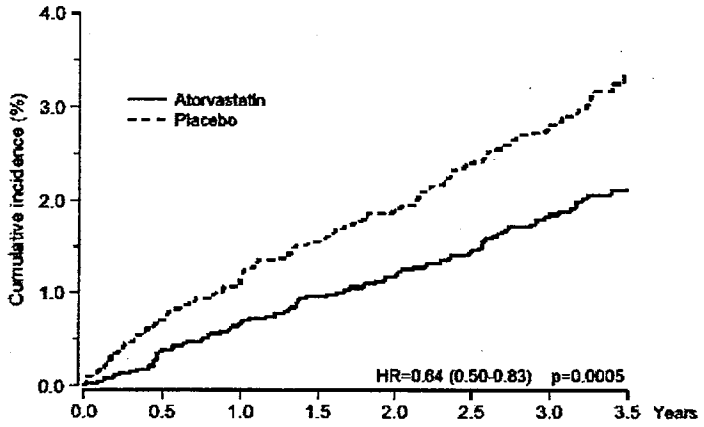
a. The sponsor proposed insertion of the following text and figure at the beginning of the Clinical Studies section:

"Prevention of Cardiovascular Disease

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of LIPITOR (atorvastatin calcium) on fatal and nonfatal coronary heart disease was assessed in 10,305 hypertensive patients 40 years of age, without a previous myocardial infarction and with TC levels <251 mg/dl (6.5 mmol/l). Additionally all patients had at least 3 of the cardiovascular risk factors [male gender (81.1%), age >55 years (84.5%), smoking (33.2%), diabetes (24.3%), history of CHD in a first-degree relative (26%), TC:HDL >6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypertrophy (14.4%), prior cerebrovascular event (9.8%), specific ECG abnormality (14.3%), proteinuria/albuminuria (6.24%)]. In this , double-blind, placebo-controlled study patients were treated with anti-hypertensive therapy (Goal BP <140/90 mm Hg for non-diabetic patients, <130/80 mm Hg for diabetic patients) and either LIPITOR 10 mg daily (n=5168) or placebo (n=5137)

LIPITOR significantly reduced the rate of coronary events (either fatal coronary heart disease 36% p=0.0005 (see Figure 1)]. The risk reduction was consistent regardless of age, smoking status, obesity, presence renal dysfunction

Figure 1



LIPITOR also significantly decreased the risk for [redacted] revascularization procedures by [redacted] There was no [redacted]

The Division and the sponsor agreed on the following changes:

In the first paragraph, first sentence, correct the upper age limit for the study to read "80" years instead of [redacted]". Add "(mean age of 63 years)" after "40-80 years of age".

In the first paragraph, second sentence, change the word [redacted] "following", and precede the listed risk factors with a colon. Correct the incidence of proteinuria/albuminuria from "6.24%" to "62.4%".

In the first paragraph, third sentence, address the issue of use of statistical minimisation [redacted] by changing the sentence to read, in two sentences, as follows:

"In this double-blind, placebo-controlled study, patients were treated with antihypertensive therapy (Goal BP <140/90 mm HG for nondiabetic patients, <130/80 mm Hg for diabetic patients) and allocated to either LIPITOR 10 mg daily (n = 5168) or placebo (n = 5137), using a covariate adaptive method which took into account the distribution of fourteen baseline characteristics of patients already enrolled and miminized the imbalance of those characteristics across the groups. Patients were followed for a median duration of 3.3 years."

[redacted] *A sentence is added in a later section of the label stating that the risk reduction was seen regardless of baseline LDL levels.*

[redacted] and substitute the following sentence: "The effect of 10 mg/day of LIPITOR on lipid levels was similar to that seen in previous clinical trials." The proposed second paragraph presented a confusing amount of information [redacted], as are commonly used. This could mislead readers, and there is no need for the information, as lipid changes in this trial were similar to that seen with atorvastatin 10 mg/day in other trials.

In the third paragraph several changes were agreed upon in order to clarify that atorvastatin [redacted] atorvastatin The [redacted], as this analysis was clearly added post-hoc, and the definition was inadequate. The recommended paragraph now reads:
"LIPITOR significantly reduced the rate of coronary events [either fatal coronary heart disease (46 events in the placebo group vs 40 events in the LIPITOR group) or nonfatal MI (108 events in the placebo group vs 60 events in the LIPITOR group)]. Relative risk reduction was 36% (based on incidences of 1.9% for LIPITOR vs 3.0% for placebo), p = 0.0005 (see Figure 1). The risk reduction was consistent regardless of age, smoking status, obesity or presence of renal dysfunction. The effect of LIPITOR was seen regardless of baseline LDL levels. Due to the small number of events, the results for women were inconclusive."

Above the figure, add a title: "Effect of LIPITOR 10 mg/day on Cumulative Incidence of Nonfatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT-LLA)"

In the fourth paragraph, language regarding reduction in risk [redacted] That paragraph now reads:
"LIPITOR also significantly decreased the relative risk for revascularization procedures by 42% [redacted] Although the reduction of fatal and nonfatal strokes did not reach a predefined level of significance of 0.01, a favorable trend was observed with a 26% relative risk reduction (incidences of 1.7% for LIPITOR and 2.3% for placebo). There was no significant difference between the treatment groups for death due to cardiovascular causes (p=0.51) or noncardiovascular causes (p=0.17)."

B. Changes in INDICATIONS AND USAGE Section

1. The sponsor proposed adding the following at the beginning of the section:

"Prevention of Cardiovascular Disease
[redacted]

- Reduce the risk of [redacted] myocardial infarction
- Reduce the risk of [redacted]

The sponsor and the Division have agreed to the following revisions intended to [redacted] LIPITOR was shown to [redacted] The new indications now read:

"In adult patients without clinically evident heart disease, but with multiple risk factors for coronary heart disease such as age ≥ 55 years, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, Lipitor is indicated to:

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

2. The sponsor then proposed placing the heading "*Hypercholesterolemia*" at the beginning of the rest of the INDICATIONS AND USAGE section.

Concur.

C. Changes in the ADVERSE EVENTS Section

In the Clinical Adverse Experiences section, immediately after table 7, the sponsor proposed the following added paragraph:

"Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)
In ASCOT (see CLINICAL PHARMACOLOGY, Clinical Studies) involving 10,305 participants treated with Lipitor 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with Lipitor was comparable to that of the group treated with placebo during a median of 3.3 years of followup."

The sponsor does not propose changes to Table 7, entitled "Adverse Events in Placebo-controlled Studies".

Concur

9.5 Comments to Applicant

No additional comments.

10 APPENDICES

10.1 Review of Individual Study Reports

Because this sNDA was based on a single study, detailed review was included in the main body of this document.

10.2 Description of Allocation of Patients to Treatment in ASCOT

Assignment of patients to treatment was handled separately for Great Britain (UK) and Scandinavia (SC) as outlined in the table below. For Scandinavia, there was a restriction that within each center the difference between number of subjects allocated to placebo and active treatment could not differ more than two. For both Scandinavia and the UK, there was a restriction that within each center, the difference between number of subjects allocated to placebo and active treatment could not differ more than eight.

In both the UK and SC, the first 8 patients in each center were randomized to treatment using block randomization. If there were more than 8 patients in a center, patients were generally assigned to treatment using a minimisation procedure (the last row of Table 10.2.1). There was a separate algorithm table for assignment to antihypertensive therapy and to lipid-lowering therapy.

Table 10.2.1: Applicant's Summary of the Allocation Scheme Used for the Lipid Arms of ASCOT

Overview of the outcome of the randomisation procedure in the lipid arm of the ASCOT study.

	Number of randomised patients		
	UK	Scandinavia	Total
Block-randomisation	251	224	**475**
Forced to lipid-group due to centre limits. Only Scandinavia, difference <= 2	-	1154	**1154**
Forced to lipid-group due to Region* limits. Difference <= 8.	642	362	**1004**
Optimal allocation: maximal T-values are equal and lipid-group are randomly select	8	5	**13**
Optimal allocation: maximal T-values are not equal and patient are forced to the lipid group that minimise the maximal T-value	3952	3707	**7659**
Total	**4853**	**5452**	**10305**

In UK, 81% are assigned using the minimisation algorithm while in Scandinavia the percentage was 68%.

The minimisation procedure was used to assign patients to treatment balancing on the following 14 variables:

Table 10.2.2: Variables Used in Minimisation Procedure

Variable	Will be balanced for
Race	Proportions of White/Europid and African/Oriental/South Asian/Mixed/Other
Other EKG	Proportions of Yes and No
LVH	Proportions of Yes and No
NIDDM	Proportions of Yes and No
Vascular	Proportions of Yes and No
Cerebrovascular	Proportions of Yes and No
Gender	Proportions of Male and Female
Age	Mean and proportions in the intervals: 40-49 year, 50-59 year, 60-69 year and 70-79 year
Microalb and protein	Proportions of positive and not positive
Mean SBP	Mean
Antihypertensive med	Proportions of Yes and No
Total Cholesterol	Mean and proportions in the intervals: >6.5 and <=6.5
Smoking habits	Proportions of Current smoker, Previous smoker and Never smoked
BMI	Mean

Extracted from Section 11 item 7.1 of the applicant's study report

The procedure was carried out at each study center that enrolled nine or more study subjects. Briefly, it worked as follows. For a given study subject, an assumption was first made that the subject would be allocated to treatment A (e.g. atorvastatin). A predesigned Visual Basic code was used to calculate a maximum t-value for those of the above 14 variables that had a pooled variance > zero. The same procedure was then done assuming that the subject would be assigned to treatment B (e.g. placebo). The subject was then randomized to the treatment that minimized the maximal t-value. If the two maximal t-values were the same, the treatment was randomly selected.

10.3 Line-by-Line Labeling Review

See section 9.4

10.4 References

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/s/

Karen Mahoney
7/30/04 11:14:15 AM
MEDICAL OFFICER

Dr. Colman please sign for Drs. Orloff and Parks

Joy Mele
7/30/04 11:53:26 AM
BIOMETRICS

Eric Colman
7/30/04 12:03:59 PM
MEDICAL OFFICER
Eric Colman for Mary Parks

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-702 /S039

CHEMISTRY REVIEW(S)

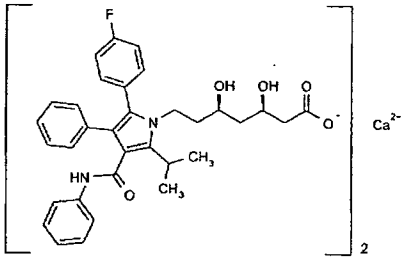
CHEMIST'S REVIEW

1. Organization CDE/HFD-510 Division Of Metabolism And Endocrine Drug Products	**2. NDA #** 20-702 Approved: 17-Dec-1996
3. Name and Address of Applicant Pfizer Ireland Pharmaceuticals[1] Pottery Road Dun Laoghaire County Dublin Ireland	**4. Supplement** SE1-039 Doc. 30-SEP-2003 **5. Name of the Drug** Lipitor Tablets **6. Nonproprietary Name** Atorvastatin Calcium
7. Supplement provides for the use of Lipitor in the prevention of cardiovascular disease in patients without clinically evident coronary heart disease	**8. Amendment** --

9. Pharmacological Category Lipid Modifier. HMG-CoA reductase inhibitor/ Antihyperlipoproteinemic agent.	**10. How Dispensed** Rx	**11. Related** -N. A.-
12. Dosage Form Tablet	**13. Potency** 10-, 20-, 40- and 80-mg	

14. Chemical Name and Structure
Atorvastatin Calcium

$(C_{33}H_{34}FN_2O_5)_2Ca$
FW = 2 x 557.7 + 40.0 = 1155.38 (anhydrous calcium salt)
CAS 134523-03-8
CAS 134523-00-5 (atorvastatin)
FW free acid $C_{33}H_{34}FN_2O_5$ = 558.66
FW calcium salt trihydrate $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$ = 1209.42



[*R*-(*R**,*R**)]-2-(4-flourophenyl)-ß, -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrole-1-heptanoic acid calcium salt (2:1)

15. Comments: This efficacy supplement provides for the use of Lipitor for the prevention of cardiovascular disease in patients without clinically evident coronary heart disease. The new indication is based on the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) lipid lowering arm results. Lipitor is proposed to be used in patients without clinically evident coronary heart disease, for the following indications: (1) To reduce the risk of [redacted] myocardial infarction, (2) To reduce the risk [redacted] and [redacted] Neither the drug substance nor the drug product has been changed. A waiver request of the requirement for an assessment of environmental impact (AEI) is provided in module 1 section 1.4.8. The applicant does not anticipate an increase in the use of active moiety as consequence of this action. To the best of their knowledge, no extraordinary circumstances exist. The waiver request for the AEI is deemed appropriate (21 CFR §25.31(b)) and granted. *Acceptable.*

16. Conclusions and Recommendations: There are no CMC changes in both drug substance and drug product. **From the chemistry viewpoint this supplement can be approved.**

17. Reviewer Name (and Signature) **Date Completed** 24-NOV-2003

Xavier Ysern, PhD

R/D Initialed by

Stephen Moore, PhD
Chemist Team Leader

filename: /nda/20702s39.doc

AP

[1] **Authorized USA Agent:** Pfizer Inc., 235 East 42nd Street, 2800 Plymouth Road, New York, NY 10017 phone: (212) 733-4394

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/s/

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Stephen Moore
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-702/S039

PHARMACOLOGY REVIEW(S)

NDA 20-702/S039
Lipitor (atorvastatin)
Pfizer

11/3/03

This supplement includes clinical outcome data from ASCOT a primary prevention study designed to evaluate separate and combined effects of blood pressure lowering and lipid lowering in patients with hypertension, 3 or more CV risk factors and normal or slightly elevated cholesterol levels. New nonclinical data has not been submitted for review. The efficacy data contained in this clinical study is not expected to alter the maximum recommended clinical dose and therefore the pharmacology/toxicology sections of the label are not affected. A pharmacology/toxicology review is not needed.

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Karen Davis-Bruno
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PHARMACOLOGIST
clinical efficacy suppl., P/T NN

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-702/S039

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

MEMO TO FILE 11/19/03

From: Hae-Young Ahn, Ph.D.

To: NDA 20-702 Supplement 39
Lipitor® (Atorvastatin Calcium) Tablets

This submission is based on the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) lipid lowering arm results and for the support of a new indication for the prevention of cardiovascular disease in patients without clinically evident coronary heart disease.

There is no new information submitted in the section of clinical pharmacology and biopharmaceutics and therefore no review will be done.

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/s/

Hae-Young Ahn
11/19/03 03:54:48 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-702/S039

ENVIRONMENTAL ASSESSMENT

ENVIRONMENTAL ASSESSMENT

Lipitor® Tablets
Supplement to NDA 20-702
Labeling Change

Claim for Categorical Exclusion According to 21 CFR Part 25.15 (a),(d)

Pfizer Inc claims a categorical exclusion to the environmental assessment requirements in compliance with categorical exclusion criteria 21 CFR Part 25.31 (a) applicable for action on a supplement to an NDA when the action does not increase the use of the active moiety. Pfizer Inc claims that to our knowledge, no extraordinary circumstances exist.

Preparers:

Jon F. Ericson, Project Leader, Environmental Sciences, Chemical Research and Development, Groton Laboratories, Pfizer Global Research and Development. Analytical Chemist with M.S. and 17 years experience in drug metabolism and environmental science.

Richard T. Williams, Ph.D., Assistant Director, Environmental Sciences, Chemical Research and Development, Groton Laboratories, Pfizer Global Research and Development. Ph.D. in Microbiology / Ecology with 20 years of experience in environmental science, including 11 years experience within Chemical Research and Development.

The undersigned person states that (1) the action requested qualifies for a categorical exclusion and meets categorical exclusion criteria 21 CFR 25.31 (a), and (2) to Pfizer Inc's knowledge, no extraordinary circumstance exist.

Name: Richard T. Williams, Ph.D.

Title: Assistant Director; Environmental Sciences

Department:
Chemical Research and Development

Pfizer Global Research and Development,
Chemical Research and Development
Groton, CT 06340

Signature for Richard T Williams PhD

07-Aug-2003
Date

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-702/S039

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

1.4.1 PATENT AND EXCLUSIVITY INFORMATION

Pfizer claims three (3) years of exclusivity for the changes approved under this sNDA, pursuant to 21 U.S.C. § 314.108(b)(5). In support of this claim, Pfizer certifies that: (a) it sponsored the investigations included in this supplement; (b) those investigations meet the definition of "new clinical investigation" set forth in 21 U.S.C. § 314.108(a); and (c) those investigations are "essential to approval" of the supplement because to the best of Pfizer's knowledge no independent studies or reports support the conditions of use for which Pfizer is seeking approval in this sNDA, without reference to the submitted investigations.

1.4.2 PATENT CERTIFICATION

This section is included by cross-reference to NDA 20-702.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

NDA NUMBER: 20-702

NAME OF APPLICANT / NDA HOLDER: Pfizer Ireland Pharmaceuticals

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME): Lipitor

ACTIVE INGREDIENT(S)	STRENGTH(S)
Atorvastatin calcium: atorvastatin; atorvastatin anion	10mg, 20mg, 40mg, 80mg

DOSAGE FORM: Tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
4,681,893	July 21, 1987	Sept. 24, 2009

d. Name of Patent Owner	Address *(of Patent Owner)*	
Warner-Lambert Co. LLC. a wholly-owned subsidiary of Pfizer Inc	235 East 42nd Street	
	City/State: New York, NY	
	ZIP Code: 10017	FAX Number *(if available)*: 212-573-1939
	Telephone Number: 212-733-7805	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2 Claim Number (*as listed in the patent*)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Peter C. Richardson	August 13, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name: **Peter C. Richardson**	
Address: **235 East 42nd Street**	City/State: **New York, NY**
ZIP Code: **10017**	Telephone Number: **212-573-7805**
FAX Number *(if available)*: **212-573-1939**	E-Mail Address *(if available)*

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

NDA NUMBER: 20-702

NAME OF APPLICANT / NDA HOLDER: Pfizer Ireland Pharmaceuticals

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME): Lipitor

ACTIVE INGREDIENT(S)	STRENGTH(S)
Atorvastatin calcium: atorvastatin; atorvastatin anion	10mg, 20mg, 40mg, 80mg

DOSAGE FORM: Tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,686,104	Nov. 11, 1997	Nov. 11, 2014

d. Name of Patent Owner	Address *(of Patent Owner)*	
Warner-Lambert Co. LLC. a wholly-owned subsidiary of Pfizer Inc	235 East 42nd Street	
	City/State: New York, NY	
	ZIP Code: 10017	FAX Number *(if available)*: 212-573-1939
	Telephone Number: 212-733-7805	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2 Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Peter C. Richardson	August 13, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name: **Peter C. Richardson**	
Address: **235 East 42nd Street**	City/State: **New York, NY**
ZIP Code: **10017**	Telephone Number: **212-573-7805**
FAX Number *(if available)*: **212-573-1939**	E-Mail Address *(if available)*:

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER: 20-702

NAME OF APPLICANT / NDA HOLDER: Pfizer Ireland Pharmaceuticals

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME): Lipitor

ACTIVE INGREDIENT(S)	STRENGTH(S)
Atorvastatin calcium: atorvastatin; atorvastatin anion	10mg, 20mg, 40mg, 80mg

DOSAGE FORM: Tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,969,156	Oct. 19, 1999	July 8, 2016

d. Name of Patent Owner: Warner-Lambert Co. LLC. a wholly-owned subsidiary of Pfizer Inc

Address *(of Patent Owner)*: 235 East 42nd Street

City/State: New York, NY

ZIP Code: 10017

FAX Number *(if available)*: 212-573-1939

Telephone Number: 212-733-7805

E-Mail Address *(if available)*:

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address *(of agent or representative named in 1.e.)*:

City/State:

ZIP Code:

FAX Number *(if available)*:

Telephone Number:

E-Mail Address *(if available)*:

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☐ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2 Claim Number (*as listed in the patent*)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Peter C. Richardson	August 13, 2003

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Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name: Peter C. Richardson	
Address: 235 East 42nd Street	City/State: New York, NY
ZIP Code: 10017	Telephone Number: 212-573-7805
FAX Number *(if available)*: 212-573-1939	E-Mail Address *(if available)*

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER: 20-702

NAME OF APPLICANT / NDA HOLDER: Pfizer Ireland Pharmaceuticals

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME): Lipitor

ACTIVE INGREDIENT(S)	STRENGTH(S)
Atorvastatin calcium: atorvastatin; atorvastatin anion	10mg, 20mg, 40mg, 80mg

DOSAGE FORM: Tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,126,971	Oct. 3, 2000	Jan. 19, 2013

d. Name of Patent Owner: Warner-Lambert Co. LLC. a wholly-owned subsidiary of Pfizer Inc

Address *(of Patent Owner)*: 235 East 42nd Street

City/State: New York, NY

ZIP Code: 10017

FAX Number *(if available)*: 212-573-1939

Telephone Number: 212-733-7805

E-Mail Address *(if available)*:

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address *(of agent or representative named in 1.e.)*:

City/State:

ZIP Code:

FAX Number *(if available)*:

Telephone Number:

E-Mail Address *(if available)*:

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☐ Yes	☒ No
4.2 Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*		

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Peter C. Richardson	August 13, 2003

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Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name: Peter C. Richardson	
Address: 235 East 42nd Street	City/State: New York, NY
ZIP Code: 10017	Telephone Number: 212-573-7805
FAX Number *(if available)*: 212-573-1939	E-Mail Address *(if available)*:

EXCLUSIVITY SUMMARY FOR NDA # 20-702 SUPPL # 039

Trade Name Lipitor Generic Name Atorvastatin

Applicant Name Pfizer HFD # 510

Approval Date If Known July 30, 2004

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_x_/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_x_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /_x__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____3 years_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /_x__/ NO /___/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

__no_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_x__/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-702 Lipitor

NDA# _____ _____

NDA# _____ _____

2. Combination product. N/A

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than

bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_x__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_x__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_x__/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_x__/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_x__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm)

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_x__/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_x__/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_Ascot-LLA_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND ~~/~~ YES /_x_/ ! NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_x_/

If yes, explain: _____

_____

Signature M.A. Simoneau Date July 16, 2004
Title: Regulatory Project Manager

Signature of Office/ Date
Division Director: David Orloff, MD

Form OGD-011347 Revised 05/10/2004

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/s/

Mary Parks
8/6/04 10:36:37 AM
for Dr. Orloff

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 20-702 Supplement Type (e.g. SE5): SE1 Supplement Number: 039

Stamp Date: October 1, 2003 Action Date: July 30, 2004

HFD 510 Trade and generic names/dosage form: Lipitor (atorvastatin) tablets

Applicant: Pfizer Therapeutic Class: Lipid Altering/statin

Indication(s) previously approved: for adults: 1. Reduce elev TG, LDL-C, Apo B, & TG & to inc. HDL-C(Fred 2A &2B)
2. Fred 1V
3. Fred III
4. Dec. TC & LDL-C with homozygous familial hypercholesterolemia

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): one

Indication # 1: In adult patients without clinically evident CHD (but with multiple risk factors), to reduce the risk of MI, and to reduce the risk of revascularization procedures and angina.

Is there a full waiver for this indication (check one)?

X Yes: Please proceed to Section A.

☐ No: Please check all that apply: ___Partial Waiver ____Deferred ___Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
X Other: Clinical manifestation does not exist in this age category.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies N/A

Age/weight range being partially waived:

Min____	kg____	mo.____	yr.____	Tanner Stage____
Max____	kg____	mo.____	yr.____	Tanner Stage____

Reason(s) for partial waiver: Other

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns

- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies N/A

Age/weight range being deferred:

Min ____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies N/A

Age/weight range of completed studies:

Min ____ kg____ mo.____ yr.___ Tanner Stage____
Max____ kg____ mo.____ yr.___ Tanner Stage____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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/s/

Mary Parks
8/6/04 10:44:05 AM
for Dr. Orloff

Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755

DUPLICATE

SE1 { 039 / 041 } PMO

July 16, 2004

RECEIVED
JUL 19 2004
FDA/CDER

David G. Orloff, MD
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, MD 20857

RE: Lipitor® (atorvastatin calcium)
NDA 20-702
General Correspondence
Request for PREA Waiver for S-039, S-041

Dear Dr. Orloff:

The following information is being furnished to the Agency on behalf of, and as agent for Pfizer Ireland Pharmaceuticals, formerly known as Warner Lambert Export, Limited.

Reference is made to the Pediatric Research Equity Act (PREA), enacted on December 3, 2003, requiring pediatric studies to be submitted with drug applications unless a waiver or deferral is granted.

By this letter, Pfizer is requesting a waiver of the requirement to do studies in pediatric patients for S-039, filed to the FDA on September 30, 2003, to support an indication for the prevention of cardiovascular disease in patients without clinically evident CHD. Pfizer also requests a waiver of the requirement to do studies in pediatric patients for S-041, filed to the FDA on March 30, 2004, to support an indication for stopping the [redacted]

Pfizer is requesting this waiver for both submissions because the indications for which these supplemental applications were filed are not needed and are not relevant in the pediatric patient population. Therefore, there is no necessity to do studies in this age group.

If you have any questions please do not hesitate to contact me by phone at 212-733-5843 or by fax at 212-857-3558.

Sincerely,

Madeleine M. Jester

Madeleine M. Jester
Director, US Regulatory Affairs

NDA #20-702

AMLODIPINE BESYLATE/ATORVASTATIN CALCIUM

ASCOT AML-NY-96-008

DEBARMENT CERTIFICATION

[FD&C Act 306(k)(l)]

Pfizer hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Signature of Company Representative

August 5, 2003
Date

AMLODIPINE BESYLATE/ATORVASTATIN CALCIUM
ASCOT (AML-NY-96-008) Submission
NDA #20-702
FINANCIAL DISCLOSURE COVER NOTE

Module 1.4.6.1

There is one covered study for this submission. The covered study was not funded via variable compensation and none of the investigators in either study hold any form of propriety interest in AMLODIPINE BESYLATE/ATORVASTATIN CALCIUM.

Information regarding Pfizer efforts to eliminate bias in the study is described in NDA Module 1.4.6.2). Pfizer has examined its financial data regarding significant payments of other sorts made to all investigators in this study and equity information as provided by the investigators, as defined in 21 CFR 54.2. Disclosure: Financial Interests and Arrangements of Clinical Investigators (NDA Module 1.4.6.3 & 1.4.6.4)

With a total of 1216 investigators listed in the multi-centered study, 9 of the listed investigators had financial information to disclose, specifically significant payments of other sorts. This information is listed in the 3455 forms in this item.

It is important to note that the investigator list for the study is not necessarily the same as that for financial disclosure. The FDA criteria for the two lists are not equivalent. There is a complete investigator population list for the covered study attached to this cover note (NDA Module 1.4.6.1). Please be advised that the data from two sites, [redacted] and [redacted] have been excluded from the efficacy analyses due to irregularities found in a for-cause audit. Although the two sites were removed from the efficacy analysis, Financial Disclosure was conducted and the Financial Disclosure data is recorded in box 1 of the 3454.

Pfizer Inc. is submitting financial disclosure information on the following covered study:

Protocol # A053:AML-NY-96-008
Study Title: ANGLO-SCANDINAVIAN CARDIAC OUTCOMES TRIAL (ASCOT): Factorial Study of the Prevention of Coronary Heart Disease and Vascular Events by Blood Pressure Lowering (comparing beta-blocker-based with amlodipine-based therapy) and by Blood Cholesterol lowering (comparing atorvastatin with placebo)

A complete list of all 1216 investigators is attached. Because this study started prior to February 2nd 1999, coupled with the transient nature of investigators, particularly sub investigators, we were unable to obtain a completed Financial Disclosure form for 266 investigators who participated in the study. Normally this inability to collect financial disclosure information was due to sites not being able to provide forwarding addresses or investigators having moved from the forwarding address provided. Although Pfizer was unable to obtain financial disclosure information specific to equity in Pfizer for 266 of the investigators, Pfizer has examined it's financial data regarding the other categories of Financial arrangements including significant payments of other sorts for all investigators in this study.

Each of the individual investigators listed was sent the Financial Disclosure Form directly or via the principal investigator for their site. In addition, if necessary we contacted the site by telephone and/or sent 2 separate follow-up letters to those individuals who did not return the Financial Disclosure Form. All investigators were contacted prior to this submission to remind them of the obligation to disclose financial information for Pfizer Inc and affiliated companies, including Warner-Lambert, Agouron, Pharmacia, Pharmacia & Upjohn, Searle/Monsanto & Sugen, which are wholly owned by Pfizer.

CERTIFICATION

Per Form 3454, certification is provided for 1207 of the 1216 investigators indicating

- Certified investigators (A total of 941 of the 1216 investigators are certified as having no Financial Arrangement as defined in 21 CFR 54.2)
- Due diligence in collecting the information on Equity. (A total of 266 of the 1216 investigators did not respond or could not be reached by our due diligence effort.)

Note that all investigators are assessed for Equity, Significant Payments of Other Sorts, Variable Compensation, & Propriety Interest. With the exception of Equity, all other financial arrangements are checked via internal Pfizer system.

DISCLOSURE

In the covered study, 9 of the 1216 investigators listed had financial information to disclose. A completed Form 3455 is attached for these investigators.
All Independent Grants associated with our investigators are paid directly to the Institution rather than to the individual investigator.

Meeting Minutes

Division of Metabolic and Endocrine Drug Products
NDA 20-702

Date: Wednesday, November 19, 2003
Location: Parklawn 14B39
Time: 3:00 PM

FDA Attendees:

Drs. Mary Parks and Karen Mahoney, Todd Sahlroot, Japo Choudhury, Xavier Ysern, and Margaret Simoneau.

This was a **Filing meeting** for Lipitor (atorvastatin) tablets, efficacy supplement S-039, dated September 30, 2003. This supplement proposes a new indication for the prevention of cardiovascular disease in patients without clinically evident coronary heart disease based on the results of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT). The file date for this supplement was November 30, 2003.

- **Clinical**- Dr. Mahoney is the primary medical reviewer. There were no filing issues and financial disclosure information was submitted.
- **Pharmacology**- Not needed (memo in DFS November 3, 2003).
- **Chemistry**- Pfizer submitted a categorical exclusion to the environmental assessment requirement. This was acceptable.
- **Biopharm**- Not needed (memo in DFS November 19, 2003).
- **Biostatistics**- No filing issues. Japo Choudhury is the primary reviewer for this supplement.
- **DSI**- No audit would be required.
- **Advisory Committee**- Not needed.
- **Review Goal Date with labeling**-
  This submission will be a standard review. The user fee goal date is August 1, 2004. Reviews are due in DFS (signed by the team leader) on June 30, 2004.

Minutes preparer: Margaret Simoneau, R.Ph.
Regulatory Project Manager
(*See appended signature page*)

Concurrence Chairman: Mary Parks, M.D.
Deputy Director/Medical Team Leader
(*See appended signature page*)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mary Parks
12/5/03 01:49:08 PM

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 26, 2003

TIME: 11:00 to 12:00

LOCATION: Telephone conference

SPONSOR: Pfizer

TYPE OF MEETING: Type C Guidance Meeting

DRUG: Lipitor (atorvastatin calcium)

APPLICATION: NDA 20-702

MEETING CHAIR: David Orloff, M.D., Division Director

MEETING RECORDER: Margaret Simoneau, Regulatory Project Manager

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1. David Orloff, M.D.	Division Director	DMEDP, HFD-510
2. Mary Parks, M.D.	Deputy Division Director	DMEDP, HFD-510
3. William Lubas, M.D.	Clinical Reviewer	DMEDP, HFD-510
4. Karen Mahoney, M.D.	Clinical Reviewer	DMEDP, HFD-510
5. Todd Sahlroot, Ph.D.	Biometrics Team Leader	OB, DB II, HFD-715
6. Japobrata Choudhury, Ph.D.	Biometrics Reviewer	OB, DB II, HFD-715
7. Margaret Simoneau, R.Ph.	Regulatory Project Manager	DMEDP, HFD-510

EXTERNAL ATTENDEES AND TITLES:

External Attendee	Title	Sponsor/Firm Name
1. Craig Audet	Director / Team Leader, Worldwide Regulatory Strategy	Pfizer
2. Dr. Bruce Beckerman	Senior Medical Director, PPG Medical & Regulatory Operations	Pfizer
3. Dr. Jan Buch	Medical Director, PPG Medical & Regulatory Operations	Pfizer
4. Dr. Frank Caridi	Senior Director, Headquarters Biometrics, Clinical Data Operations	Pfizer
5. Dr. Don Costello	Director, Regulatory Submissions, Clinical Development	Pfizer
6. Christopher Graham	Director, Worldwide Regulatory Strategy	Pfizer
7. Dr. Craig Hopkinson	Medical Director / Team Leader, PPG Medical & Regulatory Operations	Pfizer
8. Barrett Jeffers	Associate Director, Clinical Data Operations	Pfizer
9. Dr. Gary Palmer	Senior Director / Group Medical Leader, PPG Medical & Regulatory Operations	Pfizer

MEETING OBJECTIVES:

1. The purpose of the meeting was to discuss a future efficacy supplement submission based on the results the Anglo-Scandinavian Coronary Outcomes Trial (ASCOT). The meeting was to discuss the format and content of the planned submission and the appropriate methods for statistical analysis of the data.
   ASCOT is an ongoing investigator-initiated study designed to evaluate different treatment strategies to prevent cardiovascular disease in hypertensive patients. The primary endpoint of the trial is non-fatal MI and fatal CHD.

DISCUSSION:

A. Input on questions from meeting packet:

1. **Does the Agency endorse the proposed eCTD format, including the table of contents and associated cross-references to approved NDA? The documents will be submitted as an eNDA, and a map will be provided.**

FDA Response:

Technical questions regarding the eCTD submission format can be directed to esub@cder.fda.gov. *Primary point of contact is Ken Edmunds; Gary Gensinger can also answer questions.*

The Division requests that Pfizer ensure ease of navigability for reviewers, and that Pfizer provide technical support for reviewers' eCTD-related questions. The Division asks that the sponsor provide working hyperlinks from all tables, figures and lists; these links would connect to and from the appropriate text.

Pfizer agreed to include such links and to provide technical support to Division reviewers regarding eCTD questions.

The proposed table of contents appears to contain headings for all sections relevant to the clinical review, and is placed according to the eCTD draft guidance recommendation. The statistical reviewers might have other comments regarding the proposed sections.

2. **Does the agency wish Pfizer to submit data listings as well as the data set?**

FDA Response:

At the time of submission, the Division will accept the data sets without the data listings. However, should questions arise, the Division might need to request data listings.

Pfizer asked a further question regarding reconciliation of the data sets and data listings if both are submitted. Pfizer stated that, in their interpretation of the eCTD guidance, the FDA will reconcile data sets with data listings when both are submitted. Pfizer stated that, prior to submitting data listings, Pfizer would internally reconcile the data sets with the data listings. Pfizer asked if they would be expected to submit their own reconciliation report. The Division stated that, since the sponsor would prepare this analysis as part of their standard operating procedure, a request for submission of this reconciliation will likely not place a large burden on the sponsor. If the Division eventually requests submission of data listings in addition to data sets, the inclusion of the sponsor's reconciliation report is desirable.

3. **Pfizer proposes only to submit [redacted] does the Agency endorse this proposal?**

FDA Response:

The Division asked the sponsor to expand on what it means by ' [redacted]

The sponsor replied that this [redacted] *, as only one study is involved.*

4. **Does the Agency agree to Pfizer's proposal to provide Patient Profiles instead of CRFs?** ***(see pps 3-4 of info pkt)***

FDA Response:

The Division requests that Pfizer provide a sample of the proposed patient profile for review prior to NDA submission. If the patient profile contains all necessary information, and is organized to permit efficient review, the Division will likely accept it in lieu of the CRF.

Pfizer stated that this patient profile includes all the raw patient data, and that they will submit a sample prior to NDA submission.

5. **Does the Agency agree to Pfizer's proposal of submission tables, listings and figures?**

FDA Response:

The Division statistical team sent to the sponsor a list of the tables, listings, and/or figures that the division statisticians usually need for review. While the sponsor's proposed headings appear to cover most of the desired information, this Division list could help the sponsor to ensure that complete information for efficient review is submitted upfront.

6. **Does the Agency endorse Pfizer's proposed efficacy analysis?**

FDA Response:

At the beginning of the teleconference, the sponsor reported that the indication sought will be for reduction of: MI,

See full answer from statistics team.

The Division foresees problems regarding the use of statistical minimization procedures rather than randomization per se when patients were allocated to the atorvastatin and placebo arms. Such minimization procedures have not been fully validated in large populations. At the time of NDA submission, the Division will need to see a detailed explanation of the minimization procedures used, and will also need to know how the study statistical team validated or plans to validate the method.

The Division will also wish to see, at the time of NDA submission, the justification for the apparently arbitrary designation of a .01 significance value for the secondary and tertiary outcomes.

7. **Does the Agency endorse Pfizer's proposed safety analysis?**

   FDA Response:

   Yes; also see answer to question 8.

8. **The safety data will be compiled from the Pfizer safety database using Pfizer worldwide safety standards. Pfizer proposes providing detailed narratives for the following SAE terms in the Pfizer Safety database:**
   neuropathy, coma hepatic, hepatic cirrhosis, hepatic enz increased, hepatic failure, hepatic function abnormal, hepatic necrosis, hepatitis, hepatocellular damage, jaundice, muscle weakness, myalgia, myopathy, myositis, dyspnea,

   Does the Agency agree with this proposal?

   FDA Response:

   The Division asked whether narratives regarding other SAEs would be available if reviewers note an imbalance in other event rates between the placebo and atorvastatin groups is noted.

   Pfizer stated that they could make such additional narratives available, but Pfizer would have to write them at that time.

B. Additional Statistical Information:

- Dr. Todd Sahlroot requested the details of minimization stated in Section 2.8 "Randomization." He also requested that appropriate analyses for such minimization (including appropriate randomization tests) be provided in the sNDA submission.

-

- Section 3.3 "General Methodology" stated .01 level for secondary and tertiary hypotheses. This is not one of the rules our division follows. Referring to the sponsor's comment at the meeting, "When statistically significant results are found when comparing composite endpoints, the results will be broken up by each component of the composite endpoint in order to ascertain which components(s) are contributing to the statistical significance", the division expects the relevant analyses in the final report.

- All the hypotheses that may be tested should be identified in advance. Either, a fixed sequence (including the components of a composite endpoint), where any further claim of the rejection of a null hypothesis has to be stopped as soon as a non-significant p-value is encountered, has to be specified before unblinding data. Therefore, it may be advisable to put the components of a composite endpoint towards the end of the sequence instead of right after the composite endpoint. Or, a multiple comparison adjustment method has to be specified before unblinding data.

- It seems that all patients from both types of anti-hypertensive treatment will be combined for the primary analyses. We would like to look also at subgroup analyses for the two types of anti-hypertensive treatment groups separately.

- Since the anti-hypertensive treatment study is continuing, certain information is still blinded. The statistical evaluation of Lipitor cannot be finalized until all the relevant information the statistical reviewer needs to properly assess efficacy is made available by the sponsor.

Minutes Preparer:
Margaret Simoneau, R.Ph.
Project Manager, HFD-510

Chair Concurrence: /s/ 04/23/2003
David Orloff, M.D.
Division Director, HFD-510

MEETING MINUTES

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/s/

David Orloff
4/25/03 12:08:16 PM

Division of Metabolic & Endocrine Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 20-702/S-036 and S-039
Name of Drug: Lipitor (atorvastatin calcium) Tablets, 10, 20, 40, and 80 mg.
Applicant: Pfizer

Material Reviewed:

Submission Date(s):

July 1, 2003 (S-036), Package Insert (PI), Final Printer Labeling (FPL)
November 11, 2004 (S-039), PI, FPL

Background and Summary

Lipitor is approved for a variety of dyslipidemic conditions.

Supplement -036, submitted 11/26/02, and approved 5/12/03, provided for a revision to the title of Table 5 to state, "Lipid-altering Effects of Lipitor in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia".

Supplement -039, submitted 9/30/03, and approved 7/30/04, provided for new indications based on the ASCOT-LLA study: use of atorvastatin in adult patients without clinically evident coronary heart disease, but with multiple risk factors, to reduce the risk of MI and to reduce the risk for revascularization procedures and angina.

Both supplements were approved on draft labeling. The sponsor has not submitted FPL.

Review

The labeling revision that was approved with S-036 was contained in the FPL that was submitted for S-039. Therefore, the FPL for S-036 was not reviewed.

The FPL for S-039 (69-5884-00-5, LAB-0021-7, Revised July 2004) was compared to that which was attached to the 7/30/04 approval letter. They are identical with the following exceptions:
-the FPL contains the revised header for Table 5 that was approved with S-036
-The identifier has been changed
NOTE: These are appropriate revisions.

Conclusions

Since the labeling revision proposed in S-036 is contained in the FPL for S-039, the following letters should issue:
-an ACK and Retain letter should be issued for S-039
-an ACK and Retain letter should be drafted for S-036 that states that, since the changes are contained in the FPL for S-039, the FPL will not be reviewed but will be retained in the files.

The currently approved package insert for Lipitor Tablets contains the following identifier and revision date:
69-5884-00-5, LAB-0021-7, Revised July 2004

Reviewed by:
Kati Johnson
Chief, Project Management Staff
Division of Metabolic & Endocrine Drug Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kati Johnson
3/23/05 06:36:36 AM
CSO

Division of Metabolic & Endocrine Drug Products

Labeling Review

Application Number: NDA 20-702/S-039

Name of Drug: Lipitor (atorvastatin) Tablets

Sponsor: Pfizer

Submission Date: July 30, 2004 email

Background and Summary:

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.
5. as an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:
   a. LDL-C remains ≥ 190 mg/dL or
   b. LDL-C remains ≥ 160 mg/dL and:
      there is a positive family history of premature cardiovascular disease or two or more other CVD risk factors are present in the pediatric patient

It is supplied in the tablet dose strengths of 10, 20, 40 and 80 mg.

The last approved labeling supplement, S-027, was approved on May 24, 2004, which implemented a new Patient Package Insert (PPI). Prior to Supplement S-027, the last approved labeling supplement was Supplement S-037, approved on September 29, 2003 (Package Insert Identifier # 69-5884-00-3, Revised May 2003). This supplement, S-037, was a "Changes Being Effected" supplemental new drug application which provided for the addition of a 5000-count bottle for the 20 mg strength and a 500-count bottle for the 40 and 80 mg strengths. Additionally, this supplement provided for revisions to the **HOW SUPPLIED** section of the Lipitor package insert.

This supplemental New Drug Application, S-039, provides for new indications, based on the results of the Anglo-Scandinavian Cardiovascular Outcomes Trial Lipid Lowering Arm (ASCOT-LLA), for the use of atorvastatin in adult patients without clinically evident coronary heart disease (but with multiple risk factors for coronary heart disease

such as age ≥ 55 years, smoking, hypertension, low HDL-C or a family history of early coronary heart disease), to reduce the risk of myocardial infarction, and to reduce the risk for revascularization procedures and angina.

Reference is made to the addendum to the NDA Annual Report, submission dated June 18, 2004. The time period covered by the report was September 29, 2002 through September 28, 2003 and was submitted to the Agency on November 26, 2003. The addendum contained updated labeling information for Lipitor that was not available at the time of the November submission. In this report, the (Package Insert Identifier # 69-5884-00-4, Revised August 2003) is the current approved labeling for Lipitor.

Review:

This labeling review is from the electronic *MS* Word version of the last approved labeling, S-037, submitted July 1, 2003, and approved by the Agency on September 29, 2003, and the July 30, 2004 email for S-039.

This supplement provides for changes to the **CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE** and **ADVERSE EVENTS** sections of the LIPITOR package insert.

Under the **CLINICAL PHARMACOLOGY**, *Mechanism of Action* subsection, the fourth paragraph, last sentence, "The effect of Lipitor on cardiovascular morbidity and mortality has not been determined", was deleted.

Under **CLINICAL PHARMACOLOGY,** *Clinical Studies,* Prevention of Cardiovascular Disease section was added.

Under **INDICATIONS AND USAGE,** *Prevention of Cardiovascular Disease* section was added to read:

> *Prevention of Cardiovascular Disease*
> In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age ≥ 55 years, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, Lipitor is indicated to:
> - Reduce the risk of myocardial infarction
> - Reduce the risk for revascularization procedures and angina

Under **ADVERSE REACTIONS**, Clinical Adverse Experiences, a new paragraph has been added to read:

> *Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)*
> In ASCOT (see CLINICAL PHARMACOLOGY, *Clinical Studies*) involving 10,305 participants treated with Lipitor 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with Lipitor was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.

Conclusion:

Package insert, submitted July 30, 2004, for S-039, (Package Insert Identifier # 69-5884-00-4.1, Revised July 2004) was deemed acceptable by the reviewing team. Agency will issue an approval letter on this efficacy supplement.

Reviewed by: M.A. Simoneau, R.Ph., Regulatory Project Manager
(See appended electronic signature page)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Margaret Simoneau
8/6/04 03:14:05 PM
CSO

Simoneau, Margaret A

From: Young, Karen
Sent: Thursday, September 02, 2004 2:22 PM
To: Simoneau, Margaret A
Subject: FW: DFS Email - N 020702 SE1 039 30-Sep-2003 - Supplement Letters

090014648045
5cf.pdf (688 KB

Hi Margaret,

I received the electronic approval letter and labeling for Lipitor (July 2004 changes). Unfortunately, I am unable to extract the Lipitor labeling so that it can be included in the MedWatch safety labeling summary for the month of July. Would you mind just sending me the electronic Lipitor labeling again? Or, if you prefer, I can contact the Sponsor if you provide me with a contact name and number.

Much Thanks for your help,

Karen
(301) 827-7842
MedWatch

-----Original Message-----
From: CDERDocAdmin [mailto:CDERDocAdmin]
Sent: Friday, July 30, 2004 11:57 AM
To: DDMSIMT@CDER.FDA.GOV; DDMSIST@CDER.FDA.GOV; MEDWATCH@CDER.FDA.GOV; ODSCONSULTS@CDER.FDA.GOV; DRUGPRODUCTS@cder.fda.gov; OGDLRB@CDER.FDA.GOV; OTCOM_FOI@CDER.FDA.GOV; STAUFFERP@CDER.FDA.GOV; JEFFERYE@CDER.FDA.GOV; WEBMASTER@CDER.FDA.GOV; PHASE4PM@CDER.FDA.GOV; DDR_510@CDER.FDA.GOV; DDMAC@CDER.FDA.GOV
Subject: DFS Email - N 020702 SE1 039 30-Sep-2003 - Supplement Letters

Document room update the following:

		Decision Date	Decision Code
N 020702 SE1 039	30-Sep-2003	30-Jul-2004	AP:APPROVAL
N 020702 SE1 039 PW	16-Jul-2004	30-Jul-2004	AP:APPROVAL
N 020702 SE1 039 BL	26-Jul-2004	30-Jul-2004	AP:APPROVAL
N 020702 SE1 039 BL	30-Jul-2004	30-Jul-2004	AP:APPROVAL

Mail paper copy to

DISTRICT OFFICE

Mail paper copy with labeling to

HFI-20/Press Office (with labeling)

Mail labeling to

HFD-143/DRM (with labeling)
HFD-013/CDER FOI Team Leader/R.Castle (with labeling)
HFD-013/CDER FOI Team Leader/D.Taub (with labeling)
HFD-410/CDER Medwatch Safety Labeling (with labeling)
HFD-430/ODS/DDRE (with labeling)
HFD-613/OGD - Labeling Review Branch (with labeling)
HFD-013/Office Of Regulatory Policy - DIDP (FOI) (with labeling)
HFD-960/DPDD/PM/G.Carmouze (with labeling)

Simoneau, Margaret A

From: Hankin, Joan E
Sent: Friday, August 13, 2004 1:38 PM
Simoneau, Margaret A
Subject: Lipitor: New PPI with updated Indications Section

Peg:

Would you be able to provide me with the new PPI language updating the indications section (I can't find it in DFS, intranet, or the Lipitor website).

Thanks,

Joan

301-827-2831
8/30/04

Simoneau, Margaret A

To:	CDER-APPROVALS
Cc:	Orloff, David G; Parks, Mary H; Mahoney, Karen M (CDER/DMEDP); Mele, Joy D; Sahlroot, Jon T; Galliers, Enid M; Simoneau, Margaret A; Meyer, Robert J; Ripper, Leah W
Subject:	NDA 20-702/S-039 Efficacy Supplement Approval

Date of approval: July 30, 2004

NDA #: 20-702/S-039

Name of Drug: Lipitor (atorvastatin calcium) tablets

Name of Sponsor: Pfizer Inc.

Indications:

This supplemental New Drug Application provides for new indications, based on the results of the Anglo-Scandinavian Cardiovascular Outcomes Trial Lipid Lowering Arm (ASCOT-LLA), for the use of atorvastatin in adult patients without clinically evident coronary heart disease (but with multiple risk factors for coronary heart disease such as age $\geq$ 55 years, smoking, hypertension, low HDL-C or a family history of early coronary heart disease), to reduce the risk of myocardial infarction, and to reduce the risk for revascularization procedures and angina. In addition, this supplemental application provides for changes to the CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE and ADVERSE EVENTS sections of the LIPITOR package insert.

Dosage form/route of administration: oral tablet

In this dosage form/route of administration NEW? No

No RX to OTC switch

Drug class and review priority: SE1 with standard review

To FDR

Subject: Pick up package by August 9, 2004 (Monday)

Division of Metabolic and Endocrine Drug Products (HFD-510)

PM: Margaret Simoneau Phone: 301-827-6411

Location: 14B23 PKLN

No of Volumes: 1

Simoneau, Margaret A

Subject:	NDA 20-702/S-039 Lipitor (ASCOT); INDUSTRY Labeling Meeting #3
Location:	CDER 510 Calendar; CDER PKLN 14B39 Conf Room -AR
Start:	Mon 7/19/2004 2:00 PM
End:	Mon 7/19/2004 3:30 PM
Recurrence:	(none)
Meeting Status:	Meeting organizer
Required Attendees:	Simoneau, Margaret A; Parks, Mary H; Mahoney, Karen M (CDER/DMEDP); Sahlroot, Jon T; Mele, Joy D
Resources:	CDER 510 Calendar; CDER PKLN 14B39 Conf Room -AR

2 to 2:30 pm INTERNAL
2:30 to 3:30 pm INDUSTRY

Simoneau, Margaret A

From: Tran, Debi Nhu
Sent: Monday, July 19, 2004 9:10 AM
To: Simoneau, Margaret A
Subject: RE: Latest Lipitor draft labeling for S-041

Hi Peggy,

Thank you for forwarding the Lipitor label to me. I thought I would have time to take a look at it. Unfortunately, I received a rather sizable product launch submission. Due to the limited timeframe for review of launch materials, I won't be able to review the Lipitor label. Thanks again for keeping in the loop about pending applications and supplements.

Debi

-----Original Message-----
From: Simoneau, Margaret A
Sent: Thursday, July 15, 2004 3:29 PM
To: Tran, Debi Nhu
Subject: FW: Latest Lipitor draft labeling for S-041

-----Original Message-----
From: Jester, Madeleine [mailto:madeleine.jester@pfizer.com]
Sent: Thursday, July 15, 2004 12:00 PM
To: 'margaret.simoneau@fda.hhs.gov'
Subject: Latest Lipitor draft labeling for S-041

Margaret - Attached below is the latest Lipitor draft labeling for ASCOT, reflecting the discussion during our labeling negotiation session with FDA on 7/12/04. Also attached is a Word document with our rationale for efficacy in women.

I attempted to put the suggested changes in one color and our comments in another color, but for some reason the track changes function wouldn't let me do it. What I have done is to put Pfizer's comments on the changes in italics. I hope this is understandable.

If you have any questions or need clarification, please let me know.

The call in number for our meeting Monday afternoon will follow in a separate e-mail.

Thanks.

Maddy Jester
Director
US Regulatory Affairs
Pfizer Inc
212-733-5843

<<20702S039Draft2label70904.doc>> <<Gender Response.doc>>

Simoneau, Margaret A

From: Jester, Madeleine [madeleine.jester@pfizer.com]
Sent: Thursday, July 15, 2004 5:48 PM
To: 'margaret.simoneau@fda.hhs.gov'
Subject: Number for the Monday telecon with Pfizer on Lipitor label

mmsinfo.txt
(459 B)

Margaret - Here's the call-in information for the t-con on Monday afternoon on the ASCOT label change.

CALL DATE: JUL-19-2004 (Monday)
CALL TIME: 2:30 PM-3:30 PM
LEADER: MS MADELEINE JESTER

PASSCODE:

For security reasons, the passcode and the leader's name will be required to join your call.

Looking forward to our discussion. If you decide to call a little early, as you indicated might be the case, we'll be there.

Maddy Jester

Simoneau, Margaret A

Subject:	NDA 20-702/S-039 (ASCOT)/ INDUSTRY labeling meeting #1
' ocation:	CDER PKLN 14B39 Conf Room -AR; CDER 510 Calendar
art:	Mon 7/12/2004 10:00 AM
End:	Mon 7/12/2004 12:00 PM
Recurrence:	(none)
Meeting Status:	Meeting organizer
Required Attendees:	Simoneau, Margaret A; Parks, Mary H; Mahoney, Karen M (CDER/DMEDP); Sahlroot, Jon T; Mele, Joy D; CDER PKLN 14B39 Conf Room -AR
Resources:	CDER PKLN 14B39 Conf Room -AR; CDER 510 Calendar

1 JESSEN
2 ALEX PIERCE
3 3 MEDICAL K
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SIGH
4. 1 STATISTICIAN JEFFERS

JULLAPHAN
JS
NAN
JOHN BODILY

Simoneau, Margaret A

From: Jester, Madeleine [madeleine.jester@pfizer.com]
Sent: Friday, July 09, 2004 9:34 AM
To: 'Simoneau, Margaret A'
Subject: RE: NDA 20-702/S-039 (ASCOT) Draft Label #1

Margaret - This is to confirm that I have received the draft labeling for the ASCOT submission. I look forward to our discussion on Monday. Here's the call-in number:

[redacted]

PASSCODE [redacted]

Leader: Ms. Madeleine Jester

Talk to you on Monday.

Maddy

-----Original Message-----
From: Simoneau, Margaret A [mailto:SIMONEAUM@cder.fda.gov]
Sent: Friday, July 09, 2004 9:22 AM
To: 'Madeleine.jester@pfizer.com'
Cc: Parks, Mary H; Mahoney, Karen M (CDER/DMEDP); Mele, Joy D; Sahlroot, Jon T
Subject: NDA 20-702/S-039 (ASCOT) Draft Label #1

Maddy,

Here is a copy of the proposed ASCOT label for Monday's telephone discussion.
Thanks.

<<20702S039Draftlabel70904.doc>>

Margaret Simoneau, M.S., R.Ph.
FDA/CDER/HFD-510
301-827-6411
simoneaum@cder.fda.gov

"MMS <secure.pfizer.com>" made the following annotations on 07/09/2004 09:23:07 AM

24 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
5039

Simoneau, Margaret A

Subject:	NDA 20-702/S-039 Lipitor/Ascot 1ST INTERNAL LABELING MEETING
Location:	CDER 510 Calendar; CDER PKLN 14B39 Conf Room -AR
Start:	Thu 7/8/2004 8:30 AM
End:	Thu 7/8/2004 10:00 AM
Recurrence:	(none)
Meeting Status:	Meeting organizer
Required Attendees:	Parks, Mary H; Mahoney, Karen M (CDER/DMEDP); Sahlroot, Jon T; Mele, Joy D
Resources:	CDER 510 Calendar; CDER PKLN 14B39 Conf Room -AR

Simoneau, Margaret A

Subject:	Re: NDA 20-702/S-039 (ASCOT) INTERNAL Status Meeting
Location:	CDER PKLN 14B39 Conf Room -AR; CDER 510 Calendar
Start:	Mon 5/24/2004 10:00 AM
End:	Mon 5/24/2004 11:00 AM
Recurrence:	(none)
Meeting Status:	Meeting organizer
Resources:	CDER PKLN 14B39 Conf Room -AR; CDER 510 Calendar

Simoneau, Margaret A

From: Gensinger, Gary M
Sent: Wednesday, October 08, 2003 10:20 AM
To: Simoneau, Margaret A; Mahoney, Karen M (CDER/DMEDP)
Subject: RE: Trouble with an esub link

Hi,

I've looked at this. If the group feels that this is a serious issue, you should contact Pfizer and ask them to correct the link and resubmit the document. It appears as though their qc process for their electronic submission failed to alert them to an invalid link.

Gary

Gary M Gensinger
Review Technology Staff
Office of Information Management
Center for Drug Evaluation and Research
301-827-7753

-----Original Message-----
From: Simoneau, Margaret A
Sent: Wednesday, October 08, 2003 10:06 AM
To: Mahoney, Karen M (CDER/DMEDP)
Subject: Gensinger, Gary M
RE: Trouble with an esub link

To All,

I will contact both Pfizer and Gary Gensinger.

Thanks.

-----Original Message-----
From: Mahoney, Karen M (CDER/DMEDP)
Sent: Wednesday, October 08, 2003 7:55 AM
To: Parks, Mary H; Choudhury, Japobrata; Simoneau, Margaret A
Cc: Mahoney, Karen M (CDER/DMEDP)
Subject: FW: Trouble with an esub link

Dear Mary, Japo, and Peggy,
Here is the EDR's response to the problem with being unable to link from the table of contents. Is this acceptable, or should we ask the sponsor and the EDR to work together to get the link from the TOC active? I don't have any experience to know how much trouble this inactive link could cause for us. I do know that in our preNDA meeting and minutes, our main comment to the sponsor regarding the electronic submission format was that the links should work.
Let me know what you think-
Karen

-----Original Message-----
From: Selnekovic, Thomas J
Sent: Monday, October 06, 2003 1:46 PM
To: Mahoney, Karen M (CDER/DMEDP)
Cc: CDER-EDRADMIN
Subject: RE: Trouble with an esub link

Karen

The problem is with the way the applicant named the link - the 96008a.pdf link has additional folders that the EDR does not use (look under the select file button in the images). The EDR can not change the links as they appear in the submission. The work around for this would be to make the acrobat window smaller so that you can see part of the Windows Explorer window and navigate to the

<<\\CDsESUB1\N20702\S_039\2003-09-30\clinstat\ascot>>

Tom Selnekovic
EDRAdmin

-----Original Message-----
From: Mahoney, Karen M (CDER/DMEDP)
Sent: Monday, October 06, 2003 1:22 PM
To: CDER-EDRADMIN
Cc: Mahoney, Karen M (CDER/DMEDP)
Subject: Trouble with an esub link

Hi, EDR (forgive the impersonal greeting)-

I have been assigned an NDA supplement that has come in completely electronically, and I have found a link within it that I cannot get to work.

The link with which I am having trouble is reached this way:

Clinstat
clinstattoc
section 5.3.5.1.1 on the toc has 2 links in the right-hand column. The upper link works, but the one below it does not. The nonworking link is named clinstat\ascot \amlny96008a.pdf.

When I click on the link, I get a message saying that the folder can't be opened. I also tried it on another person's computer, and it didn't work there either. I called Chris Graham (212-733-4394), the Regulatory POC at Pfizer, the sponsor of this NDA. He talked to their technical people, and they say that when they use the CD that they submitted, the link is active. He suggested I contact you.

Please let me know if this email should actually go to someone else.

Thank you- Karen Mahoney (note - 2 Karen Mahoneys in CDER- I am Karen M Mahoney)
Ph 301-827-9089

Simoneau, Margaret A

Subject:	Re: NDA 20-702/S-39 Lipitor ASCOT Efficacy Supplement T-Con with Dr. Mahoney & Chris Graham of Pfizer
:ation:	Peggy's Office
Start:	Mon 10/6/2003 10:00 AM
End:	Mon 10/6/2003 10:30 AM
Recurrence:	(none)
Meeting Status:	Meeting organizer
Required Attendees:	Simoneau, Margaret A

Agenda:

Prior to filing/question regarding Module 5 (5.3.5.1.1 AML-NY-96-008 Clinical Study Report); 2nd hyperlink has no reference

Simoneau, Margaret A

From: Schumaker, Cathie L
nt: Wednesday, September 24, 2003 4:26 PM
Simoneau, Margaret A
Subject: Re: NDA 20-702 Lipitor

No it cannot. The new amendment should clearly state the fact that the data containrd in the submission correct the earlier submissionm.cs
---
Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Simoneau, Margaret A <SIMONEAUM@cder.fda.gov>
To: Schumaker, Cathie L <SCHUMAKER@cder.fda.gov>
CC: Galliers, Enid M <GALLIERS@cder.fda.gov>
Sent: Wed Sep 24 14:52:18 2003
Subject: Re: NDA 20-702 Lipitor

Cathie,

Pfizer submitted a corrected version of the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LA) dataset on September 18th 2003 that should be used with the upcoming submission to support a new indication for Lipitor. The INCORRECT version is in the EDR with a submission date of August 25th, 2003. In a September 12, 2003 general correspondence letter this error is noted. Can this INCORRECT version be removed from the EDR in order to prevent confusion?

Thanks.

Margaret Simoneau, M.S., R.Ph.
FDA/CDER/HFD-510
301-827-6411
simoneaum@cder.fda.gov

Phone call 9/25/03 completed to Pfizer

2-1

3.

Simoneau, Margaret A

From: CDER EDRFAX
nt: Tuesday, September 02, 2003 3:50 PM
CDER-FAX
c: Nathan, Jega*; Simoneau, Margaret A; CDER ESUB; CDER-EDRADMIN; Brownewell, Sharon L; Cuthbert, Gerrard*; Emmons, Prentiss*; Galliers, Enid M; Hair, Peggy*; Johnson, Kati; Selnekovic, Thomas J; Staunton, Lena*; Tagoe, Ivan*; Talastas, Hercules*; Tokoli, Thomas*
Subject: FAX=212-857-3558 N20702 "Lipitor" from Pfizer

About this FAX

If you have any questions regarding this fax or Electronic Submissions in General:

Email esub@cder.fda.gov or call Ken Edmunds 301-827-7706.

If Resubmission is Required (a check mark appears in the top table on the following page):

Send a corrected electronic submission according to the electronic NDA guidance(s) as an amendment to the application.

Send electronic NDA submissions (defined as any submission containing electronic media components) only to the CDR address.

Send the entire submission (paper and electronic media) to:

Central Document Room (HFD-94)
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

Mail/Courier Contact: CDR, phone 301-827-4210

The cover letter should state "resubmission of electronic files". Any submission that includes any electronic records should be sent in its entirety (both paper and electronic components) to the CDR. Do not send any paper accompanying an electronic submission to the division document rooms (DDR).

If Resubmission is NOT Required:

No immediate action is required if only items from the lower check list are checked. You should review the issues and correct your submission process **for** future submissions.

For information about electronic submissions to CDER - See our public web site:

http://www.fda.gov/cder/regulatory/ersr/default.htm

AMLODIPINE BESYLATE/ATORVASTATIN CALCIUM
ASCOT (AML-NY-96-008) Submission
NDA #20-702

Module 5 – Clinical Study Reports		
Description	**Review copy volume number**	**Electronic Archive File Location**
5.1 Table of Contents for Study Reports and Related Info		**clinstat\clintoc.pdf**
5.2 Tabular Listing of all Clinical Studies	**N\A**	**clinstat\tablist.pdf**
5.3 Clinical Study Reports		
5.3.1 Reports of Biopharmaceutic Studies – not applicable		
5.3.2 Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials – not applicable		
5.3.3 Reports of Human Pharmacokinetic (PK) Studies – not applicable		
5.3.4 Reports of Human Pharmacodynamic (PD) Studies – not applicable		
5.3.5 Reports of Efficacy and Safety Studies		
5.3.5.1 Study Report of Controlled Clinical Studies Pertinent to the Claimed Indication		
5.3.5.1.1 AML-NY-96-008 Clinical Study Report	**3**	**clinstat\ascot\amlny96008.pdf** **clinstat\ascot\amlny96008a.pdf** → no. linke
5.3.6 Reports of Post-Marketing Experience	**N\A**	**clinstat\postmark.pdf**
5.3.7 Case Report Forms and Individual Patient Listing		
5.3.7.1 Patient Profiles (in lieu of Case Report Forms) Table of Contents	**N\A**	**crt\profiles\protoc.pdf**
5.3.7.2 Datasets and Related Information Tabulations Table of Contents – **Submitted Separately**		
5.3.7.2.1 Data Define Document		
5.3.7.2.2 Readme File		
5.3.7.2.3 SAS Datasets		
5.3.7.2.4 SAS Programs		
5.3.7.2.5 Annotated Case Report Form		
5.4 Literature References	**N\A**	**clinstat\pubs\pubslist.pdf**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-702/S-039

Pfizer Inc.
Attention: Madeleine M. Jester
Director/US Regulatory Affairs
235 East 42nd Street
New York, NY 10017

Dear Ms. Jester:

We acknowledge receipt of your November 11, 2004 submission containing final printed labeling in response to our July 30, 2004 letter approving your supplemental new drug application for Lipitor (atorvastatin calcium).

We have reviewed the labeling that you submitted in accordance with our July 30, 2004 letter and we find it acceptable.

If you have any questions, call Margaret Simoneau, Regulatory Project Manager, at (301) 827-6411.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kati Johnson
3/23/05 06:42:19 AM
signing for David G. Orloff, MD

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS
Pfizer Inc.
235 East 42nd Street
New York, NY 10017

2. TELEPHONE NUMBER *(Include Area Code)*
(212) 573-3412

3. PRODUCT NAME
Lipitor (atorvastatin calcium)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
20-702

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

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

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____ (APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

7. 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 UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION?
☐ YES ☒ NO
(See item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
for RBC	Robert B. Clark Vice President, US Regulatory	8/14/2003

FORM FDA 3397 (1/03)

PSC Media Arts (301) 443-1090 EF

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-702

Pfizer, Inc.
Attention: Christopher Graham
Director, Worldwide Regulatory Strategy
235 East 42nd Street, 150/7/12
New York, NY 10017

Dear Mr Graham:

Please refer to the telephone conference between representatives of your firm and FDA on March 26, 2003. The purpose of the meeting was to discuss a future efficacy supplement submission based on the results the Anglo-Scandinavian Coronary Outcomes Trial (ASCOT).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Margaret Simoneau, R.Ph., Regulatory Project Manager, at (301) 827-6411.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic & Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING REVIEW LETTER

NDA 20-702/S-039

Pfizer, Inc.
Attention: Christopher A. Graham
Director, Worldwide Regulatory Strategy
235 East 42nd Street 150/7/12
New York, NY 10017

Dear Mr. Graham:

Please refer to your September 30, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lipitor (atorvastatin calcium)Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on November 30, 2003 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Margaret Simoneau, R.Ph., Regulatory Project Manager, at (301) 827-6411.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic
and Endocrine Drug Products
Office of New Drug II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Enid Galliers
12/1/03 05:09:15 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-702/S-039

Pfizer, Inc.
US Agent for Pfizer Ireland Pharmaceuticals
Attention: Robert Clark
Vice President, US Regulatory Strategy
235 East 42nd Street, 150/7/13
New York, NY 10017

Dear Mr. Clark:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Lipitor® (atorvastatin calcium) Tablets
NDA Number:	20-702
Supplement number:	S-039
Review Priority Class:	Standard (S)
Date of supplement:	September 30, 2003
Date of receipt:	October 1, 2003

This supplemental application proposes a new indication based on the results of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 30, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 1, 2004.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Margaret Simoneau
10/9/03 09:19:51 AM

Regulatory Affairs
Pfizer Inc
235 E. 42nd Street 150/7/12
New York, NY 10017
Tel 212 733 4394 Fax 212 857 3558
Email chris.a.graham@pfizer.com

ORIGINAL

Pfizer Pharmaceuticals Group

Christopher A. Graham
Director
Worldwide Regulatory Strategy

September 30, 2003

RECEIVED
OCT 01 2003
CDR/CDER

David G. Orloff, MD
Director
Division of Metabolic and Endocrine Drug Products (HFD-51)
Room 14B-19
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont Office Center II
5600 Fishers Lane
Rockville, Maryland 20857

NDA NO. 20-702 REF NO. 039
NDA SUPPL FOR SE1

RECEIVED
OCT 02 2003
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Re: Lipitor® (Atorvastatin Calcium) Tablets
NDA 20-702 Supplement 39
User Fee ID Number 4535

Dear Dr. Orloff:

The following information is being furnished to the Agency on behalf of, and as agent for Pfizer Ireland Pharmaceuticals, formerly known as Warner Lambert Export, Limited. Pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act and in accordance with Title 21 of the Code of Federal Regulations, Pfizer Inc. is submitting a Supplemental New Drug Application (SNDA) for Lipitor (atorvastatin calcium). Please reference the data set submitted to the Agency on September 18, 2003 when reviewing this SNDA.

Atorvastatin, a synthetic inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, approved for use as an adjunct to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo B), and triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C), in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia; as an adjunct to diet for the treatment of patients with elevated TG; for the treatment of patients with primary dysbetalipoproteinemia who do not respond adequately to diet; and to reduce TC and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid lowering treatments or if such treatments are unavailable; and as an adjunct to diet to reduce TC, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if, after an adequate trial of diet therapy, the following findings are present: LDL-C remains ≥ 190 mg/dL or LDL-C remains ≥ 160 mg/dL and there is a positive family history of premature cardiovascular disease or two or more other

CVD risk factors are present in the pediatric patient. These various lipid disorders are herein collectively termed dyslipidemia. The calcium salt of atorvastatin is marketed as Lipitor® in the US (NDA 20-702) at doses of 10, 20, 40, and 80 mg QD. In 2002, approval was granted by FDA for marketing starting doses of 10 mg QD, 20 mg QD, and for patients who require reductions in LDL-C >45%, 40 mg QD. Atorvastatin has been approved for marketing in at least 78 countries worldwide, and is commercially available in at least 60 countries; no regulatory authority has refused or withdrawn approval or marketing authorization.

This application is based on the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) lipid lowering arm results and supports a new indication for the prevention of cardiovascular disease in patients without clinically evident coronary heart disease.

ASCOT is being conducted in the UK, Ireland, Sweden, Finland, Denmark, Norway and Iceland. It is an ongoing investigator-initiated study designed to evaluate different treatment strategies to prevent cardiovascular disease in hypertensive patients. Specifically, it is comparing a newer treatment strategy of a calcium channel blocker, Norvasc® (amlodipine besylate) 5-10 mg tablets (to which, in the majority of patients, the angiotensin-converting enzyme inhibitor, perindopril, is added to achieve blood pressure goal) with an older regimen of a beta blocker, atenolol (to which, again in the majority of patients, a diuretic, bendrofluazide, is added to achieve blood pressure goal). The primary endpoint of the trial is non-fatal MI and fatal CHD.

In ASCOT, a further hypothesis was also tested. Namely, whether cholesterol lowering with a statin, Lipitor 10 mg tablets, would confer additional protection against CHD in hypertensive patients with a cholesterol of 250 mg/dL or less.

On September 2, 2002 the Data Safety Monitoring Board (DSMB) of ASCOT proposed to the Steering Committee that the double-blind lipid-lowering arm of ASCOT be terminated due to a highly significant reduction in the primary endpoint of coronary heart disease and a significant reduction in stroke incidence in those patients receiving Lipitor compared to placebo. The magnitude of the benefit exceeded the predefined stopping rule for this part of the trial. The ASCOT Steering Committee accepted this recommendation on October 4, 2002 and a decision to close this section of the study was taken.

NDA 20-702/S-039 for atorvastatin is presented in Common Technical Document (CTD) format in accordance with the ICH guidelines on the Common Technical Document (CTD) and the January 1999 FDA guidance entitled "Providing Regulatory Submissions in Electronic Format - NDAs". As agreed with the Division during the March 26, 2003 pre-SNDA meeting, the contents of the CTD are in accord with regulations and FDA guidances on CTD and eNDA.

The CTD Table of Contents reflects the ICH guidances M4Q, M4S, and M4E. The full archival copy of the NDA/CTD is being submitted in electronic format in accordance with the January 1999 guidance. Each folder contains a Table of Contents organized according to the CTD organizational structure, with appropriate hypertext links. The electronic archive copy is contained in a CD-ROM 303 MB in size, with 2861 files and 577 folders. The CD-ROM has been scanned with McAfee Virus Scan Version 4.5.1 SP1 and is virus free. A paper review copy that has been produced from the same document management system accompanies the electronic archive copy.

Pfizer would like to bring to the Agency's attention the following points with regard to the ASCOT submission:

Pfizer is requesting a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR §25.31(b). The description of the proposed action is included in Module one of this submission.

A guide entitled "Information for Reviewers" is included to facilitate the review of this CTD (Module 1, 1.6.7). This document highlights particular aspects of the submission that have been agreed with FDA and provides a guide to the structure of the ASCOT CTD, including a detailed mapping of the cross-referencing to the individual components NDA

Please be advised that the application user fee for this submission has been remitted in accordance with the Prescription Drug User Fee Act of 1992.

This NDA is being submitted in accordance with laws and regulations on User Fees, Financial Disclosure by Clinical Investigators, Patent Information and Certification and Debarment Certification.

We consider NDA 20-702/S-039 to be complete for review by the Division and look forward to working closely with the Division. If you have any questions regarding this matter, please do not hesitate to call me at 212-733-4394 or send a facsimile to 212-857-3558.

Sincerely,

Christopher A. Graham
Director, Worldwide Regulatory Strategy

Enclosure

Regulatory Affairs
Pfizer Inc
235 E. 42nd Street 150/7/12
New York, NY 10017
Tel 212 733 4394 Fax 212 857 3558
Email chris.a.graham@pfizer.com

ORIGINAL
SUPPL NEW CORRESP

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Pfizer Pharmaceuticals Group

Christopher A. Graham
Director
Worldwide Regulatory Strategy

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September 18, 2003

David G. Orloff, MD
Director
Division of Metabolic and Endocrine Drug Products
Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

Re: Lipitor® (Atorvastatin Calcium) Tablets
NDA 20-702
General Correspondence

Dear Dr. Orloff:

The following information is being furnished to the Agency on behalf of, and as agent for Pfizer Ireland Pharmaceuticals, formerly known as Warner Lambert Export, Limited. Reference is made to our NDA 20-702 Lipitor® (atorvastatin calcium) tablets, which is indicated for the treatment of dyslipidemia.

Please find enclosed the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA) dataset that will be part of an upcoming submission to support a new indication for Lipitor for the prevention of cardiovascular disease. The enclosed CDs contain the following information:

- Table of Contents (TOC.PDF)
- 356H Form (356H.PDF)
- Cover letter (COVER.PDF)
- Dataset (*.XPT)
- Data define document (DEFINE.PDF)
- SAS programs (SAS version 6.12)
- Annotated Case Report Form (CRF.PDF)

This electronic file has been scanned with McAfee Virus Scan v.4.5.1 SP1 and is virus free. If you have any questions regarding this matter, please do not hesitate to call me at 212-733-4394 or send a facsimile to 212-857-3558.

Sincerely,

Christopher A. Graham
Director, Worldwide Regulatory Strategy

CC: Margaret Simoneau
Enid Galliers

ORIGINAL

RECEIVED
SEP 0 2 2003
FDR/CDER

Regulatory Affairs
Pfizer Inc
235 E. 42nd Street 150/7/12
New York, NY 10017
Tel 212 733 4394 Fax 212 857 3558
Email chris.a.graham@pfizer.com

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SEP 0 2 2003
FDR/CDER

Pfizer Pharmaceuticals Group

SUPPL NEW CORRESP

Christopher A. Graham
Director
Worldwide Regulatory Strategy

RECEIVED
AUG 2 9 2003
CDR/CDER

August 25, 2003

David G. Orloff, MD
Director
Division of Metabolic and Endocrine Drug Products (HFD-51)
Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

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Sincerely,

Christopher A. Graham
Director, Worldwide Regulatory Strategy

CC: Margaret Simoneau
Enid Galliers

Regulatory Affairs
Pfizer Inc
235 E. 42nd Street 150/7/12
New York, NY 10017
Tel 212 733 4394 Fax 212 857 3558
Email chris.a.graham@pfizer.com

e-mail
K.S.
Sept. 18 resubmit

Pfizer Pharmaceuticals Group

Christopher A. Graham
Director
Worldwide Regulatory Strategy

September 12, 2003

David G. Orloff, MD
Director
Division of Metabolic and Endocrine Drug Products (HFD-51)
Room 14B-19
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont Office Center II
5600 Fishers Lane
Rockville, Maryland 20857

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NDA 20-702
General Correspondence

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As discussed with Margaret Simoneau on September 8th, 2003, please be advised that Pfizer has identified a programming error in the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA) dataset CDs submitted to the Agency on August 25th, 2003. Therefore, Pfizer will be submitting a corrected version of the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA) dataset on September 18th 2003 that shoul be used with the upcoming submission to support a new indication for Lipitor for the prevention of cardiovascular disease.

If you have any questions regarding this matter, please do not hesitate to call me at 212-733-4394 or send a facsimile to 212-857-3558.

Sincerely,

Christopher A. Graham
Director, Worldwide Regulatory Strategy

CC: Margaret Simoneau