CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-261/S-033
NDA 21-192/S-005

Trade Name: Lescol

Generic Name: fluvastatin sodium

Sponsor: Novartis Phamaceutical Company

Approval Date: May 27, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-261/S-033
NDA 21-192/S-005

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-261/S-033
NDA 21-192/S-005

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-261/S-033
NDA 21-192/S-005

Novartis Pharmaceuticals Corporation
Attention: Lisa N. Pitt, PharmD
Associate Director, Drug Regulatory Affairs
59 Route 10
East Hanover, New Jersey
07936-1080

Dear Dr. Pitt:

Please refer to your supplemental new drug applications dated July 31, 2002, received August 1, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lescol (fluvastatin sodium) Capsules (NDA 20-261) and Lescol XL (fluvastatin sodium) Extended-Release Tablets (NDA 21-192).

We acknowledge receipt of your submissions dated August 9 and November 4 (NDA 21-192), 2002, and January 16, April 2 and 29, and May 9 and 20, 2003.

These supplemental new drug applications provide for a new indication, based on the results of the Lescol Intervention Prevention Study (LIPS), for the use of fluvastatin in patients with coronary heart disease to reduce the risk of undergoing coronary revascularization procedures. In addition, these supplemental applications provide for changes to the CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, and ADVERSE REACTIONS sections of the LESCOL and LESCOL XL package insert.

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted May 20, 2003) (copy enclosed).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. 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 ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 20-261/S-033, NDA 21-192/S-005." Approval of these submissions by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. 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, HF-2
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, 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/

David Orloff
5/27/03 06:17:32 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-261/S-033
NDA 21-192/S-005

APPROVED LABELING

NOVARTIS

T2003340
89011106

Lescol®
(fluvastatin sodium)
Capsules

Lescol® XL
(fluvastatin sodium)
Extended-Release Tablets

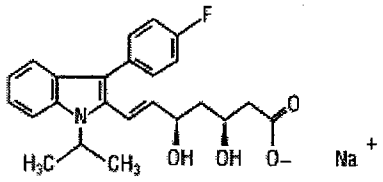
Rx only

Prescribing Information

DESCRIPTION

Lescol® (fluvastatin sodium), is a water-soluble cholesterol lowering agent which acts through the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase.

Fluvastatin sodium is [*R**,*S**-(*E*)]-(±)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1*H*-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid, monosodium salt. The empirical formula of fluvastatin sodium is $C_{24}H_{25}FNO_4$•Na, its molecular weight is 433.46 and its structural formula is:



$C_{24}H_{25}FNO_4 \cdot Na$ Mol. wt. 433.46

This molecular entity is the first entirely synthetic HMG-CoA reductase inhibitor, and is in part structurally distinct from the fungal derivatives of this therapeutic class.

Fluvastatin sodium is a white to pale yellow, hygroscopic powder soluble in water, ethanol and methanol. Lescol is supplied as capsules containing fluvastatin sodium, equivalent to 20 mg or 40 mg of fluvastatin, for oral administration. Lescol® XL (fluvastatin sodium) is supplied as extended-release tablets containing fluvastatin sodium, equivalent to 80 mg of fluvastatin, for oral administration.

Active Ingredient: fluvastatin sodium

Inactive Ingredients in capsules: gelatin, magnesium stearate, microcrystalline cellulose, pregelatinized starch (corn), red iron oxide, sodium lauryl sulfate, talc, titanium dioxide, yellow iron oxide, and other ingredients.

Capsules may also include: benzyl alcohol, black iron oxide, butylparaben, carboxymethylcellulose sodium, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide and sodium propionate.

Inactive Ingredients in extended-release tablets: microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, potassium bicarbonate, povidone, magnesium stearate, iron oxide yellow, titanium dioxide and polyethylene glycol 8000.

CLINICAL PHARMACOLOGY

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (Total-C), low density lipoprotein cholesterol (LDL-C), triglycerides (TG) and apolipoprotein B (a membrane transport complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-cholesterol (HDL-C) and its transport complex, apolipoprotein 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.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, 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.

In patients with hypercholesterolemia and mixed dyslipidemia, treatment with Lescol® (fluvastatin sodium) or Lescol® XL (fluvastatin sodium) reduced Total-C, LDL-C, apolipoprotein B, and triglycerides while producing an increase in HDL-C. Increases in HDL-C are greater in patients with low HDL-C (<35 mg/dL). Neither agent had a consistent effect on either Lp(a) or fibrinogen. The effect of Lescol or Lescol XL induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular mortality has not been determined.

Mechanism of Action

Lescol is a competitive inhibitor of HMG-CoA reductase, which is responsible for the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, a precursor of sterols, including cholesterol. The inhibition of cholesterol biosynthesis reduces the cholesterol in hepatic cells, which stimulates the synthesis of LDL receptors and thereby increases the uptake of LDL particles. The end result of these biochemical processes is a reduction of the plasma cholesterol concentration.

Pharmacokinetics/Metabolism

Oral Absorption

Fluvastatin is absorbed rapidly and completely following oral administration of the capsule, with peak concentrations reached in less than 1 hour. Following administration of a 10 mg dose, the absolute bioavailability is 24% (range 9%-50%). Administration with food reduces the rate but not the extent of absorption. At steady-state, administration of fluvastatin with the evening meal results in a two-fold decrease in C_{max} and more than two-fold increase in t_{max} as compared to administration 4 hours after the evening meal. No significant differences in

extent of absorption or in the lipid-lowering effects were observed between the two administrations. After single or multiple doses above 20 mg, fluvastatin exhibits saturable first-pass metabolism resulting in higher-than-expected plasma fluvastatin concentrations.

Fluvastatin has two optical enantiomers, an active 3R,5S and an inactive 3S,5R form. In vivo studies showed that stereo-selective hepatic binding of the active form occurs during the first pass resulting in a difference in the peak levels of the two enantiomers, with the active to inactive peak concentration ratio being about 0.7. The approximate ratio of the active to inactive approaches unity after the peak is seen and thereafter the two enantiomers decline with the same half-life. After an intravenous administration, bypassing the first-pass metabolism, the ratios of the enantiomers in plasma were similar throughout the concentration-time profiles.

Fluvastatin administered as Lescol XL 80 mg tablets reaches peak concentration in approximately 3 hours under fasting conditions, after a low-fat meal, or 2.5 hours after a low-fat meal. The mean relative bioavailability of the XL tablet is approximately 29% (range: 9%-66%) compared to that of the Lescol immediate release capsule administered under fasting conditions. Administration of a high fat meal delayed the absorption (T_{max}: 6H) and increased the bioavailability of the XL tablet by approximately 50%. Once Lescol XL begins to be absorbed, fluvastatin concentrations rise rapidly. The maximum concentration seen after a high fat meal is much less than the peak concentration following a single dose or twice daily dose of the 40 mg Lescol capsule. Overall variability in the pharmacokinetics of Lescol XL is large (42%-64% CV for C_{max} and AUC), and especially so after a high fat meal (63%-89% for C_{max} and AUC). Intrasubject variability in the pharmacokinetics of Lescol XL under fasting conditions (about 25% for C_{max} and AUC) tends to be much smaller as compared to the overall variability. Multiple peaks in plasma fluvastatin concentrations have been observed after Lescol XL administration.

Distribution

Fluvastatin is 98% bound to plasma proteins. The mean volume of distribution (VD_{ss}) is estimated at 0.35 L/kg. The parent drug is targeted to the liver and no active metabolites are present systemically. At therapeutic concentrations, the protein binding of fluvastatin is not affected by warfarin, salicylic acid and glyburide.

Metabolism

Fluvastatin is metabolized in the liver, primarily via hydroxylation of the indole ring at the 5- and 6-positions. N-dealkylation and beta-oxidation of the side-chain also occurs. The hydroxy metabolites have some pharmacologic activity, but do not circulate in the blood. Both enantiomers of fluvastatin are metabolized in a similar manner.

In vitro studies demonstrated that fluvastatin undergoes oxidative metabolism, predominantly via 2C9 isozyme systems (75%). Other isozymes that contribute to fluvastatin metabolism are 2C8 (~5%) and 3A4 (~20%). *(See PRECAUTIONS: Drug Interactions Section).*

Elimination

Fluvastatin is primarily (about 90%) eliminated in the feces as metabolites, with less than 2% present as unchanged drug. Urinary recovery is about 5%. After a radiolabeled dose of fluvastatin, the clearance was 0.8 L/h/kg. Following multiple oral doses of radiolabeled compound, there was no accumulation of fluvastatin; however, there was a 2.3 fold accumulation of total radioactivity.

Steady-state plasma concentrations show no evidence of accumulation of fluvastatin following immediate release capsule administration of up to 80 mg daily, as evidenced by a beta-elimination half-life of less than 3 hours. However, under conditions of maximum rate of absorption (i.e., fasting) systemic exposure to fluvastatin is increased 33% to 53% compared to a single 20 mg or 40 mg dose of the immediate release capsule. Following once daily administration of the 80 mg Lescol XL tablet for 7 days, systemic exposure to fluvastatin is increased (20%-30%) compared to a single dose of the 80 mg Lescol XL tablet. Terminal half-life of Lescol XL was about 9 hours as a result of the slow-release formulation.

Single-dose and steady-state pharmacokinetic parameters in 33 subjects with hypercholesterolemia for the capsules and in 35 healthy subjects for the extended-release tablets are summarized below:

Table 1
Single-dose and steady-state pharmacokinetic parameters

	C_{max} (ng/mL) mean±SD (range)	AUC (ng·h/mL) mean±SD (range)	t_{max} (hr) mean±SD (range)	CL/F (L/hr) mean±SD (range)	$t_{1/2}$ (hr) mean±SD (range)
Capsules					
20 mg single dose (n=17)	166±106 (48.9-517)	207±65 (111-288)	0.9±0.4 (0.5-2.0)	107±38.1 (69.5-181)	2.5±1.7 (0.5-6.6)
20 mg twice daily (n=17)	200±86 (71.8-366)	275±111 (91.6-467)	1.2±0.9 (0.5-4.0)	87.8±45 (42.8-218)	2.8±1.7 (0.9-6.0)
40 mg single dose (n=16)	273±189 (72.8-812)	456±259 (207-1221)	1.2±0.7 (0.75-3.0)	108±44.7 (32.8-193)	2.7±1.3 (0.8-5.9)
40 mg twice daily (n=16)	432±236 (119-990)	697±275 (359-1559)	1.2±0.6 (0.5-2.5)	64.2±21.1 (25.7-111)	2.7±1.3 (0.7-5.0)
Extended-Release Tablets 80 mg single dose (n=24)					
80 mg single dose, fasting (n=24)	126±53 (37-242)	579±341 (144-1760)	3.2± 2.6 (1-12)	-	-
80 mg single dose, fed-state high fat meal (n=-24)	183±163 (21-733)	861±632 (199-3132)	6 (2-24)	-	-
Extended-Release Tablets 80 mg following 7 days dosing (steady-state) (n-11)					
80 mg once daily, fasting (n=11)	102±42 (43.9-181)	630±326 (247-1406)	2.6±0.91. (1.5-4)	-	-

Special Populations

Renal Insufficiency: No significant (<6%) renal excretion of fluvastatin occurs in humans.

Hepatic Insufficiency: Fluvastatin is subject to saturable first-pass metabolism/sequestration by the liver and is eliminated primarily via the biliary route. Therefore, the potential exists for drug accumulation in patients with hepatic insufficiency. Caution should therefore be exercised when fluvastatin sodium is administered to patients with a history of liver disease or heavy alcohol ingestion *(see WARNINGS)*.

Fluvastatin AUC and C_{max} values increased by about 2.5 fold in hepatic insufficiency patients. This result was attributed to the decreased presystemic metabolism due to hepatic dysfunction. The enantiomer ratios of the two isomers of fluvastatin in hepatic insufficiency patients were comparable to those observed in healthy subjects.

Age: Plasma levels of fluvastatin are not affected by age.

Gender: Women tend to have slightly higher (but statistically insignificant) fluvastatin concentrations than men for the immediate release capsule. This is most likely due to body weight differences, as adjusting for body weight decreases the magnitude of the differences seen. For Lescol XL, there are 67% and 77% increases in systemic availability for women over men under fasted and high fat meal conditions.

Pediatric: No data are available. Fluvastatin is not indicated for use in the pediatric population.

CLINICAL STUDIES

Hypercholesterolemia (heterozygous familial and non familial) and Mixed Dyslipidemia

In 12 placebo-controlled studies in patients with Type IIa or IIb hyperlipoproteinemia, Lescol® (fluvastatin sodium) alone was administered to 1621 patients in daily dose regimens of 20 mg, 40 mg, and 80 mg (40 mg twice daily) for at least 6 weeks duration. After 24 weeks of treatment, daily doses of 20 mg, 40 mg, and 80 mg (40 mg twice daily) resulted in median LDL-C reductions of 22% (n=747), 25% (n=748) and 36% (n=257), respectively. Lescol treatment produced dose-related reductions in Apo B and in triglycerides and increases in HDL-C. The median (25^{th}, 75^{th} percentile) percent changes from baseline in HDL-C after 12 weeks of treatment with Lescol at daily doses of 20 mg, 40 mg and 80 mg (40 mg twice daily) were +2 (-4,+10), +5 (-2,+12), and +4 (-3,+12), respectively. In a subgroup of patients with primary mixed dyslipidemia, defined as baseline TG levels ≥200 mg/dL, treatment with Lescol also produced significant decreases in Total-C, LDL-C, TG and Apo B and variable increases in HDL-C. The median (25^{th}, 75^{th} percentile) percent changes from baseline in HDL-C after 12 weeks of treatment with Lescol at daily doses of 20 mg, 40 mg and 80 mg (40 mg twice daily) in this population were +4 (-2,+12), +8 (+1,+15), and +4 (-3,+13), respectively.

In a long-term open-label free titration study, after 96 weeks LDL-C decreases of 25% (20 mg, n=68), 31% (40 mg, n=298) and 34% (80 mg, n=209) were seen. No consistent effect on Lp(a) was observed.

Lescol® XL (fluvastatin sodium) Extended-Release Tablets have been studied in five controlled studies of patients with Type IIa or IIb hyperlipoproteinemia. Lescol XL was administered to over 900 patients in trials from 4 to 26 weeks in duration. In the three largest of these studies, Lescol XL given as a single daily dose of 80 mg significantly reduced Total-C, LDL-C, TG and Apo B. Therapeutic response is well established within two weeks, and a maximum response is achieved within four weeks. After four weeks of therapy, the median decrease in LDL-C was 38% and at week 24 endpoint the median LDL-C decrease was 35%. Significant increases in HDL-C were also observed. The median (25^{th} and 75^{th} percentile) percent changes from baseline in HDL-C for Lescol XL were +7(+0,+15) after 24 weeks of treatment.

Table 2
Median Percent Change in Lipid Parameters from Baseline to Week 24 Endpoint
All Placebo-Controlled Studies (Lescol) and Active Controlled Trials (Lescol XL)

	Total Chol.		TG		LDL		Apo B		HDL	
Dose	**N**	**% Δ**	**N**	**% Δ**	**N**	**% Δ**	**N**	**% Δ**	**N**	**% Δ**
All patients										
Lescol 20 mg[1]	747	-17	747	-12	747	-22	114	-19	747	+3
Lescol 40 mg[1]	748	-19	748	-14	748	-25	125	-18	748	+4
Lescol 40 mg twice daily[1]	257	-27	257	-18	257	-36	232	-28	257	+6
Lescol XL 80 mg[2]	750	-25	750	-19	748	-35	745	-27	750	+7
Baseline TG ≥200 mg/dL										
Lescol 20 mg[1]	148	-16	148	-17	148	-22	23	-19	148	+6
Lescol 40 mg[1]	179	-18	179	-20	179	-24	47	-18	179	+7
Lescol 40 mg twice daily[1]	76	-27	76	-23	76	-35	69	-28	76	+9
Lescol XL 80 mg[2]	239	-25	239	-25	237	-33	235	-27	239	+11

[1] Data for Lescol from 12 placebo controlled trials
[2] Data for Lescol XL 80 mg tablet from three 24 week controlled trials

In patients with primary mixed dyslipidemia (Fredrickson Type IIb) as defined by baseline plasma triglycerides levels ≥200 mg/dL, Lescol XL 80 mg produced a median reduction in triglycerides of 25%. In these patients, Lescol XL 80 mg produced median (25^{th} and 75^{th} percentile) percent change from baseline in HDL-C of +11(+3,+20). Significant decreases in Total-C, LDL-C, and Apo B were also achieved. In these studies, patients with triglycerides >400 mg/dL were excluded.

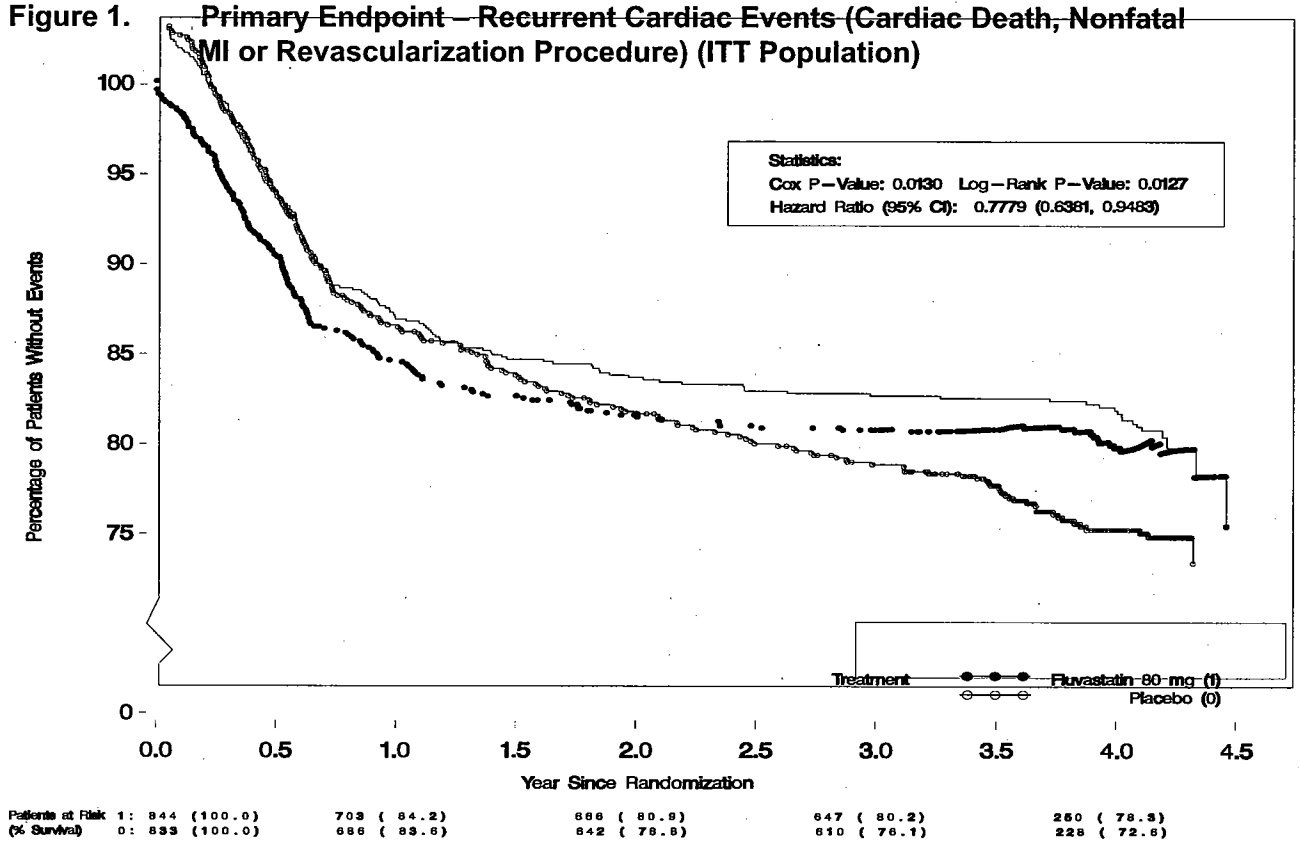
Reduction in the Risk of Recurrent Cardiac Events

In the Lescol Intervention Prevention Study, the effect of Lescol 40 mg administered twice daily on the risk of recurrent cardiac events (time to first occurrence of cardiac death, nonfatal myocardial infarction, or revascularization) was assessed in 1677 patients with coronary heart disease who had undergone a percutaneous coronary intervention (PCI) procedure (mean time from PCI to randomization = 3 days). In this multicenter, randomized, double-blind, placebo-controlled study, patients were treated with dietary/lifestyle counseling and either Lescol 40 mg (n = 844) or placebo (n = 833) given twice daily for a median of 3.9 years. The study population was 84% male, 98% Caucasian, with 37% >65 years of age. At baseline patients had total cholesterol between 100 and 367 mg/dL (mean 201 mg/dL), LDL-C between 42 and 243 mg/dL (mean 132 mg/dL), triglycerides between 15 and 270 mg/dL (mean 70 mg/dL) and HDL-C between 8 and 174 mg/dL (mean 39 mg/dL).

Lescol significantly reduced the risk of recurrent cardiac events (Figure 1) by 22% (p=0.013, 181 patients in the Lescol group vs 222 patients in the placebo group). Revascularization

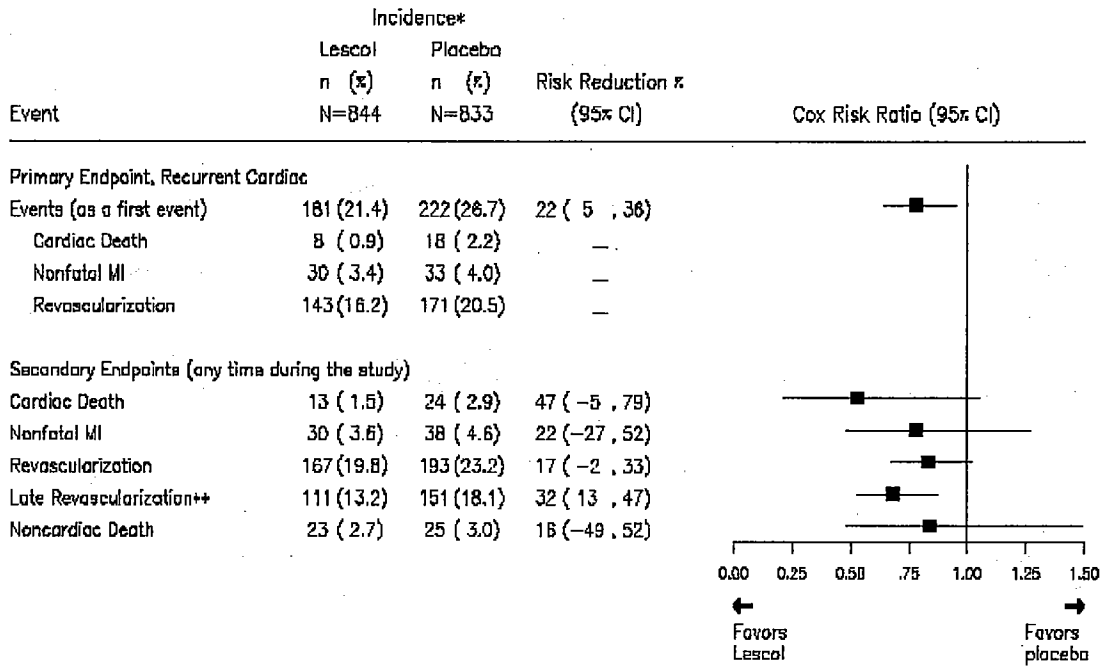
procedures comprised the majority of the initial recurrent cardiac events (143 revascularization procedures in the Lescol group and 171 in the placebo group). Consistent trends in risk reduction were observed in patients > 65 years of age.

Figure 1. Primary Endpoint – Recurrent Cardiac Events (Cardiac Death, Nonfatal MI or Revascularization Procedure) (ITT Population)



Outcome data for the Lescol Intervention Prevention Study are shown in Figure 2. After exclusion of revascularization procedures (CABG and repeat PCI) occurring within the first 6 months of the initial procedure involving the originally instrumented site, treatment with Lescol was associated with a 32% (p= 0.002) reduction in risk of late revascularization procedures (CABG or PCI occurring at the original site > 6 months after the initial procedure, or at another site).

Figure 2. Lescol Intervention Prevention Study – Primary and Secondary Endpoints



*Number of patients with events

**Excludes revascularization procedures of the target lesion within the first 6 months of the initial procedure

Atherosclerosis

In the Lipoprotein and Coronary Atherosclerosis Study (LCAS), the effect of Lescol therapy on coronary atherosclerosis was assessed by quantitative coronary angiography (QCA) in patients with coronary artery disease and mild to moderate hypercholesterolemia (baseline LDL-C range 115-190 mg/dL). In this randomized double-blind, placebo controlled trial, 429 patients were treated with conventional measures (Step 1 AHA Diet) and either Lescol 40 mg/day or placebo. In order to provide treatment to patients receiving placebo with LDL-C levels ≥160 mg/dL at baseline, adjunctive therapy with cholestyramine was added after week 12 to all patients in the study with baseline LDL-C values of ≥160 mg/dL. These baseline levels were present in 25% of the study population. Quantitative coronary angiograms were evaluated at baseline and 2.5 years in 340 (79%) angiographic evaluable patients.

Lescol significantly slowed the progression of coronary atherosclerosis. Compared to placebo, Lescol significantly slowed the progression of lesions as measured by within-patient per-lesion change in minimum lumen diameter (MLD), the primary endpoint (see Figure 1 below), percent diameter stenosis (Figure 2), and the formation of new lesions (13% of all fluvastatin patients versus 22% of all placebo patients). Additionally, a significant difference in favor of Lescol was found between all fluvastatin and all placebo patients in the distribution among the three categories of definite progression, definite regression, and mixed

or no change. Beneficial angiographic results (change in MLD) were independent of patients' gender and consistent across a range of baseline LDL-C levels.

Figure 3

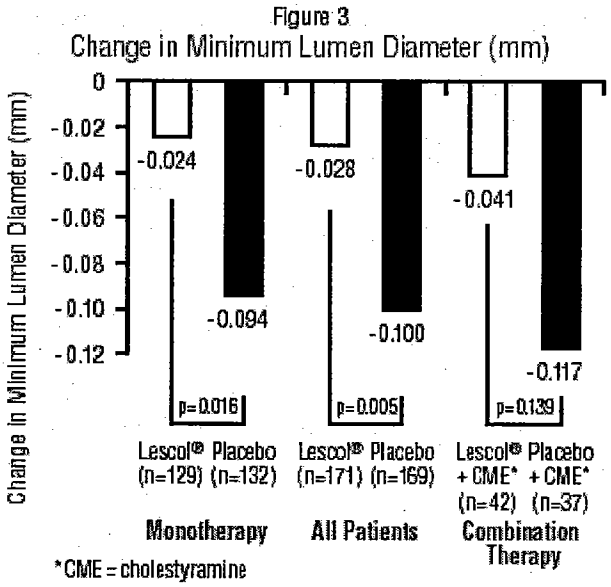
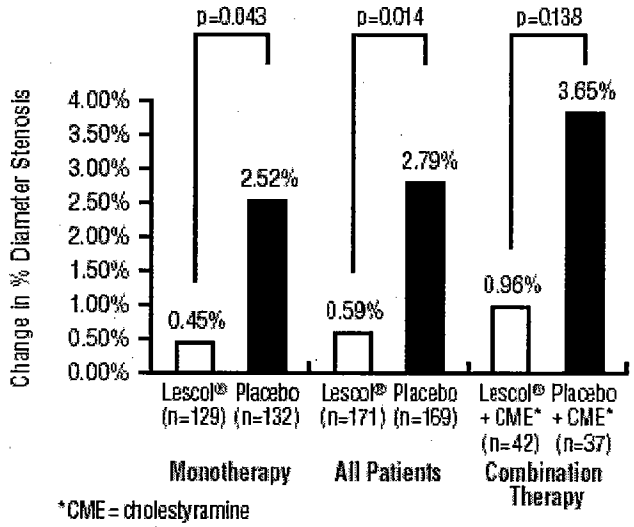


Figure 4



INDICATIONS AND USAGE

Therapy with lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol (see National Cholesterol Education Program (NCEP) Treatment Guidelines, below).

Hypercholesterolemia (heterozygous familial and non familial) and Mixed Dyslipidemia

Lescol® (fluvastatin sodium) and Lescol® XL (fluvastatin sodium) are indicated to reduce elevated total cholesterol (Total-C), LDL-C, TG and Apo B levels, and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIa and IIb) whose response to dietary restriction of saturated fat and cholesterol and other nonpharmacological measures has not been adequate.

Secondary Prevention of Coronary Events

In patients with coronary heart disease, Lescol and Lescol XL are indicated to reduce the risk of undergoing coronary revascularization procedures.

Atherosclerosis

Lescol and Lescol XL are also indicated to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total and LDL cholesterol to target levels.

Therapy with lipid-altering agents should be considered only after secondary causes for hyperlipidemia such as poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other medication, or alcoholism, have been excluded. Prior to initiation of fluvastatin sodium, a lipid profile should be performed to measure Total-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:

$$\text{LDL-C} = \text{Total-C} - \text{HDL-C} - 1/5\ \text{TG}$$

For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In many hypertriglyceridemic patients LDL-C may be low or normal despite elevated Total-C. In such cases, Lescol is not indicated.

Lipid determinations should be performed at intervals of no less than 4 weeks and dosage adjusted according to the patient's response to therapy.

The National Cholesterol Education Program (NCEP) Treatment Guidelines are summarized below:

Table 3
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† or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)††
2+ Risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥160
0-1 Risk factor†††	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

† CHD, coronary heart disease

†† Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100mg/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.

††† 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.

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

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

Table 4

Classification of Hyperlipoproteinemias

		Lipid Elevations	
Type	**Lipoproteins Elevated**	**Major**	**Minor**
I (rare)	Chylomicrons	TG	↑ → C
IIa	LDL	C	–
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C/TG	–
IV	VLDL	TG	↑ → C
V (rare)	Chylomicrons, VLDL	TG	↑ → C

C = cholesterol, TG = triglycerides, LDL = low density lipoprotein, VLDL = very low density lipoprotein, IDL = intermediate density lipoprotein

Neither Lescol nor Lescol XL have been studied in conditions where the major abnormality is elevation of chylomicrons, VLDL, or IDL (i.e., hyperlipoproteinemia Types I, III, IV, or V).

CONTRAINDICATIONS

Hypersensitivity to any component of this medication. Lescol® (fluvastatin sodium) and Lescol® XL (fluvastatin sodium) are contraindicated in patients with active liver disease or unexplained, persistent elevations in serum transaminases *(see WARNINGS)*.

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. **Fluvastatin sodium 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 class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes

Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents. Approximately 1.1% of patients treated with Lescol® (fluvastatin sodium) capsules in worldwide trials developed dose-related, persistent elevations of transaminase levels to more than 3 times the upper limit of normal. Fourteen of these patients (0.6%) were discontinued from therapy. In all clinical trials, a total of 33/2969 patients (1.1%) had persistent transaminase elevations with an average fluvastatin exposure of approximately 71.2 weeks; 19 of these patients (0.6%) were discontinued. The majority of patients with these abnormal biochemical findings were asymptomatic.

In a pooled analysis of all placebo-controlled studies in which Lescol capsules were used, persistent transaminase elevations (>3 times the upper limit of normal [ULN] on two consecutive weekly measurements) occurred in 0.2%, 1.5%, and 2.7% of patients treated with 20, 40, and 80 mg (titrated to 40 mg twice daily) Lescol capsules, respectively. Ninety-one percent of the cases of persistent liver function test abnormalities (20 of 22 patients) occurred within 12 weeks of therapy and in all patients with persistent liver function test abnormalities there was an abnormal liver function test present at baseline or by week 8.

In the pooled analysis of the 24-week controlled trials, persistent transaminase elevation occurred in 1.9%, 1.8% and 4.9% of patients treated with Lescol® XL (fluvastatin sodium) 80 mg, Lescol 40 mg and Lescol 40 mg twice daily, respectively. In 13 of 16 patients treated with Lescol XL the abnormality occurred within 12 weeks of initiation of treatment with Lescol XL 80 mg.

It is recommended that liver function tests be performed before the initiation of therapy and at 12 weeks following initiation of treatment or elevation in dose. Patients who develop transaminase elevations or signs and symptoms of liver disease should be monitored to confirm the finding and should be followed thereafter with frequent liver function tests until the levels return to normal. Should an increase in AST or ALT of three times the upper limit of normal or greater persist (found on two consecutive occasions) withdrawal of fluvastatin sodium therapy is recommended.

Active liver disease or unexplained transaminase elevations are contraindications to the use of Lescol and Lescol XL *(see CONTRAINDICATIONS)*. Caution should be exercised when fluvastatin sodium is administered to patients with a history of liver disease or heavy alcohol ingestion *(see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism)*. Such patients should be closely monitored.

Skeletal Muscle

Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with fluvastatin and with other drugs in this class. Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal, has been reported.

Myopathy should be considered in any patients 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. Fluvastatin sodium therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Fluvastatin sodium therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.

The risk of myopathy and or rhabdomyolysis during treatment with HMG-CoA reductase inhibitors has been reported to be increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. Myopathy was not observed in a clinical trial in 74 patients involving patients who were treated with fluvastatin sodium together with niacin.

Uncomplicated myalgia has been observed infrequently in patients treated with Lescol at rates indistinguishable from placebo.

The use of fibrates alone may occasionally be associated with myopathy. The combined use of HMG-CoA reductase inhibitors and fibrates should generally be avoided.

PRECAUTIONS

General

Before instituting therapy with Lescol® (fluvastatin sodium) or Lescol® XL (fluvastatin sodium), 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)*.

The HMG-CoA reductase inhibitors may cause elevation of creatine phosphokinase and transaminase levels *(see WARNINGS and ADVERSE REACTIONS)*. This should be considered in the differential diagnosis of chest pain in a patient on therapy with fluvastatin sodium.

Homozygous Familial Hypercholesterolemia

HMG-CoA reductase inhibitors are reported to be less effective in patients with rare homozygous familial hypercholesterolemia, possibly because these patients have few functional LDL receptors.

Information for Patients

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

Women should be informed that if they become pregnant while receiving Lescol or Lescol XL the drug should be discontinued immediately to avoid possible harmful effects on a developing fetus from a relative deficit of cholesterol and biological products derived from cholesterol. In addition, Lescol or Lescol XL should not be taken during nursing. *(See CONTRAINDICATIONS.)*

Drug Interactions

The below listed drug interaction information is derived from studies using immediate release fluvastatin. Similar studies have not been conducted using the Lescol XL tablet.

Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin *(See WARNINGS: Skeletal Muscle).*

In vitro data indicate that fluvastatin metabolism involves multiple Cytochrome P450 (CYP) isozymes. CYP2C9 isoenzyme is primarily involved in the metabolism of fluvastatin (~75%), while CYP2C8 and CYP3A4 isoenzymes are involved to a much less extent, i.e. ~5% and ~20%, respectively. If one pathway is inhibited in the elimination process of fluvastatin other pathways may compensate.

In vivo drug interaction studies with CYP3A4 inhibitors/substrates such as cyclosporine, erythromycin, and itraconazle result in minimal changes in the pharmacokinetics of fluvastatin, confirming less involvement of CYP3A4 isozyme. Concomitant administration of fluvastatin and phenytoin increased the levels of phenytoin and fluvastatin, suggesting predominant involvement of CYP2C9 in fluvastatin metabolism.

Niacin/Propranolol: Concomitant administration of immediate release fluvastatin sodium with niacin or propranolol has no effect on the bioavailability of fluvastatin sodium.

Cholestyramine: Administration of immediate release fluvastatin sodium concomitantly with, or up to 4 hours after cholestyramine, results in fluvastatin decreases of more than 50% for AUC and 50%-80% for C_{max}. However, administration of immediate release fluvastatin sodium 4 hours after cholestyramine resulted in a clinically significant additive effect compared with that achieved with either component drug.

Cyclosporine: Plasma cyclosporine levels remain unchanged when fluvastatin (20 mg daily) was administered concurrently in renal transplant recipients on stable cyclosporine regimens. Fluvastatin AUC increased 1.9 fold, and C_{max} increased 1.3 fold compared to historical controls.

Digoxin: In a crossover study involving 18 patients chronically receiving digoxin, a single 40 mg dose of immediate release fluvastatin had no effect on digoxin AUC, but had an 11% increase in digoxin C_{max} and small increase in digoxin urinary clearance.

Erythromycin: Erythromycin (500 mg, single dose) did not affect steady-state plasma levels of fluvastatin (40 mg daily).

Itraconazole: Concomitant administration of fluvastatin (40 mg) and itraconazole (100 mg daily x 4 days) does not affect plasma itraconazole or fluvastatin levels.

Gemfibrozil: There is no change in either fluvastatin (20 mg twice daily) or gemfibrozil (600 mg twice daily) plasma levels when these drugs are co-administered.

Phenytoin: Single morning dose administration of phenytoin (300 mg extended release) increased mean steady-state fluvastatin (40 mg) C_{max} by 27% and AUC by 40% whereas fluvastatin increased the mean phenytoin C_{max} by 5% and AUC by 20%. Patients on phenytoin should continue to be monitored appropriately when fluvastatin therapy is initiated or when the fluvastatin dosage is changed.

Diclofenac: Concurrent administration of fluvastatin (40 mg) increased the mean C_{max} and AUC of diclofenac by 60% and 25% respectively.

Tolbutamide: In healthy volunteers, concurrent administration of either single or multiple daily doses of fluvastatin sodium (40 mg) with tolbutamide (1 g) did not affect the plasma levels of either drug to a clinically significant extent.

Glibenclamide (Glyburide): In glibenclamide-treated NIDDM patients (n=32), administration of fluvastatin (40 mg twice daily for 14 days) increased the mean C_{max}, AUC, and $t_{1/2}$ of glibenclamide approximately 50%, 69% and 121%, respectively. Glibenclamide (5-20 mg daily) increased the mean C_{max} and AUC of fluvastatin by 44% and 51%, respectively. In this study there were no changes in glucose, insulin and C-peptide levels. However, patients on concomitant therapy with glibenclamide (glyburide) and fluvastatin should continue to be monitored appropriately when their fluvastatin dose is increased to 40 mg twice daily.

Losartan: Concomitant administration of fluvastatin with losartan has no effect on the bioavailability of either losartan or its active metabolite.

Cimetidine/Ranitidine/Omeprazole: Concomitant administration of immediate release fluvastatin sodium with cimetidine, ranitidine and omeprazole results in a significant increase in the fluvastatin C_{max} (43%, 70% and 50%, respectively) and AUC (24%-33%), with an 18%-23% decrease in plasma clearance.

Rifampicin: Administration of immediate release fluvastatin sodium to subjects pretreated with rifampicin results in significant reduction in C_{max} (59%) and AUC (51%), with a large increase (95%) in plasma clearance.

Warfarin: In vitro protein binding studies demonstrated no interaction at therapeutic concentrations. Concomitant administration of a single dose of warfarin (30 mg) in young healthy males receiving immediate release fluvastatin sodium (40 mg/day x 8 days) resulted in no elevation of racemic warfarin concentration. There was also no effect on prothrombin complex activity when compared to concomitant administration of placebo and warfarin. However, bleeding and/or increased prothrombin times have been reported in patients taking

coumarin anticoagulants concomitantly with other HMG-CoA reductase inhibitors. Therefore, patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when fluvastatin sodium is initiated or the dosage of fluvastatin sodium is changed.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production.

Fluvastatin exhibited no effect upon non-stimulated cortisol levels and demonstrated no effect upon thyroid metabolism as assessed by TSH. Small declines in total testosterone have been noted in treated groups, but no commensurate elevation in LH occurred, suggesting that the observation was not due to a direct effect upon testosterone production. No effect upon FSH in males was noted. Due to the limited number of premenopausal females studied to date, no conclusions regarding the effect of fluvastatin upon female sex hormones may be made.

Two clinical studies in patients receiving fluvastatin at doses up to 80 mg daily for periods of 24 to 28 weeks demonstrated no effect of treatment upon the adrenal response to ACTH stimulation. A clinical study evaluated the effect of fluvastatin at doses up to 80 mg daily for 28 weeks upon the gonadal response to HCG stimulation. Although the mean total testosterone response was significantly reduced ($p<0.05$) relative to baseline in the 80 mg group, it was not significant in comparison to the changes noted in groups receiving either 40 mg of fluvastatin or placebo.

Patients treated with fluvastatin sodium who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g., ketoconazole, spironolactone, or cimetidine) that may decrease the levels of endogenous steroid hormones.

CNS Toxicity

CNS effects, as evidenced by decreased activity, ataxia, loss of righting reflex, and ptosis were seen in the following animal studies: the 18-month mouse carcinogenicity study at 50 mg/kg/day, the 6-month dog study at 36 mg/kg/day, the 6-month hamster study at 40 mg/kg/day, and in acute, high-dose studies in rats and hamsters (50 mg/kg), rabbits (300 mg/kg) and mice (1500 mg/kg). CNS toxicity in the acute high-dose studies was characterized (in mice) by conspicuous vacuolation in the ventral white columns of the spinal cord at a dose of 5000 mg/kg and (in rat) by edema with separation of myelinated fibers of the ventral spinal tracts and sciatic nerve at a dose of 1500 mg/kg. CNS toxicity, characterized by periaxonal vacuolation, was observed in the medulla of dogs that died after treatment for 5 weeks with 48 mg/kg/day; this finding was not observed in the remaining dogs when the dose level was lowered to 36 mg/kg/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. No CNS lesions have been observed after chronic treatment for up to 2 years with fluvastatin in the mouse (at doses up to 350 mg/kg/day), rat (up to 24 mg/kg/day), or dog (up to 16 mg/kg/day).

Prominent bilateral posterior Y suture lines in the ocular lens were seen in dogs after treatment with 1, 8, and 16 mg/kg/day for 2 years.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year study was performed in rats at dose levels of 6, 9, and 18-24 (escalated after 1 year) mg/kg/day. These treatment levels represented plasma drug levels of approximately 9, 13, and 26-35 times the mean human plasma drug concentration after a 40 mg oral dose. A low incidence of forestomach squamous papillomas and 1 carcinoma of the forestomach at the 24 mg/kg/day dose level was considered to reflect the prolonged hyperplasia induced by direct contact exposure to fluvastatin sodium rather than to a systemic effect of the drug. In addition, an increased incidence of thyroid follicular cell adenomas and carcinomas was recorded for males treated with 18-24 mg/kg/day. The increased incidence of thyroid follicular cell neoplasm in male rats with fluvastatin sodium appears to be consistent with findings from other HMG-CoA reductase inhibitors. In contrast to other HMG-CoA reductase inhibitors, no hepatic adenomas or carcinomas were observed.

The carcinogenicity study conducted in mice at dose levels of 0.3, 15 and 30 mg/kg/day revealed, as in rats, a statistically significant increase in forestomach squamous cell papillomas in males and females at 30 mg/kg/day and in females at 15 mg/kg/day. These treatment levels represented plasma drug levels of approximately 0.05, 2, and 7 times the mean human plasma drug concentration after a 40 mg oral dose.

No evidence of mutagenicity was observed in vitro, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; malignant transformation assay in BALB/3T3 cells; unscheduled DNA synthesis in rat primary hepatocytes; chromosomal aberrations in V79 Chinese Hamster cells; HGPRT V79 Chinese Hamster cells. In addition, there was no evidence of mutagenicity in vivo in either a rat or mouse micronucleus test.

In a study in rats at dose levels for females of 0.6, 2 and 6 mg/kg/day and at dose levels for males of 2, 10 and 20 mg/kg/day, fluvastatin sodium had no adverse effects on the fertility or reproductive performance.

Seminal vesicles and testes were small in hamsters treated for 3 months at 20 mg/kg/day (approximately three times the 40 milligram human daily dose based on surface area, mg/m^2). There was tubular degeneration and aspermatogenesis in testes as well as vesiculitis of seminal vesicles. Vesiculitis of seminal vesicles and edema of the testes were also seen in rats treated for 2 years at 18 mg/kg/day (approximately 4 times the human C_{max} achieved with a 40 milligram daily dose).

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS.

Fluvastatin sodium produced delays in skeletal development in rats at doses of 12 mg/kg/day and in rabbits at doses of 10 mg/kg/day. Malaligned thoracic vertebrae were seen in rats at 36 mg/kg, a dose that produced maternal toxicity. These doses resulted in 2 times (rat at

12 mg/kg) or 5 times (rabbit at 10 mg/kg) the 40 mg human exposure based on mg/m^2 surface area. A study in which female rats were dosed during the third trimester at 12 and 24 mg/kg/day resulted in maternal mortality at or near term and postpartum. In addition, fetal and neonatal lethality were apparent. No effects on the dam or fetus occurred at 2 mg/kg/day. A second study at levels of 2, 6, 12 and 24 mg/kg/day confirmed the findings in the first study with neonatal mortality beginning at 6 mg/kg. A modified Segment III study was performed at dose levels of 12 or 24 mg/kg/day with or without the presence of concurrent supplementation with mevalonic acid, a product of HMG-CoA reductase which is essential for cholesterol biosynthesis. The concurrent administration of mevalonic acid completely prevented the maternal and neonatal mortality but did not prevent low body weights in pups at 24 mg/kg on days 0 and 7 postpartum. Therefore, the maternal and neonatal lethality observed with fluvastatin sodium reflect its exaggerated pharmacologic effect during pregnancy. There are no data with fluvastatin sodium in pregnant women. However, rare reports of congenital anomalies have been received following intrauterine exposure to other 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 another HMG-CoA reductase inhibitor with dextroamphetamine sulfate during the first trimester of pregnancy. **Lescol or Lescol XL 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 a woman becomes pregnant while taking Lescol or Lescol XL, the drug should be discontinued and the patient advised again as to the potential hazards to the fetus. .

Nursing Mothers

Based on preclinical data, drug is present in breast milk in a 2:1 ratio (milk:plasma). Because of the potential for serious adverse reactions in nursing infants, nursing women should not take Lescol or Lescol XL *(see CONTRAINDICATIONS)*.

Pediatric Use

Safety and effectiveness in individuals less than 18 years old have not been established. Treatment in patients less than 18 years of age is not recommended at this time.

Geriatric Use

The effect of age on the pharmacokinetics of immediate release fluvastatin sodium was evaluated. Results indicate that for the general patient population plasma concentrations of fluvastatin sodium do not vary as a function of age. *(See also CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism.)* Elderly patients (≥65 years of age) demonstrated a greater treatment response in respect to LDL-C, Total-C and LDL/HDL ratio than patients <65 years of age.

ADVERSE REACTIONS

In all clinical studies of Lescol® (fluvastatin sodium), 1.0% (32/2969) of fluvastatin-treated patients were discontinued due to adverse experiences attributed to study drug (mean exposure approximately 16 months ranging in duration from 1 to >36 months). This results in

an exposure adjusted rate of 0.8% (32/4051) per patient year in fluvastatin patients in controlled studies compared to an incidence of 1.1% (4/355) in placebo patients. Adverse reactions have usually been of mild to moderate severity.

In controlled clinical studies, 3.9% (36/912) of patients treated with Lescol® XL (fluvastatin sodium) 80 mg discontinued due to adverse events (causality not determined).

Clinically relevant adverse experiences occurring in the Lescol and Lescol XL controlled studies with a frequency >2%, regardless of causality, include the following:

Table 5
Clinically relevant adverse experiences occurring in >2% patients in Lescol and Lescol XL controlled studies

Adverse Event	Lescol[1] (%) (N=2326)	Placebo[1] (%) (N=960)	Lescol XL[2] (%) (N = 912)
Musculoskeletal			
Myalgia	5.0	4.5	3.8
Arthritis	2.1	2.0	1.3
Arthropathy	NA	NA	3.2
Respiratory			
Sinusitis	2.6	1.9	3.5
Bronchitis	1.8	1.0	2.6
Gastrointestinal			
Dyspepsia	7.9	3.2	3.5
Diarrhea	4.9	4.2	3.3
Abdominal Pain	4.9	3.8	3.7
Nausea	3.2	2.0	2.5
Flatulence	2.6	2.5	1.4
Psychiatric Disorders			
Insomnia	2.7	1.4	0.8
Genitourinary			
Urinary Tract Infection	1.6	1.1	2.7
Miscellaneous			
Headache	8.9	7.8	4.7
Influenza-Like Symptoms	5.1	5.7	7.1
Accidental Trauma	5.1	4.8	4.2
Fatigue	2.7	2.3	1.6
Allergy	2.3	2.2	1.0

[1] Controlled trials with Lescol Capsules (20 and 40 mg daily and 40 mg twice daily)
[2] Controlled trials with Lescol XL 80 mg Tablets

The following effects have been reported with drugs in this class. Not all the effects listed below have necessarily been associated with fluvastatin sodium therapy.

Skeletal: muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances, anxiety, insomnia, depression.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura,

thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: alopecia, pruritus. A variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

Concomitant Therapy

Fluvastatin sodium has been administered concurrently with cholestyramine and nicotinic acid. No adverse reactions unique to the combination or in addition to those previously reported for this class of drugs alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. *(See WARNINGS: Skeletal Muscle.)*

OVERDOSAGE

The approximate oral LD_{50} is greater than 2 g/kg in mice and greater than 0.7 g/kg in rats.

The maximum single oral dose of Lescol® (fluvastatin sodium) capsules received by healthy volunteers was 80 mg. No clinically significant adverse experiences were seen at this dose. The maximum dose administered with an extended-release formulation was 640 mg for two weeks. This dose was not well tolerated and produced a variety of GI complaints and an increase in transaminase values (i.e., SGOT and SGPT).

There has been a single report of 2 children, one 2 years old and the other 3 years of age, either of whom may have possibly ingested fluvastatin sodium. The maximum amount of fluvastatin sodium that could have been ingested was 80 mg (4 x 20 mg capsules). Vomiting was induced by ipecac in both children and no capsules were noted in their emesis. Neither child experienced any adverse symptoms and both recovered from the incident without problems.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required. The dialyzability of fluvastatin sodium and of its metabolites in humans is not known at present.

Information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Regional Poison Control Centers are listed in the Physicians' Desk Reference®.*

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving Lescol® (fluvastatin sodium) or Lescol® XL (fluvastatin sodium) and should continue on this diet during treatment with Lescol or Lescol XL. (See NCEP Treatment Guidelines for details on dietary therapy.)

For patients requiring LDL-C reduction to a goal of ≥25%, the recommended starting dose is 40 mg as one capsule, 80 mg as one Lescol XL tablet administered as a single dose in the evening or 80 mg in divided doses of the 40 mg capsule given twice daily. For patients requiring LDL-C reduction to a goal of <25% a starting dose of 20 mg may be used. The recommended dosing range is 20-80 mg/day. Lescol or Lescol XL may be taken without regard to meals, since there are no apparent differences in the lipid-lowering effects of fluvastatin sodium administered with the evening meal or 4 hours after the evening meal. Since the maximal reductions in LDL-C of a given dose are seen within 4 weeks, periodic lipid determinations should be performed and dosage adjustment made according to the patient's response to therapy and established treatment guidelines. The therapeutic effect of Lescol or Lescol XL is maintained with prolonged administration.

Concomitant Therapy

Lipid-lowering effects on total cholesterol and LDL cholesterol are additive when immediate release Lescol is combined with a bile-acid binding resin or niacin. When administering a bile-acid resin (e.g., cholestyramine) and fluvastatin sodium, Lescol should be administered at bedtime, at least 2 hours following the resin to avoid a significant interaction due to drug binding to resin. *(See also ADVERSE REACTIONS: Concomitant Therapy.)*

Dosage in Patients with Renal Insufficiency

Since fluvastatin sodium is cleared hepatically with less than 6% of the administered dose excreted into the urine, dose adjustments for mild to moderate renal impairment are not necessary. Fluvastatin has not been studied at doses greater than 40 mg in patients with severe renal impairment; therefore caution should be exercised when treating such patients at higher doses.

HOW SUPPLIED

Lescol® (fluvastatin sodium) Capsules

20 mg

Brown and light brown imprinted twice with "  " and "20" on one half and "LESCOL" and the Lescol® (fluvastatin sodium) logo twice on the other half of the capsule.

Bottles of 30 capsules.....(NDC 0078-0176-15)
Bottles of 100 capsules.....(NDC 0078-0176-05)

40 mg

Brown and gold imprinted twice with " " and "40" on one half and "LESCOL" and the Lescol® (fluvastatin sodium) logo twice on the other half of the capsule.

Bottles of 30 capsules.....(NDC 0078-0234-15)
Bottles of 100 capsules.....(NDC 0078-0234-05)

Lescol® XL (fluvastatin sodium) Extended-Release Tablets

80 mg

Yellow, round, slightly biconvex film-coated tablet with beveled edges debossed with "Lescol XL" on one side and "80" on the other.

Bottles of 30 tablets.....(NDC 0078-0354-15)
Bottle of 100 tablets.....(NDC 0078-0354-05)

Store and Dispense

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F). [See USP Controlled Room Temperature]. Dispense in a tight container. Protect from light.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-261/S-033
NDA 21-192/S-005

MEDICAL REVIEW(s)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: May 23, 2003

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 20-261/S-033
Lescol, Lescol XL (fluvastatin sodium) tablets
Novartis
Proposed changes to labeling based on LIPS

SUBJECT: NDA review issues and recommended action

Background

This sNDA proposes changes to the labeling for Lescol and Lescol XL based on the results of the Lescol Intervention Prevention Study (LIPS). This was a placebo-controlled trial of ~1600 men and women with CAD and a recent percutaneous coronary intervention (PCI) that examined the effect of a median 3.9 years duration of therapy with Lescol 80 mg vs. placebo on the time to first event among those comprising the composite CHD outcome variable: fatal CHD, NFMI, or coronary revascularization. Mean age at entry was 60 years; mean LDL-C was ~130 mg/dL.

Lescol therapy reduced the risk of a recurrent coronary events by 22% (222 events pbo vs. 181 events Lescol; 26.7% pbo vs. 21.4% drug).

Drs. Pariser and Parks have thoroughly reviewed and summarized the results of the study. This brief memo will address the rationale behind the approach to labeling based on the study.

Labeling

The use of a composite primary endpoint in this and other cardiovascular disease trials is rationalized based upon a detailed understanding of the pathogenesis and natural history of atherosclerotic disease. That is, it is a systemic vascular disease with clinical consequences in multiple vascular beds, specifically coronary, peripheral, and cerebral systems. Furthermore, and with particular reference to this trial, there exists a spectrum of manifestations in each of these areas. In the coronary tree, atherosclerosis manifests as angina, MI (fatal or non-fatal), need for revascularization, and sudden cardiac death.

As has been the case in many trials, utilizing the composite "approach," the results of the trial are usually "driven" by revascularization procedures, insofar as angioplasty/stent and CABG are intended to and do preempt events related to coronary occlusion and more dramatic myocardial ischemia. While this is a boon for patients, it means that when the results of the primary endpoint analysis are broken down by individual components of the composite, the differences

between treatment groups for each component are not always statistically significant. In inferring an effect of treatment vs. placebo, we rely first on the primary (composite endpoint) analysis showing statistically significant difference and then secondarily examine the differences between treatment groups for the elements of the composite. As a matter of policy, only those differences that are nominally statistically significant direct labeling with regard to expected benefits of therapy.

So, in LIPS, the overall composite result was significant, favoring Lescol. The analysis of the individual elements of the composite revealed that the overall effect on the composite was "driven" by revascularization events, and the difference was borderline significant (0.052). When events occurring in the first 6 months of treatment at the site of the original intervention were excluded, the risk reduction for such non-early restenosis events was greater (32%) and highly significant (p=0.002).

The drug was thus labeled in Clinical Pharmacology based on reduction in risk for "recurrent cardiac events" and a table was included that summarized the endpoint results with risk reductions and confidence intervals for the composite primary and for the secondary endpoints showing that late revascularization was the only statistically significantly impacted outcome. In Indications, the expected benefits of Lescol as supported by LIPS were described under "Secondary Prevention of Coronary Events" as intended to "reduce the risk of undergoing coronary revascularization procedures." This was based upon the fact that this was the only significant effect observed in the trial.

The sponsor and the division have agreed on this labeling.

Recommendation
Approve

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/s/

David Orloff
5/23/03 04:30:56 PM
MEDICAL OFFICER

MEDICAL TEAM LEADER'S MEMO OF EFFICACY SUPPLEMENT

NDA	20-261/S033
Sponsor	Novartis Pharmaceuticals, Inc
Drug	Lescol (fluvastatin), Lescol XL
Date of Submission	July 31, 2002
Primary Medical Officer	Anne R. Pariser, MD
Statistical Reviewer	David Hoberman, PhD Todd Sahlroot, PhD

EXECUTIVE SUMMARY

The Lescol Intervention Prevention Study (LIPS) is a clinical outcome study in a secondary prevention population whose patients were identified by the need for a percutaneous coronary intervention (PCI) procedure. This study corroborates the findings from other studies which established a reduction in risk of recurrent cardiac events associated with statin therapy.

Similar to other clinical outcome studies involving statins, the primary endpoint in LIPS was a composite measure. The rationale here is that the individual components of the combined endpoint represent different clinical manifestations of the underlying disease process. These components, when measured alone, might not occur in sufficient quantity to establish a therapeutic benefit but when combined, provide an increased number of events to establish a significant risk reduction associated with drug treatment. The results of LIPS show that fluvastatin therapy in patients with established heart disease reduced the risk of having either a fatal cardiac event, a nonfatal MI, or a revascularization procedure by 22% (p=0.013).

When reviewing these trials, however, it is important to evaluate the individual components to determine to what extent each event contributes to the overall risk reduction. In LIPS, revascularization procedures comprised the majority of initial recurrent coronary events with 77 to 79% of the two treatment groups experiencing either a PCI or CABG after study randomization. The risk of experiencing any revascularization procedure after randomization was reduced by 17% in the fluvastatin group (p=0.052). However, as these patients all had a percutaneous coronary procedure performed at baseline, some of these events may have been secondary to restenosis as opposed to atherosclerosis progression. An analysis of the revascularization procedures, taking into consideration only those events that are due atherosclerosis, revealed an statistically significant reduction in risk of undergoing a coronary revascularization procedure associated with fluvastatin therapy (32% RR, p=0.002).

Overall, fluvastatin therapy in patients with established coronary disease reduces the risk of experiencing a recurrent coronary event. In the LIPS cohort, the predominant initial coronary event was a coronary revascularization procedure. Fluvastatin therapy had its most profound effect on reducing the need for having revascularization procedure secondary to atherosclerotic heart disease.

CLINICAL STUDY DESIGN

The Lescol Intervention Prevention Study (LIPS) was a randomized, double-blind, placebo-controlled study in 1,677 patients who had undergone a percutaneous coronary intervention (PCI) procedure in the preceding 6 months. Patients were randomized to treatment with either Lescol 80 mg daily (n=844) or placebo (n=833).

The primary efficacy measure was a composite one consisting of cardiac death, nonfatal MI, or a revascularization procedure of the coronaries (CABG or PTCA).

Eligibility Criteria

Men or women, ages 18-80 years, having undergone a successful PCI of 1 or more lesions in the native coronary arteries were eligible if they had the following:

- TC ≥ 135 mg/dL and < 270 mg/dL
- fasting TG < 400 mg/dL

Patient Population

The mean age of the cohort was 60 years and 84% were male. Overall, the two treatment groups were balanced by age, gender, BMI, coronary disease (single- or double-vessel), and relevant medical history contributing to heart disease. Tables 4 and 5 from Dr. Pariser's review summarizes baseline demographics and patient characteristics in LIPS.

Mean baseline lipid levels in the cohort were: LDL-C 131.4 mg/dL, HDL-C 38.7 mg/dL, Total-C 201 mg/dL, and TG 159.4 mg/dL.

Approximately two-thirds (65%) of the cohort underwent PTCA plus an additional procedure (e.g., stent placement or rotational ablation), while 35% had PTCA alone. There were no differences in baseline intervention procedures between the two treatment groups.

Ninety-three percent of the cohort completed the trial and the median treatment period was 3.9 years. A total of 660 patients (39%) discontinued study medication with more discontinuations occurring in the placebo group (44%) than the fluvastatin group (35%). The most common reasons were poor compliance or personal although more patients in the placebo group initiated off-protocol lipid-altering therapy than the fluvastatin group.

PRIMARY EFFICACY RESULTS

The primary endpoint measure was a composite one comprised of cardiac death, nonfatal MI, or a revascularization procedure. There were 181 patients who experienced a cardiac death, nonfatal MI, or revascularization procedure in the fluvastatin group (21.4%) compared to 222 (26.7%) in the placebo group. Fluvastatin therapy significantly reduced the risk of experiencing one of these cardiac events by 22% (p=0.013).

Revascularization procedures contributed to the majority of events in this composite measure as summarized in the following table. A revascularization procedure was the initial coronary event in 79% (143/181) of the events occurring in the fluvastatin group. Similarly, 77% (171/222) of the initial coronary events experienced in the placebo group were coronary revascularization procedures.

Table 1. Incidences of Primary Endpoint and Its Components

CLINICAL ENDPOINT	FLUVASTATIN N=844	PLACEBO N=833
Primary Endpoint, MACE*	181 (21.4%)	222 (26.7%)
Cardiac Death	8 (0.9%)	18 (2.2%)
Nonfatal MI	30 (3.6%)	33 (4.0%)
Coronary Revascularizations	143 (16.9%)	171 (20.5%)

*MACE = major adverse cardiac event

The individual components of the primary endpoint were analyzed separately and their results summarized in the following table.

Table 2. Incidence of Recurrent Cardiac Events: Cardiac Death, Nonfatal MI, or Coronary Revascularizations

CLINICAL ENDPOINT	FLUVASTATIN N=844	PLACEBO N=833	RISK RED 95% CI	P-VALUE
cardiac death	13 (1.5%)	24 (2.9%)	47% (-5, 79)	0.060
nonfatal MI	30 (3.6%)	38 (4.6%)	22% (-27, 52)	0.277
coronary revascularization	167 (19.8%)	193 (23.2%)	17% (-2, 33)	0.052

This study enrolled patients based on their having a successful percutaneous coronary intervention (PCI). This procedure is often followed by acute to subacute closure (restenosis) of the instrumented vessel that is related more to arterial wall injury than to an atherosclerotic process. Patients experiencing restenosis often require repeat revascularization procedures with the majority of cases occurring within the first 6 months following the initial procedure. The sponsor analyzed the effect of excluding events attributed to restenosis (revascularization of the originally instrumented lesion in the 6 months following the initial procedure) on the primary efficacy endpoint and found that the treatment effect was even more robust with a p-value of 0.0004.

Additional Efficacy Analyses

It was evident that a significant proportion (~78%) of initial cardiac events in this patient population involved a revascularization procedure. To further evaluate the effects of fluvastatin therapy on revascularization procedures, the sponsor was asked to analyze this endpoint excluding the initial 6-month events attributed entirely to restenosis. That is, revascularization procedures occurring in the same vessel previously instrumented were not included in this analysis unless it occurred 6 months after the initial PCI.

This analysis revealed that fluvastatin therapy reduced the risk of having a late revascularization procedure or a revascularization unrelated to the initial PCI by 32% (p=.002).

SAFETY

The safety findings in this trial were similar to previous studies of fluvastatin. The most common AEs were reflective of the patient population with the most frequently reported AE being angina pectoris (fluvastatin 23% and placebo 28%).

There were no cases of rhabdomyolysis in this trial. A case of myopathy was reported in each of the two treatment groups. Hepatitis was reported in 1 patient in each treatment group. The incidence of consecutive elevations in ALT or AST ≤ 1%.

Overall, the safety of fluvastatin in this protocol have already been addressed in the current package insert.

COMMENTS ON CLINICAL STUDY

The Lescol Intervention Prevention Study (LIPS) is a clinical outcome study in a secondary prevention population whose patients were identified by the need for a percutaneous coronary intervention (PCI) procedure. This study corroborates the findings from other studies which established a reduction in risk of recurrent cardiac events associated with statin therapy.

Similar to other clinical outcome studies involving statins, the primary endpoint in LIPS was a composite measure. The rationale here is that the individual components of the combined endpoint represent different clinical manifestations of the underlying disease process. These components, when measured alone, might not occur in sufficient quantity to establish a therapeutic benefit but when combined, provide an increased number of events to establish a significant risk reduction associated with drug treatment. The results of LIPS show that fluvastatin therapy in patients with established heart disease reduced the risk of having either a fatal cardiac event, a nonfatal MI, or a revascularization procedure by 22% (p=0.013).

When reviewing these trials, however, it is important to evaluate the individual components to determine to what extent each event contributes to the overall risk reduction. In LIPS, revascularization procedures comprised the majority of initial recurrent coronary events with 77 to 79% of the two treatment groups experiencing either a PCI or CABG after study randomization. The risk of experiencing any revascularization procedure after randomization was reduced by 17% in the fluvastatin group (p=0.052). However, as these patients all had a percutaneous coronary procedure performed at baseline, some of these events may have been secondary to restenosis as opposed to atherosclerosis progression. An analysis of the revascularization procedures, taking into consideration only those events that are due atherosclerosis, revealed an statistically significant reduction in risk of undergoing a coronary revascularization procedure associated with fluvastatin therapy (32% RR, p=0.002).

Overall, fluvastatin therapy in patients with established coronary disease reduces the risk of experiencing a recurrent coronary event. In the LIPS cohort, the predominant initial coronary event was a coronary revascularization procedure. Fluvastatin therapy had its most profound effect on reducing the need for having revascularization procedure secondary to atherosclerotic heart disease.

RECOMMENDATIONS

This application should be approved.

The labeling should include description of the study design and results under the CLINICAL PHARMACOLOGY; Clinical Studies section. The primary endpoint and the individual components of this measure should be discussed in detail. Overall risk

reduction and risk reduction associated with the individual components should be summarized in this section.

As the overwhelming benefit observed with fluvastatin therapy in this trial was secondary to a reduction in risk of "late" coronary revascularization procedures, this label should be approved for the following indication:

"In patients with coronary heart disease, Lescol and Lescol XL are indicated to reduce the risk of undergoing coronary revascularization procedures."

The sponsor should be advised that promotional materials based on the results of this clinical trial cannot imply a reduction in risk of undergoing revascularization procedures to address early post-PCI restenosis.

Mary H. Parks, MD
Deputy Director
Clinical Team Leader
Division of Metabolic and Endocrine Drug Products
HFD-510

Recommendation code: AP

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
5/14/03 08:52:07 AM
MEDICAL OFFICER

David Orloff
5/14/03 05:21:48 PM
MEDICAL OFFICER

Medical Officer's Review of Supplemental NDA

NDA#:	20-261 SE1 033
	21-192 SE1 005 C
Sponsor:	Novartis Pharmaceuticals, Inc.
Drug:	Lescol (fluvastatin)
	Lescol XL (fluvastatin extended-release)
Reviewer:	Anne Pariser, M.D.
Date of Submission:	31-July-2002
Date of Review:	12-May-2003

I. Introduction and Background

A. Introduction

The sponsor (Novartis Pharmaceuticals Corporation) has submitted an efficacy supplement for Lescol (fluvastatin) and Lescol XL (fluvastatin extended-release): SNDA 20-261 SE1 033 C and SNDA 21-192 SE1 005 C, respectively, dated 31-Jul-2002. These SNDAs rely on the same data and will be considered together. The sponsor is requesting an indication for the use of Lescol and Lescol XL (heretofore referred to as Lescol) as a

[redacted] The sponsor is also requesting priority review for this application.

Lescol has been commercially available since 31-Dec-1993 and Lescol XL has been available since 06-Oct-2000. Lescol has been approved by the Agency for the following indications:

1) To reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), and apolipoprotein B (Apo B) levels, and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIa and IIb); and
2) To slow the progression of coronary atherosclerosis in patients with coronary heart disease (CHD)

The sponsor is now seeking a new indication for Lescol as follows:

[redacted]

The sponsor is also seeking inclusion of the Lescol Intervention Prevention Study (LIPS) in the Clinical Studies section of the label, and the removal of the following sentence from the Clinical Pharmacology section:

[redacted]

B. Background

Several large, randomized, long-term clinical trials have demonstrated that lowering LDL-C reduces the risk of experiencing both first and recurrent coronary events[1, 2, 3, 4, 5] (primary and secondary prevention). These trials have shown a 25% to 35% reduction in cardiovascular (CV) events at long-term follow-up, and this benefit has been shown for a wide range of high-risk patients, irrespective of their initial cholesterol levels. Angiography in clinical trials has also demonstrated that lowering cholesterol levels slows the progression and promotes the regression of coronary atherosclerosis[6].

Percutaneous transluminal coronary angioplasty (PTCA) is a widely performed treatment for coronary artery stenosis. PTCA has been shown to offer earlier and more complete relief of angina, and to lower the risk of cardiovascular morbidity and mortality compared with medical therapy alone, in selected groups of patients[7, 8, 9]. Early restenosis (abrupt closure and restenosis within 6 months of the procedure) is a frequent problem with PTCA, seen in 35%-40% of dilated lesions, and is often associated with recurrence of

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[1] Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383-1389.

[2] The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998;339:1349-1357.

[3] Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7-22.

[4] Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JMO, Wun C, Davis BR, Braunwald E for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996;335:1001-1009.

[5] Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM for the AFCAPS/TexCAPS Research Group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of AFCAPS/TexCAPS. JAMA 1998;270(20):1615-1622

[6] Roussouw JE. Lipid-lowering interventions in angiographic trials. Am J Cardiol 1995;76:86C-92C.

[7] Parisi AF, Folland ED, Hartigan P on behalf of the Veterans Affairs ACME Investigators. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. N Engl J Med 1992;326:10-16.

[8] RITA-2 Trial Participants. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. Lancet 1997;350:461-468.

[9] Wallentin L, Lagerqvist B, Husted S, Kontny F, Stahle E, Swahn E, for the FRISC II Investigators. Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: the FRISC II invasive randomised trial. Lancet 2000;356:9-16.

symptoms requiring further revascularization. The cause of early restenosis is multifactorial, with the major mechanisms thought to be immediate recoil, incorporation of thrombus and a healing process in response to arterial injury that involves myointimal proliferation and vascular remodeling. Statin medications have been shown to have a direct effect on smooth muscle cell proliferation independent of any lipid-lowering action in animal models. However, investigation of the effect of statins on the prevention of early restenosis after PTCA in clinical studies has failed to show an effect on restenosis at the target site within 6 months after PTCA in several prospective clinical trials [10, 11, 12].

The long-term outcome of patients after PTCA has also been described in several reports, and has shown that after 10 years of follow-up, the majority of post-PTCA patients are likely to experience a further cardiac event after their first angioplasty procedure[13]. In a report by Ruygrok et al[13], the 10-year outcome of 856 consecutive patients who underwent attempted coronary angioplasty at a single center between 1980 and 1985 was described [follow-up information was available in 837 patients (98%) of these patients]. The overall 5- and 10-year survival rates were 90% and 78%, respectively, and the freedom from significant cardiac events rates at 5 and 10 years (including death, MI, CABG and repeat angioplasty) were 57% and 36%, respectively. Thus, post-PTCA patients continue to be at significant risk of experiencing a CV event >6 months after the initial procedure, with these events felt to be secondary to the atherosclerotic process.

Post-revascularization patients (either PTCA or CABG) have been shown to benefit from treatment with statin medications for the prevention of recurrent CV events. In a post hoc subgroup analysis of the Cholesterol and Recurrent Events (CARE) study[14], a total of 2,245 post-revascularization patients [1,154 PTCA and 876 CABG], a subgroup of the 4,159 total CARE patients, were analyzed. These patients had undergone a revascularization procedure at least 6 months prior to randomization, and thus, any reductions in events associated with treatment with study medication (pravastatin) was

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[10] Bertrand ME, McFadden EP, Fruchart J, VanBelle E, Commeau P, Grollier G, Bassand J, Machecourt J, Cassanes J, Mossard J, Vacheron A, Castaigne A, Danchin N, Lablanche J, for the PREDICT Trial Investigators. Effect of pravastatin on angiographic restenosis after coronary balloon angioplasty. J Am Coll Cardiol 1997;30:863-869.

[11] Weintraub WS, Boccuzzi SJ, Klein JL, Kosinski AS, King SB, Ivanhoe R, Cedarholm JC, Stillabower ME, Talley JD, DeMaio SJ, O'Neill WW, Frazier JE, Cohen-Bernstein CL, Robbins DC, Brown CL, Alexander RW and the Lovastatin Restenosis Trial Study Group. Lack of effect of lovastatin on restenosis after coronary angioplasty. N Engl J Med 1994;331:1331-1337.

[12] Serruys PW, Foley DP, Jackson G, Bonnier H, Macaya C, Vrolix M, Branzi A, Shepherd J, Suryapranata J, de Feyter PJ, Melkert R, van Es GA, Pfister PF on behalf of the FLARE study group. A randomized placebo-controlled trial of fluvastatin for prevention of restenosis after successful coronary balloon angioplasty. Eur Heart J 1999;20(1):59-69.

[13] Ruygrok PN, de Jaegere PPT, van Domburg RT, van den Brand MJ, Serruys PW, de Feyter PJ. Clinical outcome 10 years after attempted percutaneous transluminal coronary angioplasty in 856 patients. J Am Coll Cardiol 1996;27:1669-1677.

[14] Flaker GC, Warnica JW, Sacks FM, Moye LA, Davis BR, Rouleau JL, Webel RR, Pfeffer MA, Braunwald E for the Cholesterol and Recurrent Events CARE Investigators. Pravastatin prevents clinical events in revascularized patients with average cholesterol concentrations. J Am Coll Cardiol 1999;34:106-112.

not an early, but rather a late effect of treatment, and was likely due to an alteration in the atherosclerotic process. The results of this analysis showed that the post-revascularization patients had a 38% relative risk reduction (RRR) for death or nonfatal MI (primary endpoint), a 39% RRR of fatal or nonfatal MI, and an 18% RRR in repeat revascularization with pravastatin treatment. The favorable effects of pravastatin treatment were seen after approximately 2 years and continued to diverge up to Year 5 of follow-up.

Fluvastatin (as Lescol and Lescol XL) does not currently have an indication as a treatment to lower cardiovascular morbidity and mortality in any group of patients. The current study was designed to demonstra[redacted], as treatment with a statin medication would not be expected to show a benefit in early restenosis.

C. Clinical Experience with Lescol

There is extensive clinical experience with Lescol, and Lescol is currently marketed worldwide, including in a large number of countries in North America, South America, Asia, Europe, and Africa. Lescol's safety and efficacy profiles are described in the current labeling.

1. Efficacy

Lescol has been studied in 12 placebo-controlled studies in patients with Type IIa and IIb hyperlipoproteinemia. In these studies, Lescol was administered to 1621 patients in daily dose regimens of 20 mg, 40 mg, and 80 mg (40 mg BID) for at least 6 weeks. After 24 weeks, Lescol produced reductions in LDL-C, Apo B, and TG, and increases in HDL-C. Lescol XL has been studied in 5 controlled studies of patients with Type IIa and IIb hyperlipoproteinemia. Lescol XL was administered to >900 patients for 4 to 26 weeks, and resulted in significant decreases in LDL-C, TC, TG, and Apo B, and significant increases in HDL-C. Pooled results for all (12) placebo-controlled Lescol trials, and 3, 24-week controlled trial with Lescol XL are summarized in the following table (for all patients, and for patients with TG $\geq$200 mg/dL at Baseline)

Table 1: Lescol and Lescol XL, Lipid Parameters from Pooled Clinical Trials

Treatment	n	Median Percent Change from Baseline at Endpoint				
		TC	TG	LDL-C	Apo B	HDL-C
All Patients						
Lescol 20 mg	747	-17	-12	-22	-19	+3
Lescol 40 mg	748	-19	-14	-25	-18	+4
Lescol 40 mg BID	257	-27	-18	-36	-28	+6
Lescol XL 80 mg	750	-25	-19	-35[1]	-27[2]	+7
Patients Baseline TG≥200 mg/dL						
Lescol 20 mg	148	-16	-17	-22	-19	+6
Lescol 40 mg	179	-18	-20	-24	-18	+7
Lescol 40 mg BID	76	-27	-23	-35	-28[3]	+9
Lescol XL 80 mg	239	-25	-25	-33[4]	-27[5]	+11

[1]n=784, [2]n=745, [3]n=69, [4]n=237, [5]n=235

In one long-term, open-label free titration study, after 96 weeks of treatment, LDL-C decreases were similar to those seen above, with mean percent decreases of –25% (20 mg, n =68), 31% (40%, n =298), and 34% (80 mg, n =209).

2. Safety

The most serious adverse effects of Lescol and other members of the HMG-CoA reductase inhibitor family are liver and muscle toxicities. Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors. Approximately 1.1% of patients treated with Lescol in clinical trials have developed dose-related persistent elevations of transaminase levels to more the 3 times the upper limit of normal (ULN) with an average fluvastatin exposure of 71.2 weeks. In a pooled analysis of all placebo-controlled studies with Lescol, persistent transaminase elevations >3 X ULN (on 2 consecutive weekly measurements) occurred in 0.2%, 1.5%, and 2.7% of patients treated with 20, 40, and 60 mg of Lescol, respectively. The majority of these patients were asymptomatic, and 91% of elevations occurred within 12 weeks of initiation of treatment.

Myopathy and rhabdomyolysis have been reported with fluvastatin and with other HMG-CoA reductase inhibitors. The incidence of myopathy and rhabdomyolysis in clinical trials with Lescol was not described in the label, but is thought to be rare.

In controlled clinical studies in 2326 Lescol-treated and 912 Lescol XL-treated patients, with a mean exposure of approximately 16 months (range 1 to >36 months), adverse experiences occurring in >2% of patients (regardless of causality) are summarized in the following table

Table 2: Lescol & Lescol XL, AEs Occurring in >2% of Patients in Controlled Studies

	Lescol	Placebo	Lescol XL
n =	2326	960	912
Adverse Event	%	%	%
Integumentary			
Rash	2.3	2.4	1.6
Musculoskeletal			
Back Pain	5.7	6.6	4.7
Myalgia	5.0	4.5	3.8
Arthralgia	4.0	4.1	1.3
Arthritis	2.1	2.0	1.3
Arthropathy	NA	NA	3.2
Respiratory			
Upper Respiratory Infection	16.2	16.5	12.5
Pharyngitis	3.8	3.8	2.4
Rhinitis	4.7	4.9	1.5
Sinusitis	2.6	1.9	3.5
Coughing	2.4	2.9	1.9
Bronchitis	1.8	1.0	2.6
Gastrointestinal			
Dyspepsia	7.9	3.2	3.5
Diarrhea	4.9	4.2	3.3
Abdominal Pain	4.9	3.8	3.7
Nausea	3.2	2.0	2.5
Constipation	3.1	3.3	2.3
Flatulence	2.6	2.5	1.4
Misc. Tooth Disorder	2.1	1.7	1.4
Central Nervous System			
Dizziness	2.2	2.5	1.9
Psychiatric Disorders			
Insomnia	2.7	1.4	0.8
Genitourinary			
Urinary Tract Infection	1.6	1.1	2.7
Miscellaneous			
Headache	8.9	7.8	4.7
Influenza-like Symptoms	5.1	5.7	7.1
Accidental Trauma	5.1	4.8	4.2
Fatigue	2.7	2.3	1.6
Allergy	2.3	2.2	1.0

II. Review of Indication

The sponsor has submitted one clinical study for review of the treatment to reduce the risk of MACE in patients with CHD who have undergone PCI procedures: The Lescol Intervention Prevention Study (LIPS).

LIPS was a randomized, double-blind, placebo-controlled, multi-center study in 1677 patients with CHD who had undergone their first PCI procedure in the preceding 6 months. Patients were treated with either Lescol 80 mg (40 mg BID) or placebo for a median of 3.9 years. The purpose of the study was to determine if fluvastatin therapy reduced the long-term risk of MACE in CHD patients after a successful PCI.

A. Lescol Intervention Prevention Study

1. Study Design for the Lescol Intervention Prevention Study

(The Lescol Intervention Prevention Study will heretofore be referred to as LIPS)

a) Study Design

LIPS, or LES-EUR-01 "International, multicenter, randomized, double-blind, placebo-controlled study of the long term effects of fluvastatin (Lescol) on major adverse cardiac events in patients with coronary heart disease after successful first Trans-Catheter therapy (TCT)", was a randomized, double-blind, placebo-controlled, parallel-group study in 1677 patients (1406 men, 271 women), ages 18 to 80 years, who had successfully undergone their first PCI of 1 or more lesions in the native coronary arteries. Patients were treated with either Lescol 80 mg/day (40 mg BID) or placebo for a median of 3.9 years. LIPS was conducted in 77 study centers in 10 countries, not including the United States. Patients were eligible if they had a TC $\geq$3.5 mmol/L (135 mg/dL) and <7.0 mmol/L (270 mg/dL), and a fasting TG <4.5 mmol/L (400 mg/dL) after at least 6 weeks without lipid-lowering therapy.

b) Study Objectives

The primary objective of the study was to evaluate the efficacy of fluvastatin 80 mg/day compared to placebo on major cardiac event-free survival time in patients after successful first PCI procedure. The secondary objectives were to compare the effect of fluvastatin 80 mg/day compared to placebo on cardiac death, cardiac death plus non-fatal MI, non-cardiac death, all death plus non-fatal MI, MACE-less restenosis in the first 6 months of follow-up, anginal status, lipid-lowering effect, and safety and tolerability of fluvastatin. Amendment 3 (04-Dec-2001) made the secondary variable of cardiac death plus non-fatal MI the most important secondary endpoint.

c) Eligibility Criteria

(1) Inclusion Criteria

Patients must have been:
1) Male and non-fertile female (s/p hysterectomy, 2 years post-menopausal, or surgically sterilized for one year), or females of child bearing potential who were using medically approved forms of contraception, aged 18-80 years, who had undergone successful first PCI procedure of 1 or more lesions in the native coronary arteries during the same hospitalization. Patients having a restenosed target lesion within 6 months of first angioplasty were to be included (Amendment 1; 24-Feb-1997)
2) TC $\geq$3.5 to <7.0 mmol/L in the absence of lipid lowering therapy for the previous 6 weeks. For patients status post MI within 24 hours to 4 weeks, TC must have been $\geq$3.5 to <5.5 mmol/L, or for those patients with type 1 or type 2 diabetes mellitus (DM), TC must have been $\geq$3.5 to $\leq$6.0 mmol/L
3) Fasting TG <4.5 mmol/L

(2) Exclusion Criteria

Patients must not have had:
1) Sustained systemic hypertension (DBP >100 mmHg or SBP >180 mmHg) despite medical therapy, undiagnosed hypertension, compromised left ventricular function with an EF <30% (by angiogram), medical history of CABG or PCI procedure more than 6 months previous, or with severe non-CHD (such as valvular disease, idiopathic cardiomyopathy or congenital heart disease)
2) Severe renal dysfunction (serum creatinine >160 micromol/L), BMI >35 kg/M^2 (increased from 30 kg/M^2; Amendment 1, 24-Feb-1997), malignant or other disease with life expectancy <4 years, with death, MI, or CABG between TCT procedure and hospital discharge, GI or liver impairment (ALT, AST or total bilirubin 2 X ULN within 4 weeks of randomization), or major surgery within 3 months of randomization
3) Treatment with probucol within 12 months prior to randomization or with lipid-lowering agents other than study medication, erythromycin, ketoconazole or anti-convulsant therapies. Medications except probucol were included in Amendment 1, and patients who could not have these medications withdrawn for ethical reasons were to be excluded
4) Currently participating in a study of any device or drug requiring clinical or angiographic follow-up except in a stent or a diagnostic registry with no angiographic follow-up, or who had previously participated in this study

The hypothyroidism exclusion criterion was removed in Amendment 1.

d) Study Visits and Procedures

Study visits and procedures are summarized below and in the following table

Table 3: LIPS Study Visits and Procedures

Weeks	-4 to 0	0[1]	6	26	52	78	104	130	156[2]	182[2]	Close out
Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Procedure											
Screening		X									
Demographics	X										
Randomization		X									
Inclusion/exclusion criteria		X									
Medical History		X									
Prior Medications		X									
Co-existent diseases and conditions		X									
Concomitant medications		X	X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X	X
Physical examination		X			X		X		X		X
Angina assessment		X	X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X	X
Biochemistry	X	X	X	X	X	X	X	X	X	X	X
Lipid assessment	X	X	X	X	X	X	X	X	X	X	X
ECG		X	X	X	X	X	X	X	X	X	X
Drug dispensing		X	X	X	X	X	X	X	X	X	
Passport check			X	X	X	X	X	X	X	X	X

[1] Week (Day) 0 = discharge from hospital
[2] Visit may be replaced by close-out visit

e) Study Medication Dispensing and Compliance

Study medication was supplied as capsules containing either 40 mg of fluvastatin or matching placebo. Patients took 1 capsule of study medication in the morning and evening. No variation in dose of study medication was permitted during the study. Study medication was to be taken for a minimum of 3 years and a maximum of 4 years. Study medication was supplied in blister packs containing a 7-day supply of medication. Patients were dispensed adequate study medication + reserve medication at each study visit.

Randomization occurred by the dispensing of sequentially numbered sets of study medication distributed to each site, and eligible patients received the next sequential medication pack at that site. Patients were allocated to treatment in the order in which they were enrolled into the study at each center according to the randomization schedule (1:1 randomization). This was a double-blind study, and the Investigators were blinded to the lipid results from Week 0 through the duration of the study.

Compliance was assessed by a pill count at each study visit. Patients returned all unused study medication at the end of the study.

f) Efficacy and Endpoint Measures

A Clinical Endpoint Committee (CEC) was formed to classify all death and myocardial infarctions. In the event a patient had multiple primary endpoints, the time to the first MACE was used for the primary analysis. For those patients who had no primary endpoints, the time from randomization to the first MACE was right-censored. Two interim analyses and a final analysis were performed as planned per the study protocol. The first interim analysis evaluated safety only. An independent Data and Safety Monitoring Board (DSMB) acted in an advisory capacity to ensure patient safety.

The null hypothesis for the study was: "There was no difference in the distributions of the variable 'time to first MACE' between the fluvastatin and placebo groups."

(1) Primary Endpoint

The primary efficacy endpoint was the composite endpoint of major adverse cardiac event-free (MACE-free) survival time. MACE was defined as:

- Cardiac death (all deaths considered to be of cardiac origin unless unequivocal cause could be established)
- Non-fatal MI
- Re-intervention, including CABG, repeat TCT, or TCT of a new lesion

(2) Secondary Endpoints

Secondary efficacy endpoints were:

- Cardiac death
- Cardiac death plus non-fatal MI
- Non-cardiac death
- All death plus non-fatal MI
- MACE-less restenosis (i.e., excluding re-TCT indicated to treat a lesion dilated at Baseline TCT) in the first 6 months of follow-up
- Anginal status, including no angina, unstable angina, stable angina, or silent ischemia with various subcategories under each of these 4 main categories
- Lipid profile, including percentage change from Baseline to each study visit and endpoint in LDL-C, HDL-C, TG, and TC. The Baseline value was defined as the last observation before randomization.

The composite endpoint of cardiac death and non-fatal MI was included in Amendment 3 (04-Dec-2001) and was the most important secondary efficacy endpoint. Amendment 3 also removed the secondary variables of cost effectiveness of fluvastatin treatment and the incidence of hospitalizations due to cerebrovascular and other atherosclerotic diseases.

(3) Safety

Safety assessments consisted of monitoring and recording of all AEs, and changes from Baseline in laboratory parameters, vital signs, ECG, and physical examinations. The

primary laboratory parameters included AST, ALT, and CK. Baseline was defined as the last observation before randomization.

(4) Study Population

The Intent-To-Treat (ITT) population was the primary efficacy analysis population and was used for the primary endpoint analyses. ITT was defined as all patients who were randomized. The Safety population was defined as all randomized patients who took at least one dose of study medication and had at least one safety evaluation.

g) Protocol Amendments

There were 3 protocol amendments:

1) Amendment 1 (24-Feb-1997):

- Altered the inclusion criteria to permit patients having a restenosis, target lesion related (TLR), within 6 months after the first angioplasty to enter; to allow blood samples for lipid analysis to be collected the day after TCT (providing results were available at randomization); and to include the lower limit of 3.5 mmol/L for TC for patients who suffered an MI.
- Altered the exclusion criteria to remove the hypothyroidism exclusion, increased BMI from 30 to 35 kg/M^2, allowed patients participating in a stent or a diagnostic registry to participate, and excluded patients treated with a lipid lowering agent, erythromycin, ketoconazole or anti-convulsant therapy.
- Changed one primary clinical endpoint such that a CK-MB was mandatory within 12 hours of a CK elevation
- Corrected errors and inconsistencies within the protocol.

2) Amendment 2 (02-Aug-1999):

- Added the incidence of death and MI as an additional secondary clinical endpoint in response to results from the FLARE[12] study (completed 1996).

3) Amendment 3 (04-Dec-2001):

- Removed the secondary endpoints of cost effectiveness of fluvastatin, and the incidence of hospitalizations due to cerebrovascular and other atherosclerotic diseases.
- Included the secondary variable composite endpoint of cardiac death and non-fatal MI, and elevated this composite endpoint in importance.
- Included age (<65 years and ≥65 years) and gender subgroup analyses.

2. Results

There were 1677 patients randomized into the study; thus, 1677 patients comprised the ITT population. Of the 1677 randomized patients, 1553 patients (93%) completed follow-up (for at least 3 years) in the study. All patients were enrolled and completed the study between 25-Apr-1996 and 31-Oct-2001.

a) Baseline Characteristics and Demographics

Overall, 84% of patients were male and 98% were Caucasian. Mean age was 60.0 years, with 60% of patients in the ≥40 to <65 years age range, and 37% of patients ≥65 years of age. Sixty-three percent (63%) of patients had single-vessel disease. The 2 treatment groups were well balanced by age, age range, gender, BMI, and coronary disease (single- vs multiple-vessel disease). Baseline characteristics and demographics are summarized in the following table

Table 4: LIPS Baseline Characteristics and Demographics

			Treatment	
		All	Fluvastatin	Placebo
Randomized (ITT) Patients, n =		1677	844	833
Demographic Measure				
Age				
Mean (years)		60.0	60.0	60.0
Min, max (years)		28, 80	29, 70	28, 80
Age Range	≥18 to <40 years, n (%)	40 (2)	24 (3)	16 (2)
	≥40 to <65 years, n (%)	1014 (60)	496 (59)	518 (62)
	≥65 to <75 years, n (%)	515 (31)	268 (32)	247 (30)
	≥75 years, n (%)	108 (6)	56 (7)	52 (6)
Gender, n (%)				
Male		1406 (84)	711 (84)	695 (83)
Female		271 (16)	133 (16)	138 (17)
Age Range, Males, n (%)				
<65 years		917 (55)	459 (54)	458 (55)
≥65 years		489 (29)	252 (30)	237 (28)
Age Range, Females, n (%)				
<65 years		127 (8)	61 (7)	76 (9)
≥65 years		134 (8)	72 (9)	62 (7)
Race, n (%)				
Caucasian		1650 (98)	833 (99)	817 (98)
Black		10 (1)	5 (1)	5 (1)
Other		17 (1)	6 (1)	11 (1)
Mean BMI (kg/M^2)		26.5	26.7	26.4
Coronary Disease, n (%)				
Single Vessel		1063 (63)	522 (62)	541 (65)
Multiple Vessel		614 (37)	322 (38)	292 (35)

Patients were evaluated for differences between the groups in Baseline Medical History, including previous MI, Q-wave vs non Q-wave MI, diabetes, hypertension, previous stroke, peripheral vascular disease, smoking, and family history of heart disease. Overall, 44% of patients had a history of previous MI, with 27% of patients having experienced a

Q-wave MI and 17% having experienced a non Q-wave MI. Twelve percent (12%) of patients had a history of diabetes, 39% had a history of hypertension, 3% had a history of previous stroke, and 6% had a history of peripheral vascular disease. For smoking history, 27% were current smokers, 45% previous smokers, and 29% had never smoked. There were 29% of patients who had a family history of heart disease. There were no important differences between the groups in Baseline medical history. The Baseline medical history is summarized in the following table

Table 5: LIPS Baseline Medical History

		Treatment	
	All	**Fluvastatin**	**Placebo**
Randomized Patients, n =	1677	844	833
Parameter			
Previous MI, any, n (%)	744 (44)	371 (44)	373 (45)
Q-wave	446 (27)	220 (26)	226 (27)
Non Q-wave	293 (17)	148 (18)	145 (17)
Previous MI, missing Q-information	5 (<1)	3 (<1)	2 (<1)
No Previous MI	933 (56)	473 (56)	460 (55)
Diabetes Mellitus, n (%)	202 (12)	120 (14)	82 (10)
Insulin dependent	39 (1)	18 (2)	21 (3)
Noninsulin Dependent	163 (10)	102 (12)	61 (7)
No history	1475 (88)	724 (86)	751 (90)
Hypertension, n (%)			
Yes	647 (39)	330 (39)	317 (38)
No	1030 (61)	514 (61)	516 (62)
Stroke, n (%)			
Yes	44 (3)	17 (2)	27 (3)
No	1633 (97)	827 (98)	806 (97)
Peripheral Vascular Disease, n (%)			
Yes	107 (6)	50 (6)	57 (7)
No	1569 (94)	793 (94)	776 (93)
Missing	1 (<1)	1 (<1)	0
Smoking, n (%)			
Never smoked	478 (29)	240 (28)	238 (29)
Previous smoker	753 (45)	393 (47)	360 (43)
Current smoker	446 (27)	211 (25)	235 (28)
Family History Heart Disease, n (%)			
Yes	490 (29)	239 (28)	251 (30)
No	1177 (70)	599 (71)	578 (69)
Missing	10 (1)	6 (1)	4 (<1)

Patients were also evaluated for post-TCT ejection fraction (EF), procedural characteristics, and pre-procedural anginal status and lesion characteristics. Patients in both groups had a mean EF of 62% (min, max: 30%, 93%), with 51% of patients in both groups having an EF between 50% and 70%. Approximately 50% of the patients in both groups had unstable angina prior to PCI, and approximately 40% had stable angina. Ninety-eight percent (98%) of patients overall had Baseline coronary occlusions of <50% in diameter. In both groups, approximately 65% of patients received balloon angioplasty plus an additional procedure, with 63% of patients overall undergoing balloon

angioplasty with stent implantation of at least one lesion, and a small number of patients receiving balloon angioplasty plus another intervention, such as rotational ablation. Approximately 35% of patients received conventional balloon angioplasty alone. There were no clinically important differences between the 2 treatment groups in any of these parameters. There were also no differences between the groups in ECG abnormalities pre-TCT, with >66% of patients having no pathological Q-waves prior to intervention. The Baseline EF, anginal status, and procedural and lesional characteristics are summarized in the following table

Table 6: LIPS Baseline Ejection Fraction, Anginal Status, and Procedural & Lesional Characteristics

		Treatment	
	All	Fluvastatin	Placebo
Randomized Patients, n =	1677	844	833
Parameter			
Ejection Fraction			
Mean, %	62.0	62.2	61.8
Median, %	60	61	60
Min, max, %	30, 93	30, 90	30, 93
EF Range, ≥30% to <50%, n (%)	206 (12)	96 (11)	110 (13)
≥50% to <70%, n (%)	857 (51)	431 (51)	426 (51)
≥70% to <90%, n (%)	444 (26)	233 (28)	211 (25)
≥90%, n (%)	4 (<1)	2 (<1)	2 (<1)
Missing, n (%)	166 (10)	82 (10)	84 (10)
Angina, n (%)			
Unstable	824 (49)	417 (49)	407 (49)
Stable	671 (40)	346 (41)	325 (39)
Silent ischemia only	163 (10)	72 (9)	91 (11)
Missing	19 (1)	9 (1)	10 (1)
Procedure, n (%)			
Conventional balloon only	582 (35)	287 (34)	295 (35)
Conventional balloon plus:	1094 (65)	557 (66)	537 (65)
Stent implantation	1055 (63)	540 (64)	515 (62)
Perfusion balloon	37 (2)	18 (2)	19 (2)
Rotational ablation	14 (1)	7 (1)	7 (1)
Directional atherectomy	9 (1)	5 (1)	4 (1)
Other	14 (1)	4 (1)	10 (1)
Excimer laser	8 (<1)	3 (<1)	5 (1)
Lesion Diameter, n (%)			
<50%	1639 (98	821 (97)	818 (98)
≥50% but no complete occlusion	42 (3)	24 (3)	18 (2)
Complete occlusion	26 (2)	15 (2)	9 (1)
Missing	8 (<1)	5 (1)	3 (<1)
Visual assessment not possible	2 (<1)	1 (<1)	1 (<1)

Baseline demographics, characteristics, and medical history were also evaluated by gender, and there were some important differences between male and female patients at Baseline. Females had a mean age of 63 years at Baseline as compared to a mean age of 59 years in males, and almost half of the female patients (49%) were ≥65 years of age at Baseline vs 35% of males. Medical history at Baseline was notable for females having been much more likely to have had hypertension than males (59% of females and 35% of

males), and were somewhat more likely to have had diabetes (15% and 12%, respectively). Males were somewhat more likely than females to have had a previous MI (45% of males vs 39% of females). These differences, particularly the older female population and much higher Baseline prevalence of hypertension, may have accounted for the higher incidence of AEs in female patients (see Safety section, AEs by Subgroup below). Selected Baseline demographics for male and female patients are summarized in the following table

Table 7: LIPS Selected Baseline Demographics and Medical History: Males vs Females

		Treatment	
	All	**Fluvastatin**	**Placebo**
Randomized Patients, n =	1677	844	833
Randomized Males, n =	1406	711	695
Randomized Females, n =	271	133	138
Age, Males			
Min, max	28, 79	29, 79	28, 79
Mean	59.4	59.3	59.5
Median	60.0	60.0	60.0
<65 years, n (% of males*)	917 (65)	459 (65)	458 (66)
≥65 years, n (% of males*)	489 (35)	252 (35)	237 (34)
Age, Females			
Min, max	36, 80	36, 79	38, 80
Mean	63.0	63.7	62.4
Median	64.0	65.0	63.5
<65 years, n (% of females**)	137 (51)	61 (46)	76 (55)
≥65 years, n (% of females**)	134 (49)	72 (54)	62 (45)
Previous MI (Yes)			
All, n (%)	744 (44)	371 (44)	373 (45)
Males*, n (%)	639 (45)	318 (45)	321 (46)
Females**, n (%)	105 (39)	53 (40)	52 (38)
Diabetes (Yes)			
All, n (%)	202 (12)	120 (14)	82 (10)
Males*, n (%)	162 (12)	96 (14)	66 (9)
Females**, n (%)	40 (15)	24 (18)	16 (12)
HTN (Yes)			
All, n (%)	647 (39)	330 (39)	317 (38)
Males*, n (%)	486 (35)	242 (34)	244 (35)
Females**, n (%)	161 (59)	88 (66)	73 (53)
Angina			
Unstable, males*, n (%)	680 (48)	344 (48)	336 (48)
Unstable females**, n (%)	144 (53)	73 (55)	71 (51)
Stable, males*, n (%)	562 (40)	293 (41)	269 (39)
Stable, females**, n (%)	109 (40)	53 (40)	56 (41)
Silent ischemia only, males*, n (%)	148 (11)	67 (9)	81 (12)
Silent ischemia only, females**, n (%)	15 (6)	5 (4)	10 (7)
Missing, males*, n (%)	16 (1)	7 (1)	9 (1)
Missing, females**, n (%)	3 (1)	2 (2)	1 (1)
Coronary Disease, n (%)			
Single Vessel			
All, n (%)	1063 (63)	522 (62)	541 (65)
Males*, n (%)	885 (63)	431 (61)	454 (65)
Females**, n (%)	178 (66)	91 (68)	87 (63)
Multiple Vessel			
All, n (%)	614 (37)	322 (38)	292 (35)
Males*, n (%)	521 (37)	280 (39)	241 (35)
Females**, n (%)	93 (34)	42 (32)	51 (37)

* percentage calculated using randomized males as the denominator
**percentage calculated using randomized females as the denominator

b) Patient Disposition

(1) Screening and Randomization

The sponsor did not include screen failure information in the submission, and indicated that screen failure information was not collected. In a personal communication with the sponsor regarding screen failure information, the sponsor stated that "monitor reports during the 27 month recruitment period indicated that all patients prospectively undergoing PCI at the investigational sites in that period, were considered for eligibility assessment." There was no indication of any recruitment bias; however, this could not be verified by this Reviewer as the data were not available for review.

One thousand six hundred seventy-seven (1677) patients were randomized and comprised the ITT population. Patients were entered at 57 clinical sites located in 10 countries: 8 countries in Europe, and in Brazil and Canada. Enrollment was highest in Spain (29% of patients randomized), followed by Italy (16%), Belgium and the Netherlands (15% each), and France (8%). Enrollment was ≤5% in the remaining countries. Patient randomization to the 2 treatment groups was relatively evenly balanced at each of the clinical sites and by country. Patient randomization by Country is summarized in the following table [a complete list of randomization by Country and by Study Center is in the Appendix]

Table 8: LIPS Enrollment by Country

		Treatment	
	All	Fluvastatin	Placebo
Randomized Patients, n =	1677	844	833
Country	n (%)	n (%)	n (%)
Spain	489 (29)	243 (29)	246 (30)
Italy	267 (16)	129 (15)	138 (17)
Belgium	258 (15)	132 (16)	126 (15)
Netherlands	253 (15)	129 (15)	124 (15)
France	134 (8)	71 (8)	63 (8)
Germany	88 (5)	46 (5)	42 (5)
Canada	67 (4)	34 (4)	33 (4)
Brazil	60 (4)	30 (4)	30 (4)
Switzerland	21 (1)	11 (1)	10 (1)
UK	40 (2)	19 (2)	21 (3)

Mean time from pre-PCI to randomization was 3 days in both treatment groups. All patient identification, recruitment, and randomization occurred while the patient was hospitalized for the initial procedure.

(2) Discontinuations

Of the 1677 randomized patients, 1553 completed follow-up (93%), 85 patients died (5%), and 39 patients (2%) did not complete follow-up. Follow-up was for a minimum of 3 years. Patient disposition is summarized in the following table

Table 9: LIPS Patient Disposition

		Treatment	
	All	**Fluvastatin**	**Placebo**
Randomized Patients, n =	1677	844	833
Completed Follow-Up, n (%)	1553 (93)	786 (93)	767 (92)
Not Completed Follow-Up, n (%)	39 (2)	22 (3)	17 (2)
Discontinued Study Medication, n (%)	660 (39)	292 (35)	368 (44)
Deaths, n (%)	85 (5)	36 (4)	49 (6)
Study Medication Never Taken, n (%)	37 (2)	22 (3)	15 (2)

The most common reasons for not completing follow-up were for patients being lost to follow-up (19 patients; 1%), and for missing information (14 patients; 1%). Patients not completing follow-up by reason, by treatment group, are summarized in the following table

Table 10: LIPS Patients Not Completing Follow-Up

		Treatment	
	All	**Fluvastatin**	**Placebo**
Randomized Patients, n =	1677	844	833
Not Completed Follow-Up, n (%)	39 (2)	22 (3)	17 (2)
Reason			
Missing, n (%)	14 (1)	11 (1)	3 (<1)
Lost to Follow-Up, n (%)	17 (1)	7 (1)	10 (1)
Withdrew Consent, n (%)	6 (<1)	4 (<1)	2 (<1)
Other, n (%)	2 (<1)	0	2 (<1)

A total of 660 patients (39%) overall discontinued study medication. The most common reasons for discontinuing study medication were for poor compliance/personal reasons (15% overall), Adverse Events (11%), and for lipid-lowering drug required (8%). More patients in the placebo group (44%) than in the fluvastatin group (35%) discontinued their study medication, with the difference between the 2 treatment groups being accounted for almost entirely by more patients in the placebo group (14%) than in the fluvastatin group (2%) requiring treatment with a lipid-lowering drug (other than study medication). It should also be noted that more patients in the fluvastatin group (13%) than in the placebo group (9%) discontinued study drug due to an Adverse Event. Study medication discontinuations by reason, by treatment group, are summarized in the following table

Table 11: LIPS Study Medication Discontinuations

		Treatment	
	All	**Fluvastatin**	**Placebo**
Randomized Patients, n =	1677	844	833
Study Medication Never Taken, n (%)	37 (2)	22 (3)	15 (2)
Safety Population	1640	822	817
Discontinued Study Medication, n (%)	660 (39)	292 (35)	368 (44)
Reason For Discontinuation			
Poor Compliance/Lack of Motivation/Personal Reasons	244 (15)	120 (15)	124 (15)
Adverse Event (Excluding MACE)	183 (11)	107 (13)	76 (9)
Serious Adverse Event (Excluding MACE)	61 (4)	27 (3)	34 (4)
Lipid Lowering Drug Required	132 (8)	17 (2)	115 (14)
Missing	28 (2)	16 (2)	12 (1)
Repeat TCT, CABG, MI	12 (1)	5 (1)	7 (1)

c) Protocol Violations and Deviations

Protocol violations were common in the study, with 45% of patients overall incurring a major protocol violation during the study. More patients in the placebo group (51%) than in the fluvastatin group (34%) had major violations of the protocol, which was accounted for mostly due to the use of statin medications (other than study medication) during the study (31% of placebo patients vs 15% of fluvastatin patients). Compliance to study medication <80% (defined as compliance <80% over the course of the entire study) was the most common major protocol violation in both groups (38% overall). Both of these major protocol violations (use of statin medications other than study drug and poor compliance) may have effected the overall study results, with the most likely outcome being an attenuation of treatment effect for fluvastatin [to be further discussed in the Efficacy Results and Conclusions sections below]. Major protocol violations by treatment group are summarized in the following table

Table 12: LIPS Major Protocol Violations

		Treatment	
	All	**Fluvastatin**	**Placebo**
Randomized Patients, n =	1677	844	833
Patients with Major Protocol Violation, n (%)	751 (45)	329 (39)	422 (51)
Major Protocol Violation			
Compliance to Study Medication <80%, n (%)	638 (38)	288 (34)	350 (42)
Treated with Statin (other than study drug), n (%)	385 (23)	124 (15)	261 (31)
TC at entry outside inclusion limits, n (%)	63 (4)	36 (4)	27 (3)
Treated with lipid-lowering therapy other than statins, n (%)	58 (3)	23 (3)	35 (4)

In addition, 6 patients had their treatment unblinded during the study, all of whom were unblinded for SAEs. Of these 6 patients, 4 were taking fluvastatin and 2 were taking placebo.

d) Patients Compliance

As stated in the Protocol Violations section above, compliance to study medication <80% was common, occurring in 38% of patients overall. Poor compliance was somewhat more common in the placebo group (42%) than in the fluvastastin group (34%).

e) Concomitant Medications

Medications taken within 3 months prior to entry through study follow-up completion were recorded, and cardiovascular medications were the only medications tracked and recorded. The cardiovascular medications accounted for in the concomitant medications dataset included: aspirin (ASA), ticlopidine, dipyridamole, heparin, coumadin, beta-blockers, calcium channel antagonists, nitrates, ACE-inhibitors, diuretics, statins (other than study drug), resins, fibrates, other lipid-lowering medications, and other cardiac medications.

Note: beta-blockers, calcium channel antagonists, nitrates, ACE-inhibitors, diuretics, statins, resins, and fibrates were recorded by medication category rather than by individual medication.

All 1677 randomized patients took at least one concomitant cardiovascular medication during the study. The most commonly reported concomitant medication used was ASA, which was used by 98% of patients in the fluvastatin group and 99% of patients in the placebo group. Beta-blockers (71% overall), ticlopidine (69%), nitrates (61%), and calcium channel antagonists (60%) were the next most commonly reported concomitant cardiovascular medications. There were no notable differences between the treatment groups by category of cardiovascular medications used, with the exception of more patients in the placebo group (31%) than in the fluvastatin group (15%) requiring other statin medications (other than study medication) during the study. Other lipid-altering drugs, including fibrates, resins, and other lipid-lowering drugs were used somewhat more commonly in placebo patients (4%) than in fluvastastin patients (3%), although the number of patients using these medications during the study was small (n = 61 for both treatment groups combined). It is possible that the difference between the 2 groups in use of statins (other than study drug) and other lipid-altering drugs could have impacted on the overall study results, with a weakening of the treatment effect of fluvastatin. The most commonly reported concomitant medications used during the study are summarized in the following table

Table 13: LIPS Study Medication Discontinuations

		Treatment	
	All	Fluvastatin	Placebo
Randomized Patients, n =	1677	844	833
Concomitant Medication			
ASA	1648 (98)	827 (98)	821 (99)
Beta-blocker	1199 (71)	595 (70)	604 (73)
Ticlopidine	1165 (69)	599 (71)	566 (68)
Nitrate	1016 (61)	512 (61)	504 (61)
Calcium channel antagonist	1000 (60)	512 (61)	488 (59)
ACE-inhibitor	655 (39)	329 (39)	326 (39)
Statin (other than study drug)	385 (23)	124 (15)	261 (31)
Diuretic	332 (20)	169 (20)	163 (20)
Heparin	175 (10)	83 (10)	92 (11)
Coumadin/warfarin	99 (6)	46 (5)	53 (6)
Dipyridamole	26 (2)	14 (2)	12 (1)
Fibrate	26 (2)	12 (1)	14 (2)
Other lipid-lowering*	32 (2)	12 (1)	20 (2)
Resin	3 (<1)	0	3 (<1)
Other cardiac**	441 (26)	228 (27)	213 (26)

*e.g., fish oil

**including a wide variety of cardiac medications, such as other antihypertensive medications (e.g., alpha blockers), digoxin, abciximab, amiodarone, and others.

f) Efficacy Results

The sponsor's efficacy results are summarized as follows:

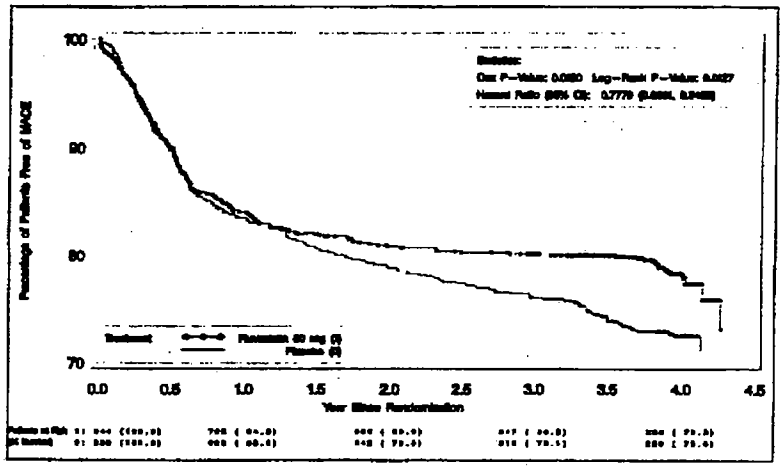
(1) Primary Efficacy Endpoint

The primary objective was to compare the effect of 80 mg of fluvastatin (40 mg BID) with placebo in the treatment of patients after successful first PCI on the major adverse cardiac event-free (MACE-free) survival time during a follow-up period of 3-4 years. The primary efficacy endpoint was the combined endpoint of MACE-free survival time in the ITT population. MACE was defined as:

- Cardiac death
- Non-fatal MI
- Re-intervention procedure

The Kaplan-Meier estimates of the time to first MACE survival distributions indicated a separation of the fluvastatin and placebo groups beginning at approximately 1.5 year, and continuing to diverge up to study termination. The log-rank test statistic comparing the time to first MACE survival distributions between the 2 treatment groups was statistically significant (p=.0127). The MACE-free survival time (the Primary Endpoint) is shown graphically in the following figure [From: SNDA #20-261 033, Volume 17; Integrated Summary of Benefits and Risks, page 7. Electronically scanned and reproduced from paper SNDA (best copy)].

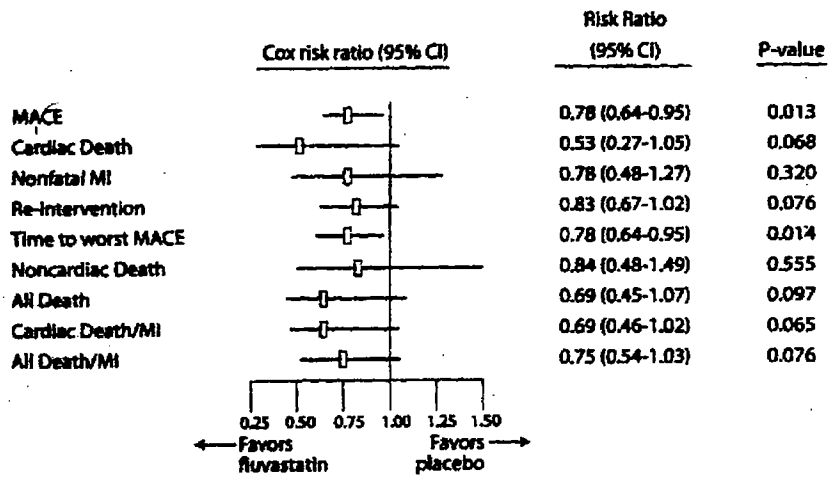
Figure 1: LIPS Primary Endpoint, MACE-Free Survival Time (ITT Population)



The Cox regression analysis of time-to-first MACE showed that the risk ratio estimate for the combined MACE endpoint was 0.78, indicating that at any specified time, patients in the fluvastatin group had a significant 22% reduction in risk of experiencing a MACE compared to the placebo group (p=.013). The risk ratios of the 3 individual components

of the combined MACE endpoint (cardiac death, non-fatal MI, and re-intervention) were all less than 1, although none of these individual results were statistically significant. The risk ratio for cardiac death was 0.53 (p=.068), for non-fatal MI was 0.78 (p=.320), and for re-intervention was 0.83 (p=.076). The risk ratio results are shown graphically in the following figure [From: SNDA #20-261 033, Volume 17; Integrated Summary of Benefits and Risks, page 9. Electronically copied and reproduced].

Figure 2: Cox Regression Analysis of Time-to-First MACE (ITT Population)



(2) Secondary Efficacy Endpoints

The secondary efficacy endpoints included:

- Time to each of the 3 individual components of MACE
- Time to cardiac death or non-fatal MI
- Time to worst MACE, where cardiac death was considered to be the most severe, non-fatal MI as the next most severe, and re-interventions being the least severe
- Time to MACE excluding re-interventions (surgical or PCI) of lesions treated at the index procedure occurring in the first 6 months of follow-up
- Incidence of any MACE and incidence of each category of MACE
- Incidence of cardiac death or non-fatal MI
- Incidence of non-cardiac death
- Incidence of death or non-fatal MI
- Lipid levels

(a) Time to Individual Components of MACE or Time to Other Secondary Endpoints

Time to each of the 3 individual components of MACE were summarized in the Cox regression analysis above, and showed non-significant risk reductions in the fluvastatin group compared to the placebo group for each component (see above). Time to cardiac

death or non-fatal MI (Cardiac Death/MI) showed a non-significant risk ratio of 0.69 (p=.065). Risk ratios (RR) for all death or non-fatal MI (All Death/MI; RR 0.69; p=.065), non-cardiac death (Noncardiac Death; RR 0.84; p=.555), and all death (All Death; RR 0.69; p=.097) were all <1, although none were statistically significant. Time to worse MACE showed a RR of 0.78, which was significant (p=.014). These results are all summarized in Figure 2 above.

(b) Incidence of Clinical Endpoints

The fluvastatin group had a significantly lower incidence of the combined MACE compared to the placebo group, with an incidence of MACE of 21% in the fluvastatin group vs. 27% in the placebo group (p=.006). There was a lower incidence of each of the individual clinical endpoints of MACE (cardiac death, non-fatal MI, and re-intervention) in the fluvastatin group compared to the placebo group; however, these results were not statistically significant. In the fluvastatin and placebo groups, cardiac death occurred at incidences of 1.5% and 2.9%, respectively (p=.060), non-fatal MI at rates of 3.6% and 4.6%, respectively (p=.277), and re-intervention at rates of 19.8% and 23.2%, respectively (p=.052).

The incidence rates for the other secondary endpoints in the study (incidence of cardiac death or MI, incidence of non-cardiac death, and incidence of death or MI), were also not significantly lower in the fluvastatin group than in the placebo group. The incidence rates of clinical endpoints measured in this study are summarized in the following table

Table 14: LIPS Incidence of Clinical Endpoints

	Fluvastatin	Placebo	p-value
n=	844	833	
Clinical Endpoint	n (%)	n (%)	
MACE[1]	181 (21.4)	222 (26.7)	.006
Cardiac Death[1]	8 (0.9)	18 (2.2)	
Non-fatal MI[1]	30 (3.6)	33 (4.0)	
Re-intervention[1,2]	143 (16.9)	171 (20.5)	
Cardiac Death	13 (1.5)	24 (2.9)	.060
Non-Fatal MI	30 (3.6)	38 (4.6)	.277
Re-Intervention[2]	167 (19.8)	193 (23.2)	.052
Cardiac death or MI	42 (5.0)	60 (7.2)	.052
Non-Cardiac Death	23 (2.7)	25 (3.0)	.645
Death or MI	65 (7.7)	84 (10.1)	.071

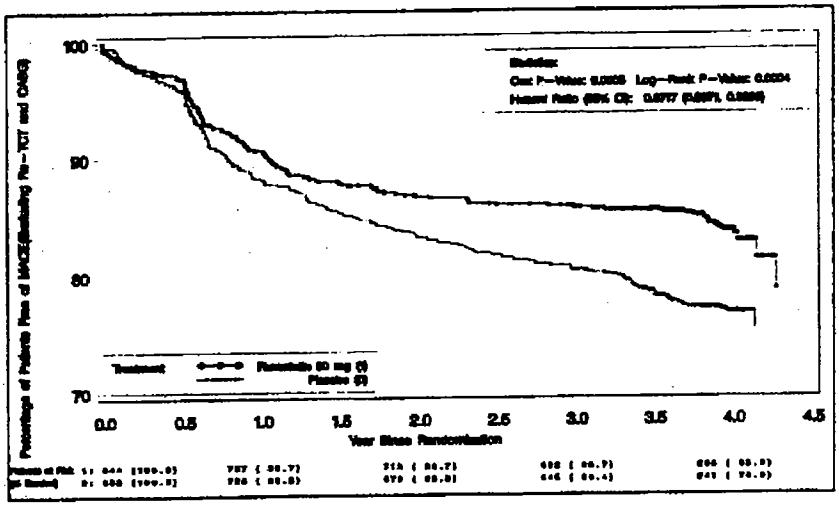
[1]First occurrence of MACE
[2]Including CABG, repeat TCT or TCT of new lesion

(c) MACE-Free Survival Time Excluding Repeat PCI and CABG within the First 6 Months on Index Target Lesion

Statin therapy does not prevent restenosis of the target lesion within the first 6 months after PCI, and thus, MACE-free survival excluding repeat PCI and CABG within the first 6 months on index target lesion was also assessed. This analysis showed that 61 patients in the fluvastatin group (7%) and 53 patients in the placebo group (6%) had a repeat re-intervention due to restenosis in the first 6 months of follow-up as first MACE. Of these,

46 and 35 patients in the fluvastatin and placebo groups, respectively, had no MACE thereafter. When repeat PCI and CABG within the first 6 months on the index target lesion are excluded from MACE-free survival time, the results show an earlier separation of the fluvastatin and placebo groups, beginning at approximately 6 months and continuing to diverge up to the end of follow-up. The log-rank test was statistically significant (p=.0004). The results are shown graphically in the following figure [From: SNDA #20-261 033, Volume 17; Integrated Summary of Benefits and Risks, page 8. Electronically copied and reproduced (best copy)]

Figure 3: MACE-Free Survival Time Excluding Repeat PCI and CABG on Index Target Lesion within First 6 Months



Further evaluation of late reinterventions alone [re-interventions excluding re-intervention (CABG or PCI) of the target lesion within 6 months of the initial procedure] showed that a significantly lower incidence of late re-interventions occurred in patients in the Lescol-treated group than in the placebo group. There were 111 Lescol-treated patients (13%) who experienced a late re-intervention compared to 151 placebo-treated patients (18%) (p=.0025). The incidence rates for late re-interventions are summarized in the following table

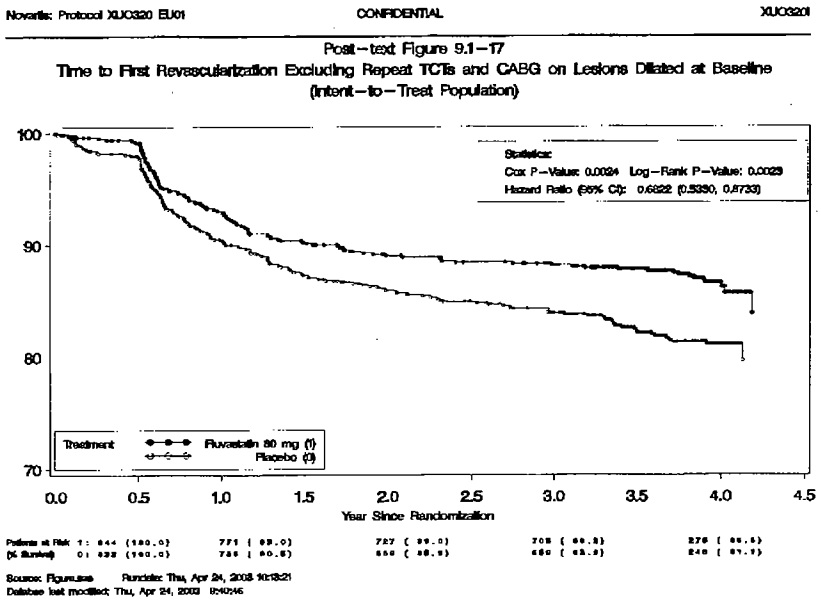
Table 15: LIPS Incidence of Late Re-interventions Alone

	Fluvastatin	Placebo	p-value
n=	844	833	
Clinical Endpoint	n (%)	n (%)	
Late Re-interventions[1]			
Number of Patients	111 (13)	151 (18)	.0025
Number of Events	140	192	

[1]Re-interventions excluding re-interventions (CABG or PCI) of target lesion within 6 months of the initial procedure

The Kaplan-Meier plot of late-re-intervention-free survival time shows a separation of the fluvastatin and placebo groups beginning at approximately 6 months and continuing to diverge up to the end of follow-up. The log-rank test was statistically significant (p=.0023). The results are shown graphically in the following figure [From: SNDA #20-261 033, amendment dated 25-Apr-2003. Electronically copied and reproduced]

Figure 4: Late Re-intervention-Free Survival Time Excluding Repeat PCI and CABG on Index Target Lesion within First 6 Months



(d) Effects on Lipid Levels

There were significant decreases in LDL-C, TC, and TG at Week 6 in the fluvastatin group compared to the placebo group. The mean percent changes in LDL-C in the fluvastatin and placebo groups were –24% and +15%, respectively (p=.0001). Mean percent changes in TC were –15% and +12%, respectively (p=.0001), and for TG were –5% and +13%, respectively (p=.0001). There was no significant difference between the 2 groups for mean percent increases in HDL-C (p=.2139), which were +14% in the fluvastatin group and +16% in the placebo group. Similar lipid changes were seen at Endpoint, with significant (compared to placebo) mean decreases in LDL-C (of –18% in the fluvastatin group and +5% in the placebo group) and TC (-9% and +7%, respectively), and non-significant mean increases in HDL-C (+25% and +26%, respectively). The lipid results at Endpoint differed from the Week 6 results for TG however, with non-significant increases in TG at Endpoint (+2% and +4%, respectively). Mean Percent changes in the lipid parameters from Baseline at Week 6 and at Endpoint are summarized in the following table

Table 16: LIPS Effects on Lipid Parameters at Week 6 and Endpoint

		Baseline	% Change from Baseline	
	n*	Mean	Mean	p-value
Lipid Parameter				
Week 6				
LDL-C (mmol/L)				.0001
Fluvastatin	696	3.4	-23.5%	
Placebo	692	3.4	+15.0%	
HDL-C (mmol/L)				.2139
Fluvastatin	697	1.0	+14.2%	
Placebo	696	1.0	+16.3%	
TC (mmol/L)				.0001
Fluvastatin	708	5.2	-15.2%	
Placebo	709	5.2	+12.0%	
TG (mmol/L)				.0001
Fluvastatin	708	1.8	-4.4%	
Placebo	708	1.7	+12.7%	
Endpoint				
LDL-C (mmol/L)				.0001
Fluvastatin	719	3.4	-18.4%	
Placebo	712	3.4	+5.4%	
HDL-C (mmol/L)				.8798
Fluvastatin	719	1.0	+25.0%	
Placebo	715	1.0	+25.6%	
TC (mmol/L)				.0001
Fluvastatin	725	5.2	-9.4%	
Placebo	724	5.2	+6.6%	
TG (mmol/L)				.8197
Fluvastatin	725	1.8	+2.2%	
Placebo	724	1.7	+3.9%	

*n = number of patients with lipid data at Baseline and Week 6, or Baseline and Endpoint

(3) Subgroup Analyses

The Cox regression analysis of time to first MACE was performed on predefined patient subgroups, including patients by age ≥65 years at randomization, gender, presence or absence of diabetes, single or multiple vessel disease, prior or no prior MI, and with Baseline LDL-C and TC ≤median or >median. The risk ratios for all of the subgroups were <1, suggesting a benefit of treatment with fluvastatin for all subgroups; however, the results were significant only in patients in the following subgroups: age ≥65 years (p=.006), males (p=.033), diabetics (p=.041), multiple vessel disease (p=.011), and Baseline LDL-C ≤median. The non-significant result for females was thought to be due to the small number of females enrolled in the study. Analysis of time to first MACE within subgroups is summarized in the following table

Table 17: LIPS Subgroup Analyses Efficacy: Time to First MACE

Subgroup	n	Risk Ratio	95% CI	p-value
Age <65 years	1054	0.89	(0.69, 1.15)	.381
Age ≥65 years	623	0.62	(0.45, 0.87)	.006
Males	1406	0.79	(0.64, 0.98)	.033
Females	271	0.66	(0.38, 1.14)	.133
Diabetics	202	0.53	(0.29, 0.97)	.041
Non-Diabetics	1475	0.83	(0.67, 1.03)	.096
Multiple vessel disease	614	0.66	(0.48, 0.91)	.011
Single vessel disease	1063	0.86	(0.66, 1.13)	.278
Prior MI	744	0.78	(0.57, 1.06)	.112
No Prior MI	933	0.79	(0.61, 1.03)	.084
Baseline TC >Median	707	0.76	(0.56, 1.04)	.089
Baseline TC ≤Median	850	0.77	(0.57, 1.02)	.068
Baseline LDL-C >Median	734	0.80	(0.58, 1.10)	.165
Baseline LDL-C ≤Median	805	0.74	(0.55, 1.00)	.047

The Cox regression analysis performed on the primary endpoint using predefined Baseline risk factors as covariates revealed significant effects only for multiple-vessel vs. single-vessel disease and for the presence vs the absence of diabetes.

For diabetics vs non-diabetics: Reductions in the risk of MACE and in the incidence of MACE between the treatment groups showed significant reductions in the risk for MACE in diabetic patients treated with fluvastatin compared with diabetic patients on placebo. Patients with diabetes had a –47% reduction in the risk of first MACE compared with the placebo group. There was no significant difference between treatments in the risk for MACE in non-diabetic patients. Patients with diabetes were more likely than non-diabetics to experience a MACE, although the results were not significant (RR 1.36; p=.060).

For multiple-vessel vs single-vessel disease: There was a significant reduction in the risk for MACE in fluvastatin-treated patients with multiple-vessel coronary disease compared with placebo, and no significant difference between treatments in the risk for MACE in patients with single-vessel disease. Patients with multiple-vessel disease in the fluvastatin group had a –34% reduction in the risk of first MACE compared to the placebo group. Patients with multiple-vessel disease were significantly more likely than single-vessel disease patients to experience a MACE (RR 1.31; p=.023).

Incidence rates of MACE for diabetics and non-diabetics, and for single- and multiple-vessel disease are summarized in the following table

Table 18: LIPS Incidence of Clinical Endpoints by Subgroup

	Fluvastatin	Placebo	p-value
n=	844	833	
Clinical Endpoint	n (%)	n (%)	
Diabetics, n =	120	82	
MACE[1]	26 (21.7)	31 (37.8)	.022
Death	2 (1.7)	3 (3.7)	
Non-fatal MI	4 (3.3)	6 (7.3)	
Re-intervention	20 (16.7)	22 (26.8)	
Non-Diabetics, n =	724	751	
MACE[1]	155 (21.4)	191 (25.4)	.050
Death	6 (0.8)	15 (2.0)	
Non-fatal MI	26 (3.6)	27 (3.6)	
Re-intervention	123 (17.0)	149 (19.8)	
Multi-vessel Disease, n =	322	292	
MACE[1]	74 (23.0)	99 (33.9)	.008
Death	4 (1.2)	7 (2.4)	
Non-fatal MI	13 (4.0)	14 (4.8)	
Re-intervention	57 (17.7)	78 (26.7)	
Single-vessel Disease, n =	522	541	
MACE[1]	107 (20.5)	123 (22.7)	.168
Death	4 (0.8)	11 (2.0)	
Non-fatal MI	17 (3.3)	19 (3.5)	
Re-intervention	86 (16.5)	93 (17.2)	

[1]First occurrence of MACE

The results from the Cox regression analysis of time-to-first MACE adjusting for demographic and risk factors as covariates showed that only treatment group was associated with a significantly reduced RR of time to first MACE (RR 0.72; p=.004). The Cox regression analysis of time-to-first MACE adjusting for demographic and risk factors is summarized in the following table

Table 19: Cox Regression Analysis of Time-to-First MACE Adjusting for Demographic and Risk Factors

Variable	Risk Ratio	95% CI	p-value
Treatment	0.72	(0.58, 0.90)	.004
Age	1.00	(0.99, 1.01)	.893
Ejection Fraction	0.99	(0.98, 1.00)	.035
Coronary Disease Status*	1.31	(1.04, 1.65)	.023
MI History (Yes vs No)	0.78	(0.60, 1.00)	.047
Baseline TC (> or < median)	1.12	(0.88, 1.41)	.359
Diabetes (Yes vs No)	1.36	(0.99, 1.88)	.060

*Multiple vessel disease vs single vessel disease

(4) Findings of the Statistical Reviewer

[The following summary of the statistical findings is from: Hoberman D. Ph.D., Statistical Review and Evaluation, SNDA #20-261/SE1-033. Additional analysis of late revascularization procedures is from review by: Sahlroot T, Ph.D. Please refer to the Statistical Reviews for the complete Statistical Results.]

For the primary endpoint, the Statistical Reviewer was in agreement with the sponsor's findings. It was noted by the Statistical Reviewer that the significant reduction in the risk of experiencing a MACE was largely due to the decreased number of re-interventions experienced by the fluvastatin group compared to the placebo group. This relative risk reduction in MACE was achieved greater significance after exclusion of re-interventions occurring during the first 6 months of study drug treatment (events thought not to be due to atherosclerosis). These findings were summarized by the Statistical Reviewer as follows [from: Hoberman D. Ph.D., Statistical Review and Evaluation, SNDA #20-261/SE1-033]:

"We may regard a patient's outcome as one of possibly eight potential outcomes, each having 3 components: reintervention or not, cardiac death or not, and non-fatal MI or not. Any subset of these 3 outcomes is possible. Obviously, the temporal order of some subsets is not free. Formally, let (C,R,M) be a vector standing for (cardiac death, reintervention, non-fatal MI) where each symbol can be 0 or 1. Then we may examine the distribution of these vectors within each treatment group. For convenience, we can produce a table whose columns list only the events which the patient experienced.

Counts of combined events

	No Event	CRM	CR	RM	R	CM	C	M
Lescol	663	0	4	24	**139**	1	8	5
Placebo	611	2	4	25	**162**	0	18	11

Percentages of combined events

	No Event	CRM	CR	RM	R	CM	C	M
Lescol	78.6	0.0	0.5	2.8	**16.5**	0.1	1.0	0.5
Placebo	73.4	0.2	0.5	3.0	**19.5**	0.0	2.2	1.2

The table suggests that the overall p-value of .0127 is due to the **bolded** difference in patients who experienced *only* a reintervention.

One of the uncontrolled features of the study was that patients could have interventions shortly after randomization. From previous studies, the sponsor concluded that reinterventions performed within 6 months would not be related to study medication. Of

the 167 Lescol patients who received a reintervention *at any time*, 40 (24%) were excluded by the 6 month 'rule'. In the placebo group, of the 193 patients who received a reintervention *at any time*, 26 (13.5%) were exclude by the 6 month rule. Since Lescol reintervention patients had almost double the percentage of 'early' reinterventions, excluding them from the analysis lowered the p-value to .0004."

An additional analysis of the late revascularization procedures [revascularization procedures excluding re-interventions of the target lesion within 6 months of the initial procedure] was also performed by the Statistical Reviewer (Dr.Sahlroot). The Statistician's results show a 31% RRR in late revascularizations in the fluvastatin group compared to the placebo group, which is slightly different from the findings of the sponsor. The findings are summarized in the following table

Table 20: LIPS Incidence of Late Re-interventions Alone, Statistician's Results

	Fluvastatin	Placebo	p-value	RRR
n=	844	833		(95% C.I.)
Clinical Endpoint	n (%)	n (%)		
Late Re-interventions[1]				
Number of Patients	115 (14)	154 (18)	.0027	31% (12%-46%)

[1]Re-interventions excluding re-interventions (CABG or PCI) of target lesion within 6 months of the initial procedure

(5) Efficacy Conclusions

The primary endpoint was the combined endpoint of major adverse cardiac event (MACE)-free survival time in patients treated with fluvastatin 80 mg/day or placebo after successful first PCI, during a follow-up of 3-4 years. There was a significant (p=.0127) difference in time to first MACE survival distributions between the 2 treatment groups, with a separation in the curves beginning at approximately 1.5 years. There was a significant 22% reduction in risk (RR 0.78) of experiencing a MACE in the fluvastatin group compared to the placebo group (p=.013). The risk ratios of the 3 individual components of MACE (cardiac death, non-fatal MI, and re-intervention) were all <1 (favoring fluvastatin); however, none of these individual results were statistically significant on their own.

The fluvastatin group had a significantly lower incidence of the combined MACE compared to the placebo group, with an incidence of MACE of 21% in the fluvastatin group vs 27% in the placebo group (p=.006), the majority of which were re-interventions. There was a lower incidence of each of the individual clinical endpoints of MACE in the fluvastatin group compared to the placebo groups. In the fluvastatin and placebo groups, cardiac death occurred at incidences of 1.5% and 2.9%, respectively (p=.060), non-fatal MI at rates of 3.6% and 4.6% (p=.277), and re-interventions at rates of 19.8% and 23.2% (p= :052).

When re-interventions occurring within the first 6 months were excluded from the combined MACE endpoint analysis [as treatment with a statin has not been shown to prevent early (non-atherosclerotic) re-stenosis], the results show greater significance of

the combined MACE endpoint (p=.004) and an earlier separation of the fluvastatin and placebo groups, beginning at approximately 6 months. Further evaluation of late reinterventions alone [re-interventions excluding re-intervention (CABG or PCI) of the target lesion within 6 months of the initial procedure] showed that a significantly lower incidence of late re-interventions occurred in patients in the Lescol-treated group than in the placebo group [111 Lescol-treated patients experienced a late re-intervention compared to 151 placebo-treated patients; p=.0025].

Other secondary endpoints examined in the study, including time to worst MACE, noncardiac death, all death, cardiac death or non-fatal MI, and all death or MI, all had relative risk ratios <1 (for the fluvastatin group), although none of these endpoints achieved statistical significance. On subgroup analysis, including by age (≥65 years and <65 years), gender, presence or absence of diabetes, single or multiple vessel disease, prior or no prior MI, and Baseline LDL-C and TG ≤median or >median, the risk ratios for all of the subgroups were <1, suggesting a benefit of treatment with fluvastatin for all subgroups. However, the results were significant only in patients age ≥65 years, males, diabetics, multiple vessel disease, and Baseline LDL-C ≤median.

Protocol violations were common in the study, with 38% of patients overall having poor compliance to study medication (<80% of study medication taken during the study), and 23% of patients being treated with a statin other than study medication over the course of the study. Poor compliance and treatment with other statins were both more common in the placebo groups. The likely outcome of these violations would be an attenuation of the treatment effect of fluvastatin. Another criticism of the study would be the combined MACE endpoint used for the study, as none of the individual components of the MACE endpoint were significant when considered individually. However, combination endpoints have been used in other secondary prevention trials, and the results seen in LIPS are consistent with these trials. Thus, it can be concluded that treatment with fluvastatin was associated with a significant decrease in time to the combined endpoint of first MACE and a risk reduction in MACE. Fluvastatin treatment was also associated with a significant decrease in the incidence of late re-interventions.

3. Review of Safety

In LIPS, 1677 patients were randomized to fluvastatin (n = 844) or placebo (n = 833). Thirty-seven (37) of these patients (2%) never took study medication: 22 patients in the fluvastatin group (3%) and 15 in the placebo group (2%). Thus, 1640 patients comprised the safety population: 822 patients in the fluvastatin group and 818 patients in the placebo group. Seven (7) patients in the fluvastatin group (1%) and 10 patients in the placebo group (1%) were lost to follow-up, and safety data for these patients were collected until the date of the last contact.

a) Description of Patient Exposure

Exposure to study medication was assessed using the safety population. Study medication was planned to have been taken for a minimum of 3 years and maximum of 4 years, and all patients were to have been followed until 3 years after recruitment of the last patient. However, both groups had actual maximum durations of follow-up and treatment of approximately 5 years and 4.5 years, respectively. This was mainly due to a recruitment period that lasted 29 months, which was considerably longer than the 12 months originally planned for the study.

The mean duration of study drug administration in the fluvastatin group was 1059 days, and in the placebo group was 962 days. The mean duration of follow-up was 1374 days in the fluvastatin group, and 1365 in the placebo group. Exposure to study medication and study follow-up are summarized in the following table

Table 21: LIPS Mean Duration Study Drug Administration and Follow-Up

	Treatment	
	Fluvastatin 80 mg	**Placebo**
Duration of Follow-Up		
n =	844	833
Mean (days)	1374	1365
Median (days)	1455	1455
Min, max (days)	20, 1793	1, 1846
Duration of study drug		
n =	822	818
Mean (days)	1059	964
Median (days)	1316	1273
Min, max (days)	1, 1663	1, 1730

Exposure to study medication was similar between treatments during the initial 6 months of treatment. Thereafter, the number of patients on study medication tended to be higher at each assessment in the fluvastatin group compared to the placebo group. Patient exposure by treatment duration is summarized in the following table

Table 22: LIPS Patient Exposure and Treatment Duration

	Treatment			
	Fluvastatin 80 mg (n = 822)		Placebo (n = 818)	
Duration	Being Followed, n (%)	On Medication, n (%)	Being Followed, n (%)	On Medication, n (%)
6 weeks	818 (100)	777 (95)	816 (100)	774 (95)
6 months	813 (99)	706 (86)	806 (99)	703 (86)
12 months	807 (98)	659 (80)	799 (98)	616 (75)
18 months	803 (98)	629 (77)	796 (97)	567 (69)
24 months	795 (97)	611 (74)	786 (96)	530 (65)
30 months	792 (96)	584 (71)	783 (96)	510 (62)
36 months	775 (94)	560 (68)	770 (94)	490 (60)
42 months	656 (80)	453 (55)	634 (78)	390 (48)
48 months	223 (27)	116 (14)	239 (29)	115 (14)

b) Adverse Events

An Adverse Event (AE) was defined as any adverse medical change from the subject's baseline (or pre-treatment) condition which occurred during the course of the clinical study, after starting treatment, whether considered treatment-related or not. "Treatment" includes all investigative agents administered during the course of the study. Adverse Events in the dataset included all AEs occurring in randomized patients who took at least one dose of double-blind study medication (the Safety population). Recurrent or continuing AEs were counted only once. Adverse Event incidence rates were calculated using the Safety population as the denominator. Clinical AEs were coded to Preferred Term and Body System using the ICD 10 dictionary.

During the study, there were 455 different AE terms reported by 1329 of the 1640 patients (81%) in the Safety population. Patients in the placebo group were somewhat more likely than patients in the fluvastatin group to report any AE during the study, with 80% of patients in the fluvastatin group and 82% of patients in the placebo group reporting any AE. Patients reporting any AE overall and by treatment group are summarized in the following table

Table 23: LIPS Patients Reporting Any AE

		Treatment	
	All	Fluvastatin	Placebo
Safety Population, n =	1640	822	817
Patients Reporting Any AE, n (%)	1329 (81)	661 (80)	668 (82)

c) Adverse Events by Body System

Adverse Events in the Symptoms, Signs & Abnormal Clinical & Laboratory Findings section and the Circulatory system were the most commonly reported, which were reported by 52% and 40%, respectively, of patients overall. Adverse Events in the Symptoms, Signs & Clinical & Laboratory Findings section were somewhat more common in the fluvastatin group (55%) than in the placebo group (49%), and AEs in the Circulatory system were somewhat more common in the placebo group (43%) than in the fluvastatin group (37%). Adverse Events in the Musculoskeletal (17%), Gastrointestinal

(15%), and Respiratory (12%) systems were the next most commonly reported, and had similar incidence rates in both treatment groups. The Endocrine, Nutritional, and Metabolic system had an AE incidence rate of 6% overall, that was lower in the fluvastatin group (3%) than in the placebo group (8%). This was due to a lower incidence of disorders of lipoprotein metabolism and lipidemias in the fluvastatin group (1%) than the placebo group (6%). There were no other notable differences between the 2 treatment groups in AEs by Body System. The incidence rates of the most commonly (≥3% incidence rates) reported AEs by Body System are summarized in the following table

Table 24: LIPS Adverse Events by Body System, Most Common (≥3% incidence rates)

		Treatment	
	All	**Fluvastatin**	**Placebo**
Safety Population, n =	1640	822	817
Body System	n (%)	n (%)	n (%)
Symptoms, Signs & Abnormal Clinical & Laboratory Findings, NEC	851 (52)	448 (55)	403 (49)
Circulatory	659 (40)	304 (37)	355 (43)
Musculoskeletal and Connective Tissue	275 (17)	144 (18)	131 (16)
Gastrointestinal and Digestive	250 (15)	118 (14)	132 (16)
Respiratory	201 (12)	99 (12)	102 (13)
Surgical Procedures	151 (9)	68 (8)	83 (10)
Genitourinary	121 (7)	52 (6)	69 (8)
Endocrine, Nutritional, & Metabolic	96 (6)	28 (3)	68 (8)
Neoplasms	95 (6)	46 (6)	49 (6)
Injury, Poisoning & Other External Causes	93 (6)	35 (4)	58 (7)
Infections & Parasitic Diseases	81 (5)	34 (4)	47 (6)
Nervous	71 (4)	35 (4)	36 (4)
Skin & Subcutaneous Tissue	65 (4)	36 (4)	29 (4)
Mental & Behavioral	54 (3)	24 (3)	30 (4)
Eye & Adnexa/Vision	49 (3)	22 (3)	27 (3)

By AE Preferred Term, angina pectoris was the most commonly reported AE term overall, with 26% of patients reporting at least one episode of angina during the study. Angina was somewhat more common in the placebo group (28%) than in the fluvastatin group (23%). Pain in throat and chest was the next most commonly reported AE term, reported by 20% of patients overall, and by 20% of patients in each of the 2 treatment groups. As noted above, disorders of lipoprotein metabolism and lipidemias were more common in the placebo group (6%) than in the fluvastatin group (1%). There were no other notable differences between the 2 treatment groups. The most commonly reported AEs (reported by ≥3% of patients) by Body System and AE Preferred Term are summarized in the following table [a complete list of all AEs reported during the study is in the Appendix]

Table 25: LIPS Most Common Adverse Events (>3% of Patients)

			Treatment	
		All	Fluvastatin	Placebo
Safety Population, n =		1640	822	817
Body System	AE Preferred Term	n (%)	n (%)	n (%)
Infectious & Parasitic	Diarrhea & gastroenteritis of presumed infectious origin	47 (3)	21 (3)	26 (3)
Circulatory System	Angina pectoris	423 (26)	192 (23)	231 (28)
	Chronic ischemic heart disease	90 (5)	34 (4)	56 (7)
	Essential (primary) hypertension	82 (5)	44 (5)	38 (5)
	Acute myocardial infarction	72 (4)	30 (4)	42 (5)
	Other peripheral vascular diseases	46 (3)	25 (3)	21 (3)
	Atrial fibrillation & flutter	39 (2)	23 (3)	16 (2)
Digestive system	Other functional intestinal disorders	47 (3)	27 (3)	20 (2)
	Gastritis & duodenitis	44 (3)	20 (2)	24 (3)
Musculoskeletal System & Connective Tissue	Other soft tissue disorders, NEC	107 (7)	60 (7)	47 (6)
	Dorsalgia	78 (5)	34 (4)	44 (5)
	Other joint disorders, NEC	43 (3)	24 (3)	19 (2)
Respiratory System	Acute nasopharyngitis [common cold]	45 (3)	25 (3)	20 (2)
	Pneumonia, organism unspecified	43 (3)	22 (3)	21 (3)
Endocrine, Nutritional & Metabolic	Disorders of lipoprotein metabolism & other lipidemias	59 (4)	10 (1)	49 (6)
Surgical Procedures	Surgery - Cardiac - TCT	53 (3)	23 (3)	30 (4)
	Surgery - Cardiac - other cardiac procedures	41 (3)	19 (2)	22 (3)
Symptoms, Signs & Abnormal Clinical & Laboratory Findings, NEC	Pain in throat & chest	321 (20)	161 (20)	160 (20)
	Abnormalities of breathing	147 (9)	69 (8)	78 (10)
	Abdominal & pelvic pain	123 (8)	70 (9)	53 (6)
	Malaise & fatigue	94 (6)	56 (7)	38 (5)
	Dizziness & giddiness	80 (5)	40 (5)	40 (5)
	Other symptoms & signs involving the digestive system & abdomen	74 (5)	41 (5)	33 (4)
	Edema, NEC	63 (4)	37 (5)	26 (3)
	Abnormalities of heart beat	61 (4)	33 (4)	28 (3)
	Headache	50 (3)	23 (3)	27 (3)
	Nausea & vomiting	49 (3)	27 (3)	22 (3)
	Other ill-defined & unspecified causes of mortality	44 (3)	16 (2)	28 (3)
	Syncope & collapse	43 (3)	22 (3)	21 (3)
	Abnormal serum enzyme levels	42 (3)	25 (3)	17 (2)

Adverse Events of particular interest to this study include AST, ALT and CK increases, myalgia, myopathy, rhabdomyolysis, and hepatitis. The AST, ALT, and CK increases will be considered under the Laboratory Abnormalities below.

A search by this Reviewer by Body System, Preferred Term, and Verbatim Term revealed that the verbatim terms of myalgia, myopathy, rhabdomyolysis, and hepatitis were grouped under larger Preferred Terms in the database.

For hepatitis, there were 2 reports of hepatitis: 1 each in the placebo and fluvastatin groups. Four (4) other complaints referable to the liver, including 1 report each of liver dysfunction, steatosis hepatitis, liver function disorder, and liver disorder were reported, and occurred in 2 patients in each treatment group.

There were no reports of rhabdomyolysis. Myopathy and myalgia, and other complaints referable to muscle pain were included in more than 50 verbatim terms, including: muscle pain, myalgia, muscle aching, diffuse muscular pain, musculoskeletal pain, myopathy of lower limbs, cortisonic myopathy, and others. These verbatim terms coded to either Diseases of Musculoskeletal system and Connective Tissue, under the preferred terms of "disorders of muscle", and "soft tissue disorders, NEC", or to the Nervous system, under "other myopathies". [Note: the sponsor specifically stated that verbatim complaints of "rheumatic pain" were coded under the Preferred Term of "dorsalgia".] Body System and Preferred Terms for the Musculoskeletal and Nervous system including all verbatim terms coding to "other soft tissue disorders", "other disorders of muscle", "other myopathies"and the selected muscle complaints from this Preferred terms (as above) are summarized as follows:

Table 26: LIPS Myopathy, Myalgias, and Other Muscle Pain

			Treatment	
		All	Fluvastatin	Placebo
Safety Population, n =		1640	822	817
Body System	AE Preferred Term	n (%)	n (%)	n (%)
Musculoskeletal	Soft tissue disorders, NEC (All*), n (%)	107 (7)	60 (7)	47 (6)
	Disorders of muscle (All**), n (%)	10 (1)	6 (1)	4 (<1)
	Selected muscle complaints, n (%)	47 (3)	27 (3)	20 (2)
Nervous	Other myopathies	2 (<1)	1 (<1)	1 (<1)

* Also included other verbatim terms, such as: leg pain, arm pain, rheumatic pain, and many others
** Also included other verbatim terms, such as: fatigue legs, inguinal weakness, and others

No matter how the myalgia and myopathy complaints were evaluated, there did not appear to be a large number of patients with these complaints, and these muscle complaints appeared to be only marginally higher in the fluvastatin group than in the placebo group.

The sponsor's results for myopathy, myalgia, and muscle pain were slightly different, likely due to somewhat different groupings by verbatim and Preferred Terms. The sponsor coded myalgia and myopathy-type AEs under soft tissue disorders NEC, and back pain or joint pain were coded separately under dorsalgia and other joint disorders NEC, respectively. The sponsor noted that the incidence of soft tissue disorders NEC was marginally higher in the fluvastatin group compared with placebo. The incidence of dorsalgia was lower in the fluvastatin group compared with placebo, whereas the incidence of other joint disorders NEC was comparable between treatments. When all verbatim terms for the AEs associated with effects on the musculoskeletal system are taken into account, the incidence rates in the fluvastatin and placebo groups were 15.8% and 14.4%, respectively.

d) Adverse Events Resulting in Drug Discontinuation

Three hundred seventy-six (376) patients (23% overall) discontinued study drug for an AE (including MACE): 174 patients (21%) in the fluvastatin group and 202 patients (25%) in the placebo group. Incidence rates for all patients discontinuing for an AE (including MACE), by treatment group, are summarized in the following table

Table 27: LIPS Incidence of All Patients Discontinuing for an AE (including MACE)

		Treatment	
	All	Fluvastatin	Placebo
Safety Population, n =	1640	822	817
Patients Discontinuing for an AE, n (%)	376 (23)	174 (21)	202 (25)

The Circulatory and Endocrine systems were the most commonly reported Body Systems for AEs resulting in study drug discontinuation, and angina pectoris was the most commonly reported AE Preferred Term overall (5% of all patients). Discontinuations for angina were marginally more common in the placebo group (5%) than in the fluvastatin group (4%). The next most commonly reported AE as the reason for study drug discontinuation was in the Endocrine system, and was almost entirely due to disorders of lipoprotein metabolism and other lipidemias (3% of patients overall). Lipoprotein disorders were more common in the placebo group (5%) than in the fluvastatin group (1%). There were no other notable differences between the 2 treatment groups. The most common AEs ($\geq$1%, or $\geq$9 patients overall) resulting in study drug discontinuation are summarized in the following table [a listing of all AEs resulting in study drug discontinuation is in the Appendix].

Note: Reviewer's results from sponsor's electronic AE dataset using JMP software.

Table 28: LIPS Most Common (>1%) AEs Resulting in Study Drug Discontinuation (including MACE)

			Treatment	
		All	Fluvastatin	Placebo
Safety Population, n =		1640	822	817
Body System	AE Preferred Term	n (%)	n (%)	n (%)
Certain infectious and parasitic diseases	Diarrhea and gastroenteritis of presumed infectious origin	13 (1)	7 (1)	6 (1)
Diseases of the circulatory system	Angina pectoris	75 (5)	33 (4)	42 (5)
	Chronic ischemic heart disease	17 (1)	4 (<1)	13 (2)
	Acute myocardial infarction	15 (1)	7 (1)	8 (1)
Diseases of the digestive system	Gastritis and duodenitis	11 (1)	6 (1)	5 (1)
	Dyspepsia	9 (1)	4 (<1)	5 (1)
	Other diseases of digestive system	9 (1)	3 (<1)	6 (1)
Diseases of the musculoskeletal system and connective tissue	Other soft tissue disorders, NEC	14 (1)	9 (1)	5 (1)
Endocrine, nutritional and metabolic diseases	Disorders of lipoprotein metabolism and other lipidemias	46 (3)	5 (1)	41 (5)
Symptoms, signs & abnormal clinical & laboratory findings, NEC	Other symptoms and signs involving the digestive system and abdomen	32 (2)	21 (3)	11 (1)
	Pain in throat and chest	32 (2)	14 (2)	18 (2)
	Abdominal and pelvic pain	28 (2)	17 (2)	11 (1)
	Abnormal serum enzyme levels	23 (1)	15 (2)	8 (1)
	Other ill-defined and unspecified causes of mortality	22 (1)	9 (1)	13 (2)
	Malaise and fatigue	16 (1)	11 (1)	5 (1)
	Nausea and vomiting	15 (1)	9 (1)	6 (1)
	Abnormalities of breathing	14 (1)	5 1)	9 (1)

Discontinuations for muscle complaints were also evaluated. No patient was discontinued for myopathy. Fourteen (14) patients were discontinued for soft tissue disorders (7 in the fluvastatin group and 4 in the placebo group), and 2 patients for muscle disorders, both of whom were in the fluvastatin group.

Table 29: Discontinuations for Myalgia, Myopathy, and Other Muscle AEs

	All	Fluvastatin	Placebo
Safety Population, n =	1640	822	817
Preferred Term			
Other disorders of muscle*	2 (<1)	2 (<1)	0
Other soft tissue disorders, NEC**	14 (1)	9 (1)	5 (1)

* Includes verbatim terms of muscle stiffness and muscular deficiency
** Includes verbatim terms of muscle pain, muscle aching, myalgia, and others

The sponsor's findings for discontinuations for AEs were somewhat different from this Reviewer's results, and from the sponsor's summary of total discontinuations [see summaries in the Results/Patient Disposition/Discontinuations section of this review and from the sponsor's Clinical Study Report section 7.1, page 38]. The sponsor's explanation for the discrepancy between the total discontinuations summary and the discontinuations for AEs was that the total discontinuations table included patients whose

primary reason for discontinuing study medication was not an AE. The total discontinuations information was taken from the medication discontinuation CRF, and the discontinuations for AEs information was taken from the AE CRF, which included only patients whose primary reason for discontinuation was due to an AE.

The discrepancies between the sponsor's results (below) and this Reviewer's results (above) are also most likely due to the sponsor noting only the primary AE resulting in discontinuation (from the AE CRF) rather than all AEs designated as resulting in discontinuation [as in the AE dataset]. The sponsor also excluded MACE from the summary. The AE dataset did not designate only the primary AE as the reason for discontinuation, nor did it designate MACE terms, making it impossible to reconcile to the 2 sources of discontinuations for AEs.

The sponsor's overall findings show that discontinuations for AEs were somewhat more common in the placebo group (24%) than in the fluvastatin group (21%). The sponsor's overall findings for discontinuations due to AEs are summarized in the following table [from the Clinical Study Report, section 10.2, page 64]

Table 30: LIPS Sponsor's Overall Findings for Discontinuations for AEs Results

		Treatment	
	All	**Fluvastatin**	**Placebo**
Safety Population, n =	1640	822	818
AE Discontinuations, n (%)	370 (23)	174 (21.2)	196 (24.0)
SAE discontinuations, n (%)	141 (9)	62 (7.5)	79 (9.5)
Non-SAE discontinuations, n (%)	249 (15)	119 (14.5)	130 (15.9)
Drug-related AE discontinuations, n (%)	153 (9)	86 (10.5)	67 (8.2)

By Body System and Preferred Term, the sponsors results show that the most commonly reported Body System for discontinuations due to AEs were in the Symptoms, Signs & Abnormal Clinical & Laboratory Findings Body System, with 10% of patients overall discontinuing for AEs in this Body System. AEs in the Symptoms, Signs system were more common in the fluvastatin group (11%) than in the placebo group (8%). The most common AE Preferred Terms in this section were other symptoms and signs involving the digestive system and abdomen (2% overall), abdominal and pelvic pain (1%), and abnormal serum enzyme levels (1%), all of which were somewhat more common in the fluvastatin group (2% for each AE Term) than in the placebo group (1% for each AE Term). The next most commonly reported Body System was the Circulatory system (5% overall), with angina pectoris being the most commonly reported AE Term (3%). Circulatory system AEs resulting in discontinuations were somewhat more common in the placebo group (6%) than in the fluvastatin group (4%), as was angina pectoris [3% in the placebo group and 2% in the fluvastatin group]. The sponsor's results by most common (≥1%) AE Preferred Terms [from the Clinical Study Report, section 10.2.2, page 67]

Table 31: LIPS Sponsor's Results, Most Common (≥1%) AEs Resulting in Study Drug Discontinuation (excluding MACE)

			Treatment	
		All	Fluvastatin	Placebo
Safety Population, n =		1640	822	818
All Patients who Discontinued Study Medication for AEs, n (%)		370 (23)	174 (21)	196 (24)
Body System	AE Preferred Term	n (%)	n (%)	n (%)
Symptoms, signs & abnormal clinical & laboratory findings, NEC	All	159 (10)	91 (11)	68 (8)
	Other symptoms and signs involving the digestive system and abdomen	30 (2)	19 (2)	11 (1)
	Abdominal and pelvic pain	24 (1)	15 (2)	9 (1)
	Abnormal serum enzyme levels	22 (1)	14 (2)	8 (1)
	Nausea and vomiting	12 (1)	8 (1)	4 (1)
Diseases of the circulatory system	All	76 (5)	30 (4)	46 (6)
	Angina pectoris	42 (3)	14 (2)	28 (3)
	Chronic ischemic heart disease	10 (1)	2 (<1)	8 (1)
Diseases of the digestive system	All	40 (2)	18 (2)	22 (3)
Endocrine, nutritional and metabolic diseases	All	42 (3)	4 (1)	38 (5)
	Disorders of lipoprotein metabolism and other lipidemias	42 (3)	4 (1)	38 (5)
Diseases of the musculoskeletal system and connective tissue	All	22 (1)	13 (2)	9 (1)
	Other soft tissue disorders, NEC	12 (1)	8 (1)	4 (1)
Neoplasm	All	24 (1)	13 (2)	11 (1)
Certain Infections & Parasitic Diseases	All	13 (1)	8 (1)	5 (1)
Disease of the Skin & Subcutaneous Tissue	All	12 (1)	8 (1)	4 (1)

e) Serious Adverse Events

Eight hundred five (805) patients (49%) experienced any Serious Adverse Event (SAE), including MACE, during the study: 384 patients (47%) in the fluvastatin group and 421 patients (52%) in the placebo group. Patients experiencing an SAE (including MACE) during the study are summarized in the following table

Table 32: LIPS Incidence of All SAEs (including MACE)

		Treatment	
	All	Fluvastatin	Placebo
Safety Population, n =	1640	822	817
Patients Experiencing an SAE, n (%)	788 (48)	372 (45)	416 (51)
All Deaths	82	36	46*

*Does not include 3 placebo patients who died but did not receive any study drug (excluded from Safety Population)

The most commonly reported SAEs were in the Circulatory System. Angina pectoris was the most commonly reported SAE Preferred Term overall (20%), and was somewhat more common in the placebo group (21%) than in the fluvastatin group (18%). Other cardiac-related SAEs were also marginally more common in the placebo group than in the fluvastatin group, including acute MI (5% and 4%, respectively), chronic ischemic heart disease (5% and 4%), Surgery–Cardiac–TCT (4% and 3%), and Surgery-CABG (2% and <1%), although the numbers of these events by AE Preferred Term were small.

There were no other notable differences in SAEs between the 2 treatment groups. The most common SAEs (≥1%, or ≥9 patients overall) including MACE are summarized in the following table [a listing of all SAEs is in the Appendix]

Table 33: LIPS Most Common (≥1%) Serious Adverse Events (including MACE)

			Treatment	
		All	Fluvastatin	Placebo
Safety Population, n =		1640	822	817
Body System	**AE Preferred Term**	**n (%)**	**n (%)**	**n (%)**
Circulatory System	Angina pectoris	323 (20)	149 (18)	174 (21)
	Acute myocardial infarction	70 (4)	29 (4)	41 (5)
	Chronic ischemic heart disease	70 (4)	27 (4)	43 (5)
	Other peripheral vascular diseases	17 (1)	8(1)	9 (1)
	Atrial fibrillation and flutter	15 (1)	9 (1)	6 (1)
	Heart failure	15 (1)	6 (1)	9 (1)
	Stroke, not specified as hemorrhage or infarction	14 (1)	5 (1)	9 (1)
	Cardiac arrest	10 (1)	4 (<1)	6 (1)
Digestive System	Other diseases of digestive system	14 (1)	6 (1)	8 (1)
	Inguinal hernia	11 (1)	2 (<1)	9 (1)
Genitourinary System	Hyperplasia of prostate	10 (1)	2 (<1)	8 (1)
Nervous System	Transient cerebral ischemic attacks and related syndromes	10 (1)	8 (1)	2 (<1)
Respiratory System	Pneumonia, organism unspecified	22 (1)	10 (1)	12 (1)
Neoplasms	Malignant neoplasm of prostate	11 (1)	9 (1)	2 (<1)
Surgical procedures	Surgery – Cardiac - TCT	53 (3)	23 (3)	30 (4)
	Surgery – Cardiac – other cardiac procedures	31 (2)	14 (2)	17 (2)
	Surgery – Cardiac – CABG	21 (1)	7 (<1)	14 (2)
	Surgery – Digestive system	9 (1)	4 (<1)	5 (1)
Symptoms, signs and abnormal clinical and laboratory findings, NEC	Pain in throat and chest	141 (9)	70 (9)	71 (9)
	Other ill-defined and unspecified causes of mortality	43 (3)	16 (2)	27 (3)
	Syncope and collapse	23 (1)	12 (1)	11 (1)
	Abnormalities of breathing	22 (1)	10 (1)	12 (1)
	Abdominal and pelvic pain	21 (1)	10 (1)	11 (1)
	Abnormalities of heart beat	11 (1)	6 (1)	5 (1)
	Malaise and fatigue	9 (1)	6 (1)	3 (<1)

The sponsor's results for SAEs were similar to this Reviewer's results (above). The sponsor also summarized all SAEs by Body System, as follows (from Clinical Study Report Section 10.2.1, page 66)

Table 34: LIPS Sponsor's Results Most Common (>1%) SAEs (including MACE) by Body System

		Treatment	
	All	Fluvastatin	Placebo
Safety Population, n =	1640	822	817
Patients with SAEs, n (%)	788 (48)	372 (45)	416 (51)
Body System	**n (%)**	**n (%)**	**n (%)**
Circulatory System	476 (29)	217 (26)	259 (32)
Symptoms, Signs & Abnormal Clinical & Laboratory Findings, NEC	265 (16)	129 (16)	136 (17)
Surgical Procedures	127 (8)	56 (7)	71 (9)
Neoplasms	79 (5)	41 (5)	38 (5)
Diseases of Digestive System	67 (4)	32 (4)	45 (6)
Diseases of the Respiratory System	48 (3)	19 (2)	29 (4)
Diseases of the Genitourinary System	37 (2)	14 (2)	23 (3)
Diseases of the Musculoskeletal System & Connective Tissue	30 (2)	17 (2)	13 (2)
Injury, Poisoning & Certain Other Consequences of External Causes	29 (2)	11 (1)	18 (2)
Certain Infections & Parasitic Diseases	19 (1)	6 (1)	13 (2)
Diseases of the Nervous System	17 (1)	11 (1)	6 (1)
Endocrine, Nutritional & Metabolic Diseases	11 (1)	2 (<1)	9 (1)

f) Deaths

The sponsor summarized deaths using the randomized (ITT) study population as 3 patients in the placebo group died prior to receiving study medication and would not have been included in the safety population. Overall, 85 patients died during the study: 36 patients (4%) in the fluvastatin group and 49 patients (6%) in the placebo group. Cardiac deaths were somewhat more common in the placebo group (3%) than in the fluvastatin group (2%), and were included in the primary efficacy endpoint analysis (see Efficacy Results). Non-cardiac deaths were more common than Cardiac deaths (48 non-cardiac deaths overall vs 37 cardiac deaths overall), and were about as common in each of the treatment groups. Cancer was the most commonly reported diagnosis reported under non-cardiac death (32 patients overall; 2%). Deaths are summarized in the following table

Table 35: LIPS Sponsor's Results, All Deaths (Randomized Population)

		Treatment	
	All	Fluvastatin	Placebo
Randomized (ITT) Population, n =	1677	844	833
All Deaths	85 (5)	36 (4)	49 (6)
Cardiac Deaths	37 (2)	13 (2)	24 (3)
Non-Cardiac Deaths	48 (3)	23 (3)	25 (3)
Cancer	32 (2)	14 (2)	18 (2)
Respiratory failure	5 (<1)	3 (<1)	2 (<1)
Other death	4 (<1)	3 (<1)	1 (<1)
Stroke	3 (<1)	2 (<1)	1 (<1)
Sepsis	4 (<1)	1 (<1)	3 (<1)

g) Adverse Events by Subgroup

Adverse Events were further evaluated by gender and by age (≥65 years vs <65 years). Subgroup analysis by race was not possible due to the small number of non-Caucasian patients entered into the study.

(1) By Gender

Adverse Events were evaluated for male and female patients. It should be noted that at Baseline, females were older (mean age 63 years) than males (mean 59 years), and a larger percentage of female patients than male patients were ≥65 years of age (49% vs 35%, respectively). Females were also more likely to have had hypertension (59%) than males (35%), and were more likely to have had angina [unstable + stable] (93%) than males (88%). The age difference and higher prevalence of some co-morbid features at Baseline may have accounted, at least in some part, for the higher incidence of AEs in female patients than male patients. The AE results by gender are summarized below.

(a) Adverse Events

Females were more likely than males to report any AE, with any AE reported by 87% of females overall and by 79% of males overall. The higher incidence of any AE by gender was consistent across both treatment groups. Patients reporting any AE, by gender, are summarized in the following table

Table 36: LIPS Patients Experiencing Any AE by Gender

	All	Treatment	
		Fluvastatin	Placebo
Safety Population, n =	1640	823	818
Safety Population, Male, n =	1392	696	686
Safety Population, Female, n =	259	127	132
Patients experiencing any AE, All, n (%)	1329 (81)	661 (80)	668 (82)
Males experiencing any AE, n (%)	1103 (79)	552 (79)	551 (80)
Females experiencing any AE, n (%)	226 (87)	109 (86)	117 (89)

The most commonly reported AEs (occurring in ≥3% of patients overall) were evaluated by gender. Most AEs occurred in a relatively small number of patients by subgroup. Most AEs also tended to be somewhat more common or about as common in females as in males, and were about as common by gender across the treatment groups. As with the AE results overall, angina pectoris was the most commonly reported AE in males and females, and was more common in females (34% overall) than in males (24%). This was most likely due to the higher prevalence of angina in females than males at Baseline. Also similar to the results overall, angina was more common in the placebo group than in the fluvastatin group, regardless of gender. There were no other notable differences between males and females for AEs. The AE results by gender, by treatment group, are summarized in the following table

Table 37: LIPS Most Common AEs by Gender

Safety Population, n =			All M = 1392 F = 259	Fluvastatin M = 696 F = 127	Placebo M = 686 F = 132
Body System	**Preferred Term**	**M/F**			
Certain infectious and parasitic diseases	Diarrhea and gastroenteritis of presumed infectious origin	M	39 (3)	18 (3)	21 (3)
		F	8 (3)	3 (2)	5 (4)
Diseases of the circulatory system	Angina pectoris	M	334 (24)	154 (22)	180 (26)
		F	89 (34)	38 (30)	51 (39)
	Chronic ischemic heart disease	M	74 (5)	26 (4)	48 (7)
		F	16 (6)	8 (6)	8 (6)
	Essential (primary) hypertension	M	61 (4)	31 (4)	30 (4)
		F	21 (8)	13 (10)	8 (6)
	Acute myocardial infarction	M	56 (4)	23 (3)	33 (5)
		F	16 (6)	7 (6)	9 (7)
	Other peripheral vascular diseases	M	40 (3)	21 (3)	19 (3)
		F	6 (2)	4 (3)	2 (2)
	Atrial fibrillation and flutter	M	33 (2)	21 (3)	12 (2)
		F	6 (2)	2 (2)	4 (3)
Diseases of the digestive system	Other functional intestinal disorders	M	44 (3)	25 (4)	19 (3)
		F	3 (1)	2 (2)	1 (1)
	Gastritis and duodenitis	M	30 (2)	15 (2)	15 (2)
		F	14 (5)	5 (4)	9 (7)
Diseases of the musculoskeletal system &connective tissue	Other soft tissue disorders, NEC	M	85 (6)	50 (7)	35 (5)
		F	22 (8)	10 (8)	12 (9)
	Dorsalgia	M	59 (4)	25 (4)	34 (5)
		F	19 (7)	9 (7)	10 (8)
	Other joint disorders, NEC	M	37 (3)	19 (3)	18 (3)
		F	6 (2)	5 (4)	1 (1)
Diseases of the respiratory system	Acute nasopharyngitis [common cold]	M	39 (3)	22 (3)	17 (2)
		F	6 (2)	3 (2)	3 (2)
	Pneumonia, organism unspecified	M	34 (2)	17 (2)	17 (2)
		F	9 (3)	5 (4)	4 (3)
Endocrine, nutritional and metabolic diseases	Disorders of lipoprotein metabolism and other lipidemias	M	51 (4)	10 (1)	41 (6)
		F	8 (3)	0	8 (6)
Surgical procedures	Surgery - Cardiac - TCT	M	48 (3)	22 (3)	26 (4)
		F	5 (2)	1 (1)	4 (3)
	Surgery - Cardiac - other cardiac procedures	M	40 (3)	19 (3)	21 (3)
		F	1 (<1)	0	1 (1)
Symptoms, signs &abnormal clinical & laboratory findings, NEC	Pain in throat and chest	M	267 (19)	138 (20)	129 (19)
		F	54 (21)	23 (18)	31 (23)
	Abnormalities of breathing	M	122 (9)	56 (8)	66 (10)
		F	25 (10)	13 (10)	12 (9)
	Abdominal and pelvic pain	M	98 (7)	56 (8)	42 (6)
		F	25 (10)	14 (11)	11 (8)
	Malaise and fatigue	M	72 (5)	46 (7)	26 (4)
		F	22 (8)	10 (8)	12 (9)
	Dizziness and giddiness	M	56 (4)	27 (4)	29 (4)
		F	24 (9)	13 (10)	11 (8)

Table 37: LIPS Most Common AEs by Gender

		All	Fluvastatin	Placebo
Other symptoms & signs involving the digestive system & abdomen	M	55 (4)	27 (4)	28 (4)
	F	19 (7)	14 (11)	5 (4)
Edema, NEC	M	40 (3)	27 (4)	13 (2)
	F	23 (9)	10 (8)	13 (10)
Abnormalities of heart beat	M	48 (3)	24 (3)	24 (3)
	F	13 (5)	9 (7)	4 (3)
Headache	M	34 (2)	17 (2)	17 (2)
	F	16 (6)	6 (5)	10 (8)
Nausea and vomiting	M	34 (2)	17 (2)	17 (2)
	F	15 (6)	10 (8)	5 (4)
Other ill-defined and unspecified causes of mortality	M	36 (3)	12 (2)	24 (3)
	F	8 (3)	4 (3)	4 (3)
Syncope and collapse	M	36 (3)	17 (2)	19 (3)
	F	7 (3)	5 (4)	2 (2)
Abnormal serum enzyme levels	M	37 (3)	21 (3)	16 (2)
	F	5 (2)	4 (3)	1 (1)

The AEs of particular interest to this study, including myalgia, myopathy and other muscle AEs, were also evaluated by gender. There were no notable differences between males and females for muscle complaints. Muscle complaints by gender, by treatment group are summarized in the following table

Table 38: LIPS Myalgia, Myopathy, and Other Muscle AEs by Gender

Safety Population, n =			All M = 1392 F = 259	Fluvastatin M = 696 F = 127	Placebo M = 686 F = 132
Body System	**Preferred Term**	**M/F**			
Diseases of the musculoskeletal system & connective tissue	Other disorders of muscle	M	7 (1)	5 (1)	2 (<1)
		F	3 (1)	1 (1)	2 (2)
	Other soft tissue disorders, NEC	M	85 (6)	50 (7)	35 (4)
		F	22 (8)	10 (8)	12 (9)
Diseases of the nervous system	Other myopathies	M	2 (<1)	1 (<1)	1 (<1)
		F	0	0	0

(b) Adverse Events Resulting in Discontinuation

Female patients were somewhat more likely than males to discontinue study drug for an AE, with 24% of females overall and 22% of males overall discontinuing study drug due to an AE. Similar to the study drug discontinuations due to an AE results overall, females in the placebo group (30%) were more likely to discontinue study drug than females in the fluvastatin group (24%), and males in the placebo group (24%) were more likely to discontinue study drug than males in the fluvastatin group (21%). Discontinuations for AEs by gender are summarized in the following table

Table 39: LIPS Discontinuations for AEs by Gender

	All	Treatment	
		Fluvastatin	Placebo
Safety Population, n =	1640	823	818
Safety Population, Male, n =	1392	696	686
Safety Population, Female, n =	259	127	132
Patients dc'ing for any AE, All, n (%)	376 (23)	174 (21)	202 (25)
Males dc'ing for any AE, n (%)	307 (22)	144 (21)	163 (24)
Females dc'ing for any AE, n (%)	69 (24)	30 (24)	39 (30)

The most commonly reported AEs (occurring in ≥1% of patients overall) resulting in drug discontinuation were evaluated by gender. Angina pectoris was the most commonly reported AE resulting in discontinuation in males and females, and was more common in females (6% overall) than in males (3%), most likely due to the higher prevalence of angina in females than males at Baseline. There were no other notable differences by gender. The most common discontinuations for AE by gender, by treatment group, are summarized in the following table

Table 40: LIPS Most Common Discontinuations for AEs by Gender

				Treatment	
Safety Population, n =			**All** M = 1392 F = 259	**Fluvastatin** M = 696 F = 127	**Placebo** M = 686 F = 132
Body System	**Preferred Term**	**M/F**			
Certain infectious and parasitic diseases	Diarrhea and gastroenteritis of presumed infectious origin	M	8 (1)	3 (<1)	5 (1)
		F	2 (1)	1 (1)	1 (1)
Diseases of the circulatory system	Angina pectoris	M	44 (3)	20 (3)	24 (3)
		F	15 (6)	7 (6)	8 (6)
	Chronic ischemic heart disease	M	12 (1)	3 (<1)	9 (1)
		F	1 (<1)	1 (1)	0
	Acute myocardial infarction	M	6 (<1)	4 (1)	2 (<1)
		F	3 (1)	0	3 (2)
Diseases of the digestive system	Gastritis and duodenitis	M	8 (1)	5 (1)	3 (<1)
		F	3 (1)	1 (1)	2 (2)
	Dyspepsia	M	2 (<1)	1 (<1)	1 (<1)
		F	2 (1)	2 (2)	0
	Other diseases of digestive system	M	3 (<1)	1 (<1)	2 (<1)
		F	2 (1)	1 (1)	1 (1)
Diseases of the musculoskeletal system & connective tissue	Other soft tissue disorders, NEC	M	7 (1)	4 (1)	3 (<1)
		F	3 (1)	2 (2)	1 (1)
Endocrine, nutritional & metabolic diseases	Disorders of lipoprotein metabolism and other lipidemias	M	26 (2)	2 (<1)	24 (3)
		F	4 (2)	0	4 (3)
Symptoms, signs & abnormal clinical & laboratory findings, NEC	Other symptoms and signs involving the digestive system and abdomen	M	20 (1)	11 (2)	9 (1)
		F	5 (2)	4 (3)	1 (1)
	Pain in throat and chest	M	22 (2)	7 (1)	15 (2)
		F	3 (1)	2 (2)	1 (1)
	Abdominal and pelvic pain	M	13 (1)	8 (1)	5 (1)
		F	4 (2)	2 (2)	2 (2)
	Abnormal serum enzyme levels	M	16 (1)	11 (2)	5 (1)
		F	1 (<1)	1 (1)	0
	Other ill-defined and unspecified causes of mortality	M	12 (1)	5 (1)	7 (1)
		F	4 (2)	2 (2)	2 (2)
	Malaise and fatigue	M	8 (1)	6 (1)	2 (<1)
		F	3 (1)	2 (2)	1 (1)
	Nausea and vomiting	M	6 (<1)	5 (1)	1 (<1)
		F	2 (1)	1 (1)	1 (1)
	Abnormalities of breathing	M	6 (<1)	1 (<1)	5 (1)
		F	2 (1)	1 (1)	1 (1)

Discontinuations for muscle complaints were also evaluated by gender. There were no notable differences between males and females for muscle complaints. The results are summarized in the following table

Table 41: LIPS Discontinuations for Myalgia, Myopathy, and Other Muscle AEs by Gender

Safety Population, n =		All M = 1392 F = 259	Fluvastatin M = 696 F = 127	Placebo M = 686 F = 132
Preferred Term	**M/F**			
Other disorders of muscle*	M	2 (<1)	2 (<1)	0
	F	0	0	0
Other soft tissue disorders, NEC**	M	11 (1)	7 (1)	4 (1)
	F	3 (1)	2 (2)	1 (1)

* Includes verbatim terms of muscle stiffness and muscular deficiency
** Includes verbatim terms of muscle pain, muscle aching, myalgia, and others

(c) Serious Adverse Events

Females were more likely than males to report any SAE, with any SAE reported by 55% of females overall and by 46% of males overall. As with the SAE results overall, SAEs were reported more commonly in the placebo group than in the fluvastatin group for both males and females. Patients reporting any SAE, by gender, by treatment group are summarized in the following table

Table 42: LIPS Patients Experiencing Any SAE by Gender

	All	Treatment	
		Fluvastatin	Placebo
Safety Population, n =	1640	823	818
Safety Population, Male, n =	1392	696	686
Safety Population, Female, n =	259	127	132
Patients experiencing any SAE, All, n (%)	788 (48)	372 (45)	416 (51)
Males experiencing any SAE, n (%)	646 (46)	306 (44)	340 (50)
Females experiencing any SAE, n (%)	142 (55)	66 (52)	76 (58)

The most commonly reported SAEs (occurring in ≥1% of patients overall) were evaluated by gender. Angina pectoris was the most commonly reported SAE in males and females, and was more common in females (27% overall) than in males (18%), most likely due to the higher prevalence of angina in females than males at Baseline. Acute MI was also somewhat more common in females (6% overall) than males (4%). As with the overall SAE results, both angina pectoris and acute MI were more common in the placebo group than in the fluvastatin group for both male and female patients. There were no other notable differences by gender. The most common SAEs by gender, by treatment group, are summarized in the following table

Table 43: LIPS Most Common SAEs by Gender

Safety Population, n =			All M = 1392 F = 259	Treatment Fluvastatin M = 696 F = 127	Placebo M = 686 F = 132
Body System	**Preferred Term**	**M/F**			
Diseases of the circulatory system	Angina pectoris	M	253 (18)	117 (17)	136 (20)
		F	70 (27)	32 (25)	38 (29)
	Acute myocardial infarction	M	54 (4)	22 (3)	32 (5)
		F	16 (6)	7 (6)	9 (7)

Table 43: LIPS Most Common SAEs by Gender

			Treatment		
			All	Fluvastatin	Placebo
	Chronic ischemic heart disease	M	58 (4)	22 (3)	36 (5)
		F	12 (5)	5 (4)	7 (5)
	Other peripheral vascular diseases	M	16 (1)	7 (1)	9 (1)
		F	1 (<1)	1 (1)	0
	Heart failure	M	9 (1)	4 (1)	5 (1)
		F	6 (2)	2 (2)	4 (3)
	Atrial fibrillation and flutter	M	13 (1)	9 (1)	4 (1)
		F	2 (1)	0	2 (2)
	Stroke, not specified as hemorrhage or infarction	M	10 (1)	4 (1)	6 (1)
		F	4 (1)	1 (1)	3 (2)
	Cardiac arrest	M	8 (1)	4 (1)	4 (1)
		F	2 (1)	0	2 (2)
	Other cardiac arrhythmias	M	5 (<1)	0	5 (1)
		F	1 (<1)	0	1 (1)
Diseases of the digestive system	Other diseases of digestive system	M	11 (1)	4 (1)	7 (1)
		F	3 (1)	2 (2)	1 (1)
	Inguinal hernia	M	9 (1)	2 (<1)	7 (1)
		F	2 (1)	0	2 (2)
Diseases of the genitourinary system	Hyperplasia of prostate	M	10 (1)	2 (<1)	8 (1)
Diseases of the nervous system	Transient cerebral ischemic attacks and related syndromes	M	10 (1)	8 (1)	2 (<1)
		F	0	0	0
Diseases of the respiratory system	Pneumonia, organism unspecified	M	15 (1)	7 (1)	8 (1)
		F	7 (3)	3 (2)	4 (3)
Factors influencing health status & contact with health services	Adjustment and management of implanted device	M	7 (1)	1 (<1)	6 (1)
		F	0	0	0
Neoplasms	Malignant neoplasm of prostate	M	11 (1)	9 (1)	2 (<1)
	Malignant neoplasm of bronchus and lung	M	6 (<1)	5 (1)	1 (<1)
		F	2 (1)	1 (1)	1 (1)
	Malignant neoplasm of colon	M	5 (<1)	2 (<1)	3 (<1)
		F	2 (1)	0	2 (2)
	Malignant neoplasm of larynx	M	5 (<1)	0	5 (1)
		F	0	0	0
Surgical procedures	Surgery - Cardiac - TCT	M	48 (3)	22 (3)	26 (4)
		F	5 (2)	1 (1)	4 (3)
	Surgery - Cardiac - other cardiac procedures	M	30 (2)	14 (2)	16 (2)
		F	1 (<1)	0	1 (1)
	Surgery - Cardiac - CABG	M	18 (1)	7 (1)	11 (2)
		F	3 (1)	0	3 (2)
	Surgery - Digestive system	M	6 (<1)	3 (<1)	3 (<1)
		F	3 (1)	1 (1)	2
	Surgery - Genitourinary system	M	7 (1)	4 (1)	3 (<1)
		F	1 (<1)	1 (1)	0
Symptoms, signs & abnormal clinical & laboratory findings, NEC	Pain in throat and chest	M	119 (9)	63 (9)	56 (8)
		F	22 (8)	7 (6)	15 (11)
	Other ill-defined and unspecified causes of mortality	M	35 (3)	12 (2)	23 (3)
		F	8 (3)	4 (3)	4 (3)

Table 43: LIPS Most Common SAEs by Gender

		All	Treatment	
			Fluvastatin	Placebo
Syncope and collapse	M	21 (2)	11 (2)	10 (1)
	F	2 (1)	1 (1)	1 (1)
Abnormalities of breathing	M	20 (1)	9 (1)	11 (2)
	F	2 (1)	1 (1)	1 (1)
Abdominal and pelvic pain	M	14 (1)	7 (1)	7 (1)
	F	7 (3)	3 (2)	4 (3)
Abnormalities of heart beat	M	9 (1)	4 (1)	5 (1)
	F	2 (1)	2 (2)	0
Malaise and fatigue	M	9 (1)	6 (1)	3 (<1)
	F	1 (<1)	1 (1)	0
Other sudden death, cause unknown	M	7 (1)	4 (1)	3 (<1)
	F	1 (<1)	1 (1)	0
Nausea and vomiting	M	4 (<1)	4 (1)	0
	F	2 (1)	1 (1)	1 (1)

(2) By Age

Patients were evaluated by age: ≥65 years [Geriatric (G)] vs <65 years of age [Non-Geriatric (NG)].

(a) Adverse Events

Geriatric patients were somewhat more likely than non-geriatric patients to report any AE, with any AE reported by 82% of geriatric patients overall and by 77% of non-geriatric patients overall. Patients reporting any AE, by age, are summarized in the following table

Table 44: LIPS Patients Experiencing Any AE by Age

	All	Treatment	
		Fluvastatin	Placebo
Safety Population, n =	1640	823	818
Safety Population, Non-Geriatric (NG), n =	1054 (64)	520 (63)	534 (65)
Safety Population, Geriatric (G), n =	623 (38)	324 (39)	299 (37)
Patients experiencing any AE, All, n (%)	1329 (81)	661 (80)	668 (82)
NG experiencing any AE, n (%)	816 (77)	402 (77)	414 (78)
G experiencing any AE, n (%)	513 (82)	259 (80)	254 (85)

The most commonly reported AEs (occurring in ≥3% of patients overall) were evaluated by age. Angina pectoris was the most common AE overall, and was about as common in geriatric and non-geriatric patients. There were small imbalances between geriatric and non-geriatric patients for some AEs; however, as the numbers of patients with these AEs (by subgroup) was small, no conclusions will be drawn from these results. The most common AEs by Age are summarized in the following table

Table 45: LIPS Most Common AEs by Age

Safety Population, n =			All NG = 1054 G = 623	Fluvastatin NG = 520 G = 324	Placebo NG = 534 G = 299
Body System	**Preferred Term**	**NG/G**			
Certain infectious & parasitic diseases	Diarrhea and gastroenteritis of presumed infectious origin	NG	18 (2)	9 (2)	9 (2)
		G	14 (2)	2 (1)	12 (4)
Diseases of the circulatory system	Angina pectoris	NG	240 (23)	114 (22)	126 (24)
		G	135 (22)	59 (18)	76 (25)
	Chronic ischemic heart disease	NG	44 (4)	18 (3)	26 (5)
		G	29 (5)	12 (4)	17 (6)
	Essential (primary) hypertension	NG	39 (4)	20 (4)	19 (4)
		G	17 (3)	9 (3)	8 (3)
	Acute myocardial infarction	NG	27 (3)	12 (2)	15 (3)
		G	21 (3)	6 (2)	15 (5)
	Other peripheral vascular diseases	NG	15 (1)	9 (2)	6 (1)
		G	21 (3)	13 (4)	8 (3)
	Atrial fibrillation and flutter	NG	13 (1)	10 (2)	3 (1)
		G	10 (2)	4 (1)	6 (2)
Diseases of the digestive system	Other functional intestinal disorders	NG	13 (1)	7 (1)	6 (1)
		G	20 (3)	12 (4)	8 (3)
	Gastritis and duodenitis	NG	25 (2)	12 (2)	13 (2)
		G	13 (2)	6 (2)	7 (2)
Diseases of the musculoskeletal system & connective tissue	Other soft tissue disorders, NEC	NG	53 (5)	30 (6)	23 (4)
		G	32 (5)	16 (5)	16 (5)
	Dorsalgia	NG	30 (4)	15 (3)	15 (3)
		G	23 (4)	6 (2)	17 (6)
	Other joint disorders, NEC	NG	15 (1)	7 (1)	8 (1)
		G	15 (2)	11 (3)	4 (1)
Diseases of the respiratory system	Acute nasopharyngitis [common cold]	NG	22 (2)	15 (3)	7 (1)
		G	15 (2)	6 (2)	9 (3)
	Pneumonia, organism unspecified	NG	19 (2)	9 (2)	10 (2)
		G	13 (2)	8 (2)	5 (2)
Endocrine, nutritional & metabolic diseases	Disorders of lipoprotein metabolism & other lipidemias	NG	31 (3)	3 (1)	28 (5)
		G	8 (1)	1 (<1)	7 (2)
Surgical procedures	Surgery - Cardiac - TCT	NG	22 (2)	10 (2)	12 (2)
		G	13 (2)	3 (1)	10 (3)
	Surgery - Cardiac - other cardiac procedures	NG	20 (2)	10 (2)	10 (2)
		G	6 (1)	1 (<1)	5 (2)
Symptoms, signs & abnormal clinical & laboratory findings, NEC	Pain in throat and chest	NG	177 (17)	87 (17)	90 (17)
		G	89 (14)	42 (13)	47 (16)
	Abnormalities of breathing	NG	45 (4)	20 (4)	25 (5)
		G	56 (9)	27 (8)	29 (10)
	Abdominal and pelvic pain	NG	54 (5)	38 (7)	16 (3)
		G	30 (5)	14 (4)	16 (5)
	Malaise and fatigue	NG	36 (3)	18 (3)	18 (3)
		G	27 (4)	19 (6)	8 (3)
	Dizziness and giddiness	NG	25 (2)	9 (2)	16 (3)
		G	26 (4)	15 (5)	11 (4)
	Other symptoms & signs involving the digestive system & abdomen	NG	34 (3)	20 (4)	14 (3)
		G	20 (3)	9 (3)	11 (4)

Table 45: LIPS Most Common AEs by Age

		All	Fluvastatin	Placebo
Edema, NEC	NG	20 (2)	11 (2)	9 (2)
	G	23 (4)	16 (5)	7 (2)
Abnormalities of heart beat	NG	21 (2)	11 (2)	10 (2)
	G	16 (3)	8 (2)	8 (3)
Headache	NG	15 (1)	6 (1)	9 (2)
	G	12 (2)	6 (2)	6 (2)
Nausea and vomiting	NG	15 (1)	7 (1)	8 (1)
	G	19 (3)	15 (5)	4 (1)
Other ill-defined and unspecified causes of mortality	NG	5 (<1)	2 (<1)	3 (1)
	G	19 (3)	9 (3)	10 (3)
Syncope and collapse	NG	9 (1)	4 (1)	5 (1)
	G	14 (2)	8 (2)	6 (2)
Abnormal serum enzyme levels	NG	23 (2)	14 (3)	9 (2)
	G	7 (1)	5 (2)	2 (1)

(b) Adverse Events Resulting in Discontinuation

Geriatric patients were somewhat more likely than non-geriatric patients to discontinue study drug for an AE, with 26% of geriatric patients overall and 21% of non-geriatric patients overall discontinuing study drug. As was seen with the discontinuations due to an AE results overall, geriatric patients in the placebo group (27%) were more likely to discontinue study drug than geriatric patients in the fluvastatin group (24%), and non-geriatric patients in the placebo group (23%) were more likely to discontinue study drug than non-geriatric patients in the fluvastatin group (18%). Discontinuations for AEs by age are summarized in the following table

Table 46: LIPS Discontinuations for AEs by Age

		Treatment	
	All	Fluvastatin	Placebo
Safety Population, n =	1640	823	818
Safety Population, NG, n =	1054 (64)	520 (63)	534 (65)
Safety Population, G, n =	623 (38)	324 (39)	299 (37)
Patients dc'ing for any AE, All, n (%)	376 (23)	174 (21)	202 (25)
NG dc'ing for any AE, n (%)	217 (21)	96 (18)	121 (23)
G dc'ing for any AE, n (%)	159 (26)	78 (24)	81 (27)

The most commonly reported AEs (occurring in ≥1% of patients overall) resulting in drug discontinuation were evaluated by age. As previously mentioned, angina pectoris was the most commonly reported AE resulting in discontinuation, and was about as common in geriatric and non-geriatric patients. There were no notable differences in the incidence rates of discontinuations for AEs between geriatric and non-geriatric patients. The most common discontinuation for AEs by age, by treatment group, are summarized in the following table

Table 47: LIPS Most Common Discontinuations for AEs by Age

Safety Population, n =			Treatment		
			All	Fluvastatin	Placebo
			NG = 1054 G = 623	NG = 520 G = 324	NG = 534 G = 299
Body System	**Preferred Term**	**NG/G**			
Certain infectious and parasitic diseases	Diarrhea and gastroenteritis of presumed infectious origin	NG	6 (1)	3 (1)	3 (1)
		G	4 (1)	1 (<1)	3 (1)
Diseases of the circulatory system	Angina pectoris	NG	33 (3)	13 (3)	20 (4)
		G	26 (4)	14 (4)	12 (4)
	Chronic ischemic heart disease	NG	10 (1)	4 (1)	6 (1)
		G	3 (<1)	0	3 (1)
	Acute myocardial infarction	NG	6 (1)	2 (<1)	4 (1)
		G	3 (<1)	2 (1)	1 (<1)
Diseases of the digestive system	Gastritis and duodenitis	NG	6 (1)	2 (<1)	4 (1)
		G	5 (1)	4 (1)	1 (<1)
	Dyspepsia	NG	2 (<1)	2 (<1)	0
		G	2 (<1)	1 (<1)	1 (<1)
	Other diseases of digestive system	NG	1 (<1)	0	1 (<1)
		G	4 (1)	2 (1)	2 (1)
Diseases of the musculoskeletal system & connective tissue	Other soft tissue disorders, NEC	NG	6 (1)	4 (1)	2 (<1)
		G	4 (1)	2 (1)	2 (1)
Endocrine, nutritional & metabolic diseases	Disorders of lipoprotein metabolism and other lipidemias	NG	23 (2)	1 (<1)	22 (4)
		G	7 (1)	1 (<1)	6 (2)
Symptoms, signs & abnormal clinical & laboratory findings, NEC	Other symptoms and signs involving the digestive system and abdomen	NG	17 (2)	10 (2)	7 (1)
		G	8 (1)	5 (2)	3 (1)
	Pain in throat and chest	NG	16 (2)	5 (1)	11 (2)
		G	9 (1)	4 (1)	5 (2)
	Abdominal and pelvic pain	NG	9 (1)	5 (1)	4 (1)
		G	8 (1)	5 (2)	3 (1)
	Abnormal serum enzyme levels	NG	14 (1)	11 (2)	3 (1)
		G	3 (<1)	1 (<1)	2 (1)
	Other ill-defined and unspecified causes of mortality	NG	3 (<1)	1 (<1)	2 (<1)
		G	13 (2)	6 (2)	7 (2)
	Malaise and fatigue	NG	4 (<1)	2 (<1)	2 (<1)
		G	7 (1)	6 (2)	1 (<1)
	Nausea and vomiting	NG	3 (<1)	2 (<1)	1 (<1)
		G	5 (1)	4 (1)	1 (<1)
	Abnormalities of breathing	NG	2 (<1)	1 (<1)	1 (<1)
		G	6 (1)	1 (<1)	5 (2)

(c) Serious Adverse Events

Geriatric patients were more likely than non-geriatric patients to report any SAE, with any SAE reported by 52% of geriatric patients overall and by 44% of non-geriatric patients overall. As with the SAE results overall, patients in the placebo group were more likely than patients in the fluvastatin group to report any SAE for both geriatric and non-geriatric patients. Patients reporting any SAE by age, by treatment group, are summarized in the following table

Table 48: LIPS Patients Experiencing Any SAE by Age

	All	Treatment	
		Fluvastatin	Placebo
Safety Population, n =	1640	823	818
Safety Population, NG, n =	1054 (64)	520 (63)	534 (65)
Safety Population, G, n =	623 (38)	324 (39)	299 (37)
Patients experiencing any SAE, All, n (%)	788 (48)	372 (45)	416 (51)
NG experiencing any SAE, n (%)	461 (44)	223 (43)	238 (45)
G experiencing any SAE, n (%)	327 (52)	149 (46)	178 (60)

The most commonly reported SAEs (occurring in ≥1% of patients overall) were evaluated by age. Angina pectoris was the most commonly reported SAE in geriatric and non-geriatric patients, and was about as common in both subgroups. There were no notable differences between geriatric and non-geriatric patients in SAEs reported during the study. The most common SAEs by age, by treatment group, are summarized in the following table

Table 49: LIPS Most Common SAEs by Age

Safety Population, n =			**All** NG = 1054 G = 623	**Treatment** Fluvastatin NG = 520 G =324	Placebo NG = 534 G = 299
Body System	**Preferred Term**	**NG/G**			
Diseases of the circulatory system	Angina pectoris	NG	197 (19)	93 (18)	104 (19)
		G	126 (20)	56 (17)	70 (23)
	Acute myocardial infarction	NG	40 (4)	18 (3)	22 (4)
		G	30 (5)	11 (3)	19 (6)
	Chronic ischemic heart disease	NG	38 (4)	14 (3)	24 (4)
		G	32 (5)	13 (4)	19 (6)
	Other peripheral vascular diseases	NG	7 (1)	2 (<1)	5 (1)
		G	10 (2)	6 (2)	4 (1)
	Heart failure	NG	3 (<1)	2 (<1)	1 (<1)
		G	12 (2)	4 (1)	8 (3)
	Atrial fibrillation and flutter	NG	8 (1)	7 (1)	1 (<1)
		G	7 (1)	2 (1)	5 (2)
	Stroke, not specified as hemorrhage or infarction	NG	5 (<1)	3 (1)	2 (<1)
		G	9 (1)	2 (1)	7 (2)
	Cardiac arrest	NG	6 (1)	3 (1)	3 (1)
		G	4 (1)	1 (<1)	3 (1)
	Other cardiac arrhythmias	NG	2 (<1)	0	2 (<1)
		G	4 (1)	0	4 (1)
Diseases of the digestive system	Other diseases of digestive system	NG	7 (1)	3 (1)	4 (1)
		G	7 (1)	3 (1)	4 (1)
	Inguinal hernia	NG	5 (<1)	2 (<1)	3 (1)
		G	6 (1)	0	6 (2)
Diseases of the genitourinary system	Hyperplasia of prostate	NG	4 (<1)	0	4 (1)
		G	6 (1)	2 (1)	4 (1)
Diseases of the nervous system	Transient cerebral ischemic attacks and related syndromes	NG	5 (<1)	5 (1)	0
		G	5 (1)	3 (1)	2 (1)
Diseases of the respiratory system	Pneumonia, organism unspecified	NG	12 (1)	5 (1)	7 (1)
		G	10 (2)	5 (2)	5 (2)

Table 49: LIPS Most Common SAEs by Age

			Treatment		
			All	**Fluvastatin**	**Placebo**
Factors influencing health status and contact with health services	Adjustment and management of implanted device	NG	4 (<1)	1 (<1)	3 (1)
		G	3 (<1)	0	3 (1)
Neoplasms	Malignant neoplasm of prostate	NG	3 (<1)	2 (<1)	1 (<1)
		G	8 (1)	7 (2)	1 (<1)
	Malignant neoplasm of bronchus & lung	NG	3 (<1)	2 (<1)	1 (<1)
		G	5 (1)	4 (1)	1 (<1)
	Malignant neoplasm of colon	NG	1 (<1)	1 (<1)	0
		G	6 (1)	1 (1)	5 (2)
	Malignant neoplasm of larynx	NG	2 (<1)	0	2 (<1)
		G	3 (<1)	0	3 (1)
Surgical procedures	Surgery - Cardiac - TCT	NG	34 (3)	18 (3)	16 (3)
		G	19 (3)	5 (2)	14 (5)
	Surgery - Cardiac - other cardiac procedures	NG	20 (2)	9 (2)	11 (2)
		G	11 (2)	5 (2)	6 (2)
	Surgery - Cardiac - CABG	NG	11 (1)	5 (1)	6 (1)
		G	10 (2)	2 (1)	8 (3)
	Surgery - Digestive system	NG	6 (1)	4 (1)	2 (<1)
		G	3 (<1)	0	3 (1)
	Surgery - Genitourinary system	NG	3 (<1)	3 (1)	0
		G	5 (1)	2 (1)	3 (1)
Symptoms, signs & abnormal clinical & laboratory findings, NEC	Pain in throat and chest	NG	88 (8)	44 (8)	44 (8)
		G	53 (9)	26 (8)	27 (9)
	Other ill-defined and unspecified causes of mortality	NG	13 (1)	5 (1)	8 (1)
		G	30 (5)	11 (3)	19 (6)
	Syncope and collapse	NG	7 (1)	4 (1)	3 (1)
		G	16 (3)	8 (2)	8 (3)
	Abnormalities of breathing	NG	5 (<1)	2 (<1)	3 (1)
		G	17 (3)	8 (2)	9 (3)
	Abdominal and pelvic pain	NG	12 (1)	7 (1)	5 (1)
		G	9 (1)	3 (1)	6 (2)
	Abnormalities of heart beat	NG	3 (<1)	1 (<1)	2 (<1)
		G	8 (1)	5 (2)	3 (1)
	Malaise and fatigue	NG	4 (<1)	3 (1)	1 (<1)
		G	5 (1)	3 (1)	2 (1)
	Other sudden death, cause unknown	NG	4 (<1)	2 (<1)	2 (<1)
		G	4 (1)	3 (1)	1 (<1)
	Nausea and vomiting	NG	2 (<1)	2 (<1)	0
		G	4 (1)	3 (1)	1 (<1)

h) Laboratory Abnormalities

Laboratory results of particular interest to this study were changes in AST, ALT and CK values from Baseline. Liver enzyme (AST and ALT) elevations were included (by the sponsor) under the AE Preferred Term of "serum enzyme elevations" (which included the verbatim terms of: elevated liver enzymes, increased liver enzymes; ALAT-ASAT too high, rise in ASAT/ALAT, elevated transaminases, and others). There were 31 reports of liver enzyme elevations: 17 in the fluvastatin group and 14 in the placebo group. Also

included under the preferred term of "serum enzyme elevations" were CK increases (including the verbatim terms of elev. CK, CPK elevated, CK-MB elevated, and others), which were reported in 8 patients: 6 patients in the fluvastatin group and 2 patients in the placebo group. In addition, 3 patients were noted to have elevations in alkaline phosphatase (alk phos) or GGT, or both: 2 patients in the fluvastatin group and 1 patients in the placebo group.

The sponsor's results are summarized as follows:

Notable elevations in AST and ALT were defined as elevations >3 X ULN on 2 consecutive occasions. Notable elevations in CK were defined as elevations ≥10 X ULN on any occasion. There were no significant differences between the 2 groups in rates of CK, AST, or ALT elevations. Minor elevations in CK (≥2 to <5 X ULN) and in AST and ALT (≥2 to ≤3 X ULN) were more common in the fluvastatin group, but notable elevations in CK (≥10 X ULN) were similar between the two groups. Notable elevations in ALT and AST (≥3 X ULN on 2 consecutive occasions) were somewhat more common in the fluvastatin group, but the number of patients reported were small. The sponsor's results for elevations in AST, ALT, and CK are summarized in the following table

Table 50: LIPS AST, ALT, and CK Elevations (Sponsor's Results)

	Fluvastatin	Placebo
n =	822	818
Laboratory Parameter	n (%)	n (%)
CK		
≥2 to <5 X ULN	42 (5)	20 (2)
≥5 to <10 X ULN	4 (1)	2 (<1)
Notable (≥10 X ULN)	0	3 (<1)
AST		
≥2 to ≤3 X ULN	16 (2)	8 (1)
>3 X ULN (1 occasion)	5 (1)	5 (1)
Notable*	4 (1)	1 (<1)
ALT		
≥2 to ≤3 X ULN	28 (3)	24 (3)
>3 X ULN (1 occasion)	16 (2)	11 (1)
Notable*	10 (1)	2 (<1)

* >3 X ULN on 2 consecutive occasions

This Reviewer's findings are summarized as follows (summarized from the CHEM dataset):

For ALT: 41 patients had at least 1 elevation in ALT ≥3 X ULN at anytime during the study (not including Visit 1): 27 patients in the fluvastatin group and 14 in the placebo group. Of these patients, 22 met the pre-specified definition of notable elevation, defined as an elevation >3 X ULN on 2 consecutive occasions (or 1 elevation with no available follow-up): 16 patients in the fluvastatin group and 6 patients in the placebo group. [Patients with notable ALT elevations during the study are summarized in the Appendix.]

For AST: 16 patients had at least 1 elevation in AST >3 X ULN at anytime during the study (not including Baseline Visit): 9 patients in the fluvastatin group and 7 patients in the placebo group. Of these, 9 patients met the definition of notable elevation: 6 in the fluvastatin group and 3 in the placebo group. [Patients with notable AST elevations during the study are summarized in the Appendix.]

For CK: There were 3 patients with a notable CK elevation, defined as >10 X ULN on at least one occasion (not including Baseline visit), all 3 of whom were in the placebo group. [Patients with notable CK elevations during the study are summarized in the Appendix.]

This Reviewer's findings were not notably different from the sponsor's findings, and will not be discussed on further.

i) Other Safety Assessments

There were no other noteworthy changes in any other laboratory parameters during the study. Vital signs showed small numbers of notable changes overall, which were similar in both treatment groups [notable criteria for vital sign changes defined in the following table]. The most frequently reported vital sign abnormality was high systolic blood pressure. Patients with notable vital sign abnormalities are summarized (by the sponsor) in the following table

Table 51: LIPS Changes in Vital Signs

			Treatment	
		All	Fluvastatin	Placebo
Safety Population, n =		1640	822	818
Parameter	Notable Criteria	n (%)	n (%)	n (%)
SBP (mmHg)	Total	161 (10)	88 (11)	73 (9)
	High (>200 or ≥180 + ≥40 increase)	145 (9)	78 (10)	67 (8)
	Low (<75 or ≤90 + ≥30 decrease)	17 (1)	10 (1)	7 (1)
	Missing	53 (3)	24 (3)	29 (4)
DBP (mmHg)	Total	72 (4)	40 (5)	32 (4)
	High (>115 or ≥105 + ≥30 increase)	47 (3)	28 (3)	19 (2)
	Low (<40 or ≤50 + ≥20 decrease)	25 (2)	12 (2)	13 (2)
	Missing	53 (3)	24 (3)	29 (4)
Heart Rate (BPM)	Total	72 (4)	30 (4)	42 (5)
	High (>130 or ≥120 + ≥30 change)	18 (1)	7 (1)	11 (1)
	Low (<40 or ≤50 + ≥30 change)	54 (3)	23 (3)	31 (4)
	Missing	53 (3)	24 (3)	29 (4)

There were no other clinically relevant changes in any other safety parameter reported, including physical exam and ECG changes.

j) Safety Conclusions

In general, the safety findings seen in this study were similar to the safety findings seen in previous clinical studies with Lescol. Adverse events were commonly reported in both treatment groups. Serious AEs reflected the underlying medical history of the patients enrolled in the study, that is, were predominantly in the cardiovascular system, and were somewhat more frequently reported in the placebo group. The most frequently reported AEs were: angina pectoris (by 26% of patients overall), pain in throat & chest (20%), abnormalities of breathing (9%), and abdominal and pelvic pain (8%). There were no reports of rhabdomyolysis, and myopathy occurred in 2 patients overall: one patient in each of the treatment groups. Accounting for all AE verbatim terms associated with any effect on the musculoskeletal system, 16% of patients in the fluvastatin group and 14% of patients in the placebo group had any musculoskeletal complaint during the study. CK increases >10 X the ULN occurred in 3 patients, all of whom were in the placebo group. There were 2 reports of hepatitis in the study, in 1 patient in each of the treatment groups. Notable AST and ALT increases (defined as AST or ALT >3 X ULN on 2 consecutive occasions) occurred infrequently (1% of patients overall), and were marginally more common in the fluvastatin group. Nine (9) patients had notable AST elevations: 6 patients in the fluvastatin group and 3 patients in the placebo group. Twenty-two (22) patients had notable ALT elevations: 16 patients in the fluvastatin group and 6 in the placebo group. Adverse Events resulting in drug discontinuation (including MACE) occurred in 23% of patients overall and were more common in the placebo group (25%) than in the fluvastatin group (21%). The most commonly reported reasons for discontinuation due to an AE were angina pectoris (5% of patients overall) and disorders of lipoprotein metabolism (3%). Angina pectoris was marginally more common in the placebo group (5%) than in the fluvastatin group (4%), and lipoprotein disorders were more common in the placebo group (5%) than in the fluvastatin group (1%). Serious Adverse Events (including MACE) occurred in 49% of patients overall: in 47% of patients in the fluvastatin group and in 52% of the placebo group. The most commonly reported SAEs were in the cardiovascular system. Angina pectoris was the most commonly reported SAE (20% of patients overall), and was somewhat more common in the placebo group (21%) than in the fluvastatin group (18%). The remaining SAEs occurred about as frequently in both treatment groups. Eighty-five (85) patients died during the study, 36 patients in the fluvastatin group and 49 patients in the placebo group. Cardiac deaths occurred in 37 patients: 13 in the fluvastatin group and 24 in the placebo group. Non-cardiac deaths were similar between the 2 treatment groups.

Adverse Events were also analyzed by subgroup by age and gender. There were too few non-Caucasian patients to evaluate by race. Females were more likely than males to report any AE; however, this was consistent across the treatment groups. For the most commonly reported AES, females were more likely than males to report angina pectoris, and were also more likely to discontinue study drug due to an AE and to experience an SAE (most commonly angina pectoris for both discontinuations and SAEs). This is most likely due to Baseline differences between male and female patients. Females had a mean age 4 years higher than males at Baseline, there was a higher percentage (49%) of

female patients age ≥65 years at Baseline than male patients (35%), and more females entered the study with angina pectoris (34%) than males (24%). For geriatric vs non-geriatric patients, geriatric patients were somewhat more likely than non-geriatric patients to experience any AE, to discontinue study medication due to an AE, and to experience an SAE; however, these differences were small.

In summary, fluvastatin was generally well-tolerated, and AEs reported during this study are consistent with AEs reported in previous clinical studies with fluvastatin. Adverse Events, SAEs, and discontinuations due to AEs tended to reflect the underlying patient population with AEs in the cardiovascular system being the most common. Patients in the placebo group were more likely than patients in the fluvastatin group to experience an SAE (including death), with the difference between the 2 treatment groups being due to the higher incidence of cardiovascular AEs in the placebo group.

Administrative Issues

B. Clinical Site Audits

No clinical site audits were conducted for this SNDA.

C. Financial Disclosure

Investigator financial information was submitted by the sponsor as referenced under 21 CFR Part 54, [21 CFR 54.2(d), Form 3454 Certification: Financial Interests and Arrangements of Clinical Investigators]. The sponsor stated that no principal investigators are full or part-time employees of Novartis Pharmaceuticals Corporation, and no disclosable financial information was reported by any of the investigators participating in LIPS who submitted financial disclosure forms. In Europe (LES EUR 01, or LIPS Study), 54% of investigators responded to (multiple) requests by Novartis for financial disclosure information (54/73 participating Principal Investigators) [a summary of Investigators' Form 3454 is in the submission: SNDA #20-261 033, Volume 1, section 19].

D. Other: Study Safety Updates

As the LIPS Study concluded in 31-Oct-2001 and the final study report has been completed, there are no further safety updates expected for this study.

III. Conclusions

Treatment of patients with fluvastatin after first successful PCI procedure, for a treatment period of 3 to 5 years, resulted in statistically significant relative risk reductions in the combined endpoint of major adverse cardiac events (MACE). There was a significant (p=.0127) difference in time to first MACE survival distributions between the 2 treatment groups, with a separation of the curves beginning at approximately 1.5 years. There was a significant 22% reduction in risk (RR 0.78) of experiencing a MACE in the fluvastatin group compared to the placebo group (p=.013). The risk ratios of the 3 individual components of MACE (cardiac death, non-fatal MI, and re-intervention) were all <1 (favoring fluvastatin); however, none of these individual results were statistically significant on their own. The fluvastatin group had a significantly lower incidence of the combined MACE compared to the placebo group, with an incidence of MACE of 21% in the fluvastatin group vs 27% in the placebo group (p=.006), the majority of which were re-interventions. There was a lower incidence of each of the individual clinical endpoints of MACE in the fluvastatin group compared to the placebo groups. In the fluvastatin and placebo groups, cardiac death occurred at incidences of 1.5% and 2.9%, respectively (p=.060), non-fatal MI at rates of 3.6% and 4.6% (p=.277), and re-interventions at rates of 19.8% and 23.2% (p= .052). When re-interventions occurring within the first 6 months were excluded from the combined MACE endpoint analysis [as treatment with a statin has not been shown to prevent early (non-atherosclerotic) re-stenosis], the results show greater significance of the combined MACE endpoint (p=.004) and an earlier separation of the fluvastatin and placebo groups, beginning at approximately 6 months. Further evaluation of late reinterventions alone [re-interventions excluding re-intervention (CABG or PCI) of the target lesion within 6 months of the initial procedure] showed that a significantly lower incidence of late re-interventions occurred in patients in the Lescol-treated group than in the placebo group [111 Lescol-treated patients experienced a late re-intervention compared to 151 placebo-treated patients; p=.0025]. Other secondary endpoints examined in the study, including time to worst MACE, noncardiac death, all death, cardiac death or non-fatal MI, and all death or MI, all had relative risk ratios <1 (for the fluvastatin group), although none of these endpoints achieved statistical significance.

In general, the safety findings seen in this study were similar to safety findings seen in previous clinical studies with Lescol. Adverse events were commonly reported in both treatment groups. Serious AEs reflected the underlying medical history of the patients enrolled in the study, that is, were predominantly in the cardiovascular system, and were somewhat more frequently reported in the placebo group. The most frequently reported AEs were: angina pectoris (by 26% of patients overall) and pain in throat & chest (20%). Serious Adverse Events (including MACE) occurred in 49% of patients overall: in 47% of patients in the fluvastatin group and in 52% of the placebo group. The most commonly reported SAEs were in the cardiovascular system. Angina pectoris was the most commonly reported SAE (20% of patients overall), and was somewhat more common in the placebo group (21%) than in the fluvastatin group (18%). Eighty-five (85) patients died during the study, 36 patients in the fluvastatin group and 49 patients in

the placebo group. Cardiac deaths occurred in 37 patients: 13 in the fluvastatin group and 24 in the placebo group. Non-cardiac deaths were similar between the 2 treatment groups.

Limitations of this clinical study included:

1. Protocol violations were common in the study, with 38% of patients overall having poor compliance to study medication (<80% of study medication taken during the study), and 23% of patients being treated with a statin other than study medication over the course of the study. Poor compliance and treatment with other statins were both more common in the placebo groups. The likely outcome of these violations would be an attenuation of the treatment effect of fluvastatin.
2. The primary endpoint for the study was a combined endpoint (time to first MACE) and none of the individual components of the MACE endpoint achieved statistical significance when considered individually. However, combination endpoints have been used in other secondary prevention trials, and the results seen in LIPS are consistent with results from previous secondary prevention trials. The significance of the MACE results were predominantly due to re-intervention procedures. As only late re-interventions (re-interventions occurring >6 months after the initial procedure in the target lesion, or re-interventions occurring in the non-target lesion) would be expected to show a decrease with Lescol treatment, late re-interventions were analyzed alone and found to show a significant decrease (p=.0025).

In summary, it can be concluded that treatment with fluvastatin was associated with a significant decrease in time to first major adverse cardiac event (MACE) and a risk reduction in MACE. However, on analysis of the individual components of MACE (cardiac death, nonfatal MI, and re-interventions), none of the individual components of MACE was significant on its own. Further evaluation of late reinterventions alone [re-interventions excluding re-intervention of the target lesion within 6 months of the initial procedure] showed that a significantly lower incidence of late re-interventions occurred in patients in the Lescol-treated group than in the placebo group. Fluvastatin was generally well-tolerated, and AEs reported during this study are consistent with AEs reported in previous clinical studies with fluvastatin. Adverse Events, SAEs, and discontinuations due to AEs tended to reflect the underlying patient population, with AEs in the cardiovascular system being the most common. Patients in the placebo group were more likely than patients in the fluvastatin group to experience an SAE (including death), with the difference between the 2 treatment groups being due to the higher incidence of cardiovascular AEs in the placebo group.

IV. Recommendations

It is the recommendation of this Reviewer that Lescol (and Lescol XL)

However, it is recommended that Lescol receive a new indication to reduce the risk coronary revascularization procedures

the proposed label as follows. The recommended changes to the label include:

1. [redacted]

2. In the Indications and Usage section, addition of Secondary Prevention of Coronary Events header, and the sentence: "In patients with coronary heart disease, Lescol and Lescol XL are indicated to reduce the risk [redacted] coronary revascularization procedures [redacted] In addition, the introductory sentence (after the Indications and Usage Section Heading) is to read: "Therapy with lipid-altering agents should be [redacted] used in addition to a diet restricted in saturated fat and cholesterol (see National Cholesterol Education Program [NCEP] Treatment Guidelines, below)."

3. In the Adverse Reactions section, Table 5, [redacted]

4. In the Clinical Studies section, addition of Reduction in the Risk of Recurrent Cardiac Events header and a description of the Lescol Intervention Prevention Study. Recommended changes to the proposed wording for this section are summarized in the proposed labeling in Appendix 1 (to follow).

25 Page(s) Withheld

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

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 20-214 S033

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VI. Appendix 2 – Additional Tables

A. Enrollment

Enrollment by Country and by Study Center is summarized in the following table

Table 52: LIPS Enrollment by Country and by Study Center

		Treatment	
	All	Fluvastatin	Placebo
Randomized Patients, n =	**1677**	**844**	**833**
Country/Study Center	n (%)	n (%)	n (%)
Belgium, All	**258 (15)**	**132 (16)**	**126 (15)**
	87 (5)	43 (5	44 (5)
	44 (3)	22 (3	22 (3)
	47 (3)	24 (3	23 (3)
	29 (2)	16 (2)	13 (2)
	17 (1)	9 (1)	8 (1)
	10 (1)	5 (1)	5 (1)
	24 (1)	13 (2)	11 (1)
Canada, All	**67 (4)**	**34 (4)**	**33 (4)**
	35 (2)	19 (2)	16 (2)
	10 (1)	5 (1)	5 (1)
	18 (1)	9 (1)	9 (1)
	4 (<1)	1 (<1)	3 (<1)
France, All	**134 (8)**	**71 (8)**	**63 (8)**
	12 (1)	7 (1)	5 (1)
	2 (<1)	0	2 (<1)
	1 (<1)	1 (<1)	0
	42 (3)	22 (3)	20 (2)
	9 (1)	4 (<1)	5 (1)
	9 (1)	7 (1)	2 (<1)
	40 (2)	22 (3)	18 (2)
	2 (<1)	1 (<1)	1 (<1)
	9 (1)	4 (<1)	5 (1)
	7 (<1)	3 (<1)	4 (<1)
	1 (<1)	0	1 (<1)
Germany, All	**88 (5)**	**46 (5)**	**42 (5)**
	24 (1)	11 (1)	13 (2)
	45 (3)	25 (3)	20 (2)
	19 (1)	10 (1)	9 (1)
Italy, All	**267 (16)**	**129 (15)**	**138 (17)**
	12 (1)	5 (1)	7 (1)
	35 (2)	17 (2)	18 (2)
	2 (<1)	2 (<1)	0
	30 (2)	15 (2)	15 (2)
	19 (1)	9 (1)	10 (1)
	18 (1)	9 (1)	9 (1)
	25 (1)	12 (1)	13 (2)
	41 (2)	20 (2)	21 (3)
	2 (<1)	0	2 (<1)
	29 (2)	13 (2)	16 (2)

Table 52: LIPS Enrollment by Country and by Study Center

		Treatment	
	All	**Fluvastatin**	**Placebo**
	2 (<1)	1 (<1)	1 (<1)
	14 (1)	7 (1)	7 (1)
	24 (1)	12 (1)	12 (1)
	14 (1)	7 (1)	7 (1)
Netherlands, All	**253 (15)**	**129 (15)**	**124 (15)**
	30 (2)	16 (2)	14 (2)
	20 (1)	12 (1)	8 (1)
	72 (4)	34 (4)	38 (5)
	33 (2)	17 (2)	16 (2)
	12 (1)	6 (1)	6 (1)
	46 (3)	24 (3)	22 (3)
	40 (2)	20 (2)	20 (2)
Spain, All	**489 (29)**	**243 (29)**	**246 (30)**
	120 (7)	60 (7)	60 (7)
	75 (4)	37 (4)	38 (5)
	54 (3)	26 (3)	28 (3)
	107 (6)	54 (6)	53 (6)
	41 (2)	21 (2)	20 (2)
	67 (4)	33 (4)	34 (4)
	25 (1)	12 (1)	13 (2)
Switzerland, All	**21 (1)**	**11 (1)**	**10 (1)**
	21 (1)	11 (1)	10 (1)
UK, All	**40 (2)**	**19 (2)**	**21 (3)**
	40 (2)	19 (2)	21 (3)
Brazil, All	**60 (4)**	**30 (4)**	**30 (4)**
	20 (1)	10 (1)	10 (1)
	40 (2)	20 (2)	20 (2)

B. Adverse Events

All AEs reported during the study are summarized in the following table

Table 53: LIPS All Adverse Events

			Treatment	
		All	Fluvastatin	Placebo
Safety Population, n =		1640	822	817
Body System	**AE Preferred Term**			
Infectious & Parasitic	Diarrhea & gastroenteritis of presumed infectious origin	47 (3)	21 (3)	26 (3)
	Zoster [herpes zoster]	17 (1)	8 (1)	9 (1)
	Other septicemia	3 (<1)	2 (<1)	1 (<1)
	Aspergillosis	2 (<1)	0	2 (<1)
	Erysipelas	2 (<1)	2 (<1)	0
	Bacterial infection of unspecified site	1 (<1)	0	1 (<1)
	Herpesviral [herpes simplex] infections	1	0	1 (<1)
	Other & unspecified infectious diseases	1 (<1)	0	1 (<1)
	Other bacterial intestinal infections	1 (<1)	1 (<1)	0
	Other rickettsioses	1 (<1)	0	1 (<1)
	Other salmonella infections	1 (<1)	0	1 (<1)
	Strongyloidiasis	1 (<1)	0	1 (<1)
	Unspecified malaria	1 (<1)	0	1 (<1)
	Viral agents as the cause of diseases classified to other chapters	1 (<1)	0	1 (<1)
	Viral infection of unspecified site	1 (<1)	0	1 (<1)
Blood, Blood-Forming Organs, & Immune Mechanism	Other anemias	12 (1)	6 (1)	6 (1)
	Iron deficiency anemia	4 (<1)	2 (<1)	2 (<1)
	Purpura & other hemorrhagic conditions	3 (<1)	1 (<1)	2 (<1)
	Other nutritional anemias	1 (<1)	0	1 (<1)
	Vitamin B12 deficiency anemia	1 (<1)	1 (<1)	0
Circulatory System	Angina pectoris	423 (26)	192 (23)	231 (28)
	Chronic ischemic heart disease	90 (5)	34 (4)	56 (7)
	Essential (primary) hypertension	82 (5)	44 (5)	38 (5)
	Acute myocardial infarction	72 (4)	30 (4)	42 (5)
	Other peripheral vascular diseases	46 (3)	25 (3)	21 (3)
	Atrial fibrillation & flutter	39 (2)	23 (3)	16 (2)
	Heart failure	21 (1)	8 (1)	13 (2)
	Hypotension	19 (1)	11 (1)	8 (1)
	Stroke, not specified as hemorrhage or infarction	19 (1)	6 (1)	13 (2)
	Other cardiac arrhythmias	16 (1)	5 (1)	11 (1)
	Phlebitis & thrombophlebitis	13 (1)	6 (1)	7 (1)
	Cardiac arrest	10 (1)	4 (<1)	6 (1)
	Hemorrhoids	9 (1)	4 (<1)	5 (1)
	Atrioventricular & left bundle-branch block	8 (<1)	4 (<1)	4 (<1)
	Aortic aneurysm & dissection	7 (<1)	2 (<1)	5 (1)
	Other disorders of arteries & arterioles	7 (<1)	3 (<1)	4 (<1)
	Other diseases of pericardium	6 (<1)	3 (<1)	3 (<1)
	Pulmonary embolism	6 (<1)	4 (<1)	2 (<1)
	Occlusion & stenosis of precerebral arteries,	5 (<1)	3 (<1)	2 (<1)

Table 53: LIPS All Adverse Events

			Treatment	
		All	Fluvastatin	Placebo
	not resulting in cerebral infarction			
	Paroxysmal tachycardia	5 (<1)	4 (<1)	1 (<1)
	Other aneurysm	4 (<1)	1 (<1)	3 (<1)
	Varicose veins of lower extremities	4 (<1)	3 (<1)	1 (<1)
	Nonrheumatic aortic valve disorders	3 (<1)	1 (<1)	2 (<1)
	Other conduction disorders	3 (<1)	1 (<1)	2 (<1)
	Atherosclerosis	2 (<1)	0	2 (<1)
	Cerebral infarction	2 (<1)	2 (<1)	0
	Complications & ill-defined descriptions of heart disease	2 (<1)	2 (<1)	0
	Nonrheumatic mitral valve disorders	2 (<1)	0	2 (<1)
	Other cerebrovascular diseases	2 (<1)	1 (<1)	1 (<1)
	Other disorders of veins	2 (<1)	1 (<1)	1 (<1)
	Other venous embolism & thrombosis	2 (<1)	0	2 (<1)
	Sequelae of cerebrovascular disease	2 (<1)	0	2 (<1)
	Arterial embolism & thrombosis	1 (<1)	0	1 (<1)
	Hypertensive heart disease	1 (<1)	1 (<1)	0
	Hypertensive renal disease	1 (<1)	0	1 (<1)
	Other & unspecified disorders of circulatory system	1 (<1)	0	1 (<1)
	Other nontraumatic intracranial hemorrhage	1 (<1)	0	1 (<1)
Digestive system	Other functional intestinal disorders	47 (3)	27 (3)	20 (2)
	Gastritis & duodenitis	44 (3)	20 (2)	24 (3)
	Dyspepsia	35 (2)	17 (2)	18 (2)
	Other diseases of digestive system	24 (1)	9 (1)	15 (2)
	Inguinal hernia	18 (1)	4 (<1)	14 (2)
	Diaphragmatic hernia	14 (1)	6 (1)	8 (1)
	Gastric ulcer	14 (1)	8 (1)	6 (1)
	Gastro-esophageal reflux disease	13 (1)	6 (1)	7 (1)
	Cholelithiasis	12 (1)	6 (1)	6 (1)
	Diverticular disease of intestine	7 (<1)	4 (<1)	3 (<1)
	Other diseases of anus & rectum	6 (<1)	4 (<1)	2 (<1)
	Other noninfective gastroenteritis & colitis	6 (<1)	4 (<1)	2 (<1)
	Esophagitis	5 (<1)	3 (<1)	2 (<1)
	Peptic ulcer, site unspecified	5 (<1)	1 (<1)	4 (<1)
	Unspecified hernia of abdominal cavity	5 (<1)	1 (<1)	4 (<1)
	Diseases of pulp & periapical tissues	4 (<1)	3 (<1)	1 (<1)
	Other diseases of liver	4 (<1)	2 (<1)	2 (<1)
	Cholecystitis	3 (<1)	1 (<1)	2 (<1)
	Diseases of salivary glands	3 (<1)	2 (<1)	1 (<1)
	Duodenal ulcer	3 (<1)	1 (<1)	2 (<1)
	Fissure & fistula of anal & rectal regions	3 (<1)	1 (<1)	2 (<1)
	Other diseases of stomach & duodenum	3 (<1)	1 (<1)	2 (<1)
	Unspecified appendicitis	3 (<1)	1 (<1)	2 (<1)
	Ventral hernia	3 (<1)	1 (<1)	2 (<1)
	Other diseases of esophagus	2 (<1)	0	2 (<1)
	Other disorders of teeth & supporting structures	2 (<1)	1 (<1)	1 (<1)
	Other inflammatory liver diseases	2 (<1)	1 (<1)	1 (<1)

Table 53: LIPS All Adverse Events

			Treatment	
		All	Fluvastatin	Placebo
	Paralytic ileus & intestinal obstruction without hernia	2 (<1)	1 (<1)	1 (<1)
	Stomatitis & related lesions	2 (<1)	1 (<1)	1 (<1)
	Acute appendicitis	1 (<1)	0	1 (<1)
	Acute pancreatitis	1 (<1)	0	1 (<1)
	Crohn's disease [regional enteritis]	1 (<1)	0	1 (<1)
	Dental caries	1 (<1)	0	1 (<1)
	Diseases of tongue	1 (<1)	1 (<1)	0
	Gingivitis & periodontal diseases	1 (<1)	0	1 (<1)
	Irritable bowel syndrome	1 (<1)	0	1 (<1)
	Other abdominal hernia	1 (<1)	1 (<1)	0
	Other diseases of intestine	1 (<1)	1 (<1)	0
	Other diseases of jaws	1 (<1)	0	1 (<1)
	Other diseases of lip & oral mucosa	1 (<1)	1 (<1)	0
	Other diseases of pancreas	1 (<1)	0	1 (<1)
	Other disorders of peritoneum	1 (<1)	1 (<1)	0
	Ulcerative colitis	1 (<1)	1 (<1)	0
	Vascular disorders of intestine	1 (<1)	1 (<1)	0
Ear & Mastoid Process	Disorders of vestibular function	5 (<1)	4 (<1)	1 (<1)
	Suppurative & unspecified otitis media	5 (<1)	4 (<1)	1 (<1)
	Other disorders of ear, NEC	4 (<1)	3 (<1)	1 (<1)
	Other hearing loss	3 (<1)	2 (<1)	1 (<1)
	Cholesteatoma of middle ear	1 (<1)	1 (<1)	0
	Otalgia & effusion of ear	1 (<1)	0	1 (<1)
	Other diseases of inner ear	1 (<1)	0	1 (<1)
Eye & Adnexa	Other cataract	26 (2)	13 (2)	13 (2)
	Visual disturbances	9 (1)	5 (1)	4 (<1)
	Glaucoma	3 (<1)	1 (<1)	2 (<1)
	Other disorders of eye & adnexa	3 (<1)	1 (<1)	2 (<1)
	Blindness & low vision	2 (<1)	1 (<1)	1 (<1)
	Retinal vascular occlusions	2 (<1)	0	2 (<1)
	Conjunctivitis	1 (<1)	1 (<1)	0
	Disorders of globe	1 (<1)	0	1 (<1)
	Disorders of lacrimal system	1 (<1)	0	1 (<1)
	Other disorders of conjunctiva	1 (<1)	0	1 (<1)
	Paralytic strabismus	1 (<1)	0	1 (<1)
	Retinal disorders in diseases classified elsewhere	1 (<1)	0	1 (<1)
Genitourinary System	Other disorders of urinary system	27 (2)	11 (1)	16 (2)
	Hyperplasia of prostate	25 (2)	7 (1)	18 (2)
	Other disorders of penis	22 (1)	11 (1)	11 (1)
	Calculus of kidney & ureter	9 (1)	2 (<1)	7 (1)
	Orchitis & epididymitis	7 (<1)	4 (<1)	3 (<1)
	Unspecified renal colic	6 (<1)	4 (<1)	2 (<1)
	Cystitis	4 (<1)	2 (<1)	2 (<1)
	Hypertrophy of breast	4 (<1)	2 (<1)	2 (<1)
	Other disorders of male genital organs	3 (<1)	0	3 (<1)
	Other disorders of prostate	3 (<1)	1 (<1)	2 (<1)
	Tubulo-interstitial nephritis, not specified as	3 (<1)	3 (<1)	0

Table 53: LIPS All Adverse Events

			Treatment	
		All	Fluvastatin	Placebo
	acute or chronic	3 (<1)	1 (<1)	2 (<1)
	Unspecified renal failure	2 (<1)	2 (<1)	0
	Calculus of lower urinary tract	2 (<1)	2 (<1)	0
	Excessive, frequent & irregular menstruation	2 (<1)	0	2 (<1)
	Hydrocele & spermatocele	2 (<1)	0	2 (<1)
	Inflammatory diseases of prostate	2 (<1)	1 (<1)	1 (<1)
	Other abnormal uterine & vaginal bleeding	2 (<1)	1 (<1)	1 (<1)
	Other disorders of kidney & ureter, NEC	1 (<1)	0	1 (<1)
	Acute renal failure	1 (<1)	1 (<1)	0
	Chronic renal failure	1 (<1)	0	1 (<1)
	Obstructive & reflux uropathy	1 (<1)	0	1 (<1)
	Other disorders of bladder	1 (<1)	1 (<1)	0
	Other disorders of breast	1 (<1)	0	1 (<1)
	Urethral stricture	107 (7)	60 (7)	47 (6)
Musculoskeletal System & Connective Tissue	Other soft tissue disorders, NEC	78 (5)	34 (4)	44 (5)
	Dorsalgia	43 (3)	24 (3)	19 (2)
	Other joint disorders, NEC	15 (1)	6 (1)	9 (1)
	Other arthrosis	13 (1)	8 (1)	5 (1)
	Gonarthrosis [arthrosis of knee]	13 (1)	5 (1)	8 (1)
	Shoulder lesions	10 (1)	7 (1)	3 (<1)
	Other arthritis	10 (1)	6 (1)	4 (<1)
	Other disorders of muscle	8 (<1)	3 (<1)	5 (1)
	Gout	7 (<1)	4 (<1)	3 (<1)
	Other intervertebral disc disorders	6 (<1)	3 (<1)	3 (<1)
	Other enthesopathies	5 (<1)	2 (<1)	3 (<1)
	Coxarthrosis [arthrosis of hip]	4 (<1)	2 (<1)	2 (<1)
	Other rheumatoid arthritis	3 (<1)	0	3 (<1)
	Osteoporosis without pathological fracture	3 (<1)	2 (<1)	1 (<1)
	Spondylosis	2 (<1)	1 (<1)	1 (<1)
	Enthesopathies of lower limb, excluding foot	2 (<1)	1 (<1)	1 (<1)
	Fibroblastic disorders	2 (<1)	0	2 (<1)
	Other bursopathies	2 (<1)	1 (<1)	1 (<1)
	Other dorsopathies, not elsewhere classified	2 (<1)	1 (<1)	1 (<1)
	Pyogenic arthritis	1 (<1)	1 (<1)	0
	Acquired deformities of fingers & toes	1 (<1)	0	1 (<1)
	Internal derangement of knee	1 (<1)	1 (<1)	0
	Osteomyelitis	1 (<1)	0	1 (<1)
	Osteonecrosis	1 (<1)	1 (<1)	0
	Other disorders of bone	1 (<1)	1 (<1)	0
	Other disorders of cartilage	1 (<1)	0	1 (<1)
	Other disorders of synovium & tendon	1 (<1)	1 (<1)	0
	Other inflammatory spondylopathies	1 (<1)	0	1 (<1)
	Other necrotizing vasculopathies	1 (<1)	0	1 (<1)
	Scoliosis	1 (<1)	0	1 (<1)
	Soft tissue disorders related to use, overuse & pressure	1 (<1)	1 (<1)	0
	Synovitis & tenosynovitis			

Table 53: LIPS All Adverse Events

			Treatment	
		All	Fluvastatin	Placebo
Nervous System	Transient cerebral ischemic attacks & related syndromes	19 (1)	11 (1)	8 (1)
	Sleep disorders	13 (1)	8 (1)	5 (1)
	Other extrapyramidal & movement disorders	7 (<1)	3 (<1)	4 (<1)
	Mononeuropathies of upper limb	6 (<1)	2 (<1)	4 (<1)
	Epilepsy	5 (<1)	1 (<1)	4 (<1)
	Alzheimer's disease	3 (<1)	1 (<1)	2 (<1)
	Disorders of trigeminal nerve	3 (<1)	2 (<1)	1 (<1)
	Hemiplegia	3 (<1)	0	3 (<1)
	Other degenerative diseases of nervous system, NEC	2 (<1)	0	2 (<1)
	Other myopathies	2 (<1)	1 (<1)	1 (<1)
	Other paralytic syndromes	2 (<1)	1 (<1)	1 (<1)
	Other polyneuropathies	2 (<1)	0	2 (<1)
	Disorders of autonomic nervous system	1 (<1)	0	1 (<1)
	Facial nerve disorders	1 (<1)	0	1 (<1)
	Hereditary & idiopathic neuropathy	1 (<1)	0	1 (<1)
	Hydrocephalus	1 (<1)	1 (<1)	0
	Migraine	1 (<1)	1 (<1)	0
	Mononeuropathies of lower limb	1 (<1)	0	1 (<1)
	Multiple sclerosis	1 (<1)	0	1 (<1)
	Myasthenia gravis & other myoneural disorders	1 (<1)	1 (<1)	0
	Other headache syndromes	1 (<1)	1 (<1)	0
	Other mononeuropathies	1 (<1)	1 (<1)	0
	Spinal muscular atrophy & related syndromes	1 (<1)	1 (<1)	0
Respiratory System	Acute nasopharyngitis [common cold]	45 (3)	25 (3)	20 (2)
	Pneumonia, organism unspecified	43 (3)	22 (3)	21 (3)
	Influenza, virus not identified	36 (2)	15 (2)	21 (3)
	Bronchitis, not specified as acute or chronic	28 (2)	16 (2)	12 (1)
	Other respiratory disorders	17 (1)	8 (1)	9 (1)
	Other chronic obstructive pulmonary disease	16 (1)	8 (1)	8 (1)
	Acute bronchitis	8 (<1)	3 (<1)	5 (1)
	Pulmonary oedema	8 (<1)	2 (<1)	6 (1)
	Unspecified acute lower respiratory infection	6 (<1)	1 (<1)	5 (1)
	Acute pharyngitis	5 (<1)	2 (<1)	3 (<1)
	Acute upper respiratory infections of multiple or unspecified sites	5 (<1)	2 (<1)	3 (<1)
	Asthma	3 (<1)	0	3 (<1)
	Vasomotor & allergic rhinitis	3 (<1)	2 (<1)	1 (<1)
	Chronic sinusitis	2 (<1)	1 (<1)	1 (<1)
	Diseases of vocal cords & larynx, NEC	2 (<1)	0	2 (<1)
	Influenza due to identified influenza virus	2 (<1)	0	2 (<1)
	Other disorders of nose & nasal sinuses	2 (<1)	0	2 (<1)
	Other interstitial pulmonary diseases	2 (<1)	1 (<1)	1 (<1)

Table 53: LIPS All Adverse Events

			Treatment	
		All	Fluvastatin	Placebo
	Pleural effusion, NEC	2 (<1)	1 (<1)	1 (<1)
	Respiratory failure, NEC	2 (<1)	2 (<1)	0
	Acute sinusitis	1 (<1)	0	1 (<1)
	Acute tonsillitis	1 (<1)	1 (<1)	0
	Bacterial pneumonia, NEC	1 (<1)	0	1 (<1)
	Chronic laryngitis & laryngotracheitis	1 (<1)	1 (<1)	0
	Chronic rhinitis, nasopharyngitis & pharyngitis	1 (<1)	0	1 (<1)
	Emphysema	1 (<1)	0	1 (<1)
	Nasal polyp	1 (<1)	0	1 (<1)
	Other diseases of upper respiratory tract	1 (<1)	0	1 (<1)
	Other pleural conditions	1 (<1)	0	1 (<1)
	Pneumonitis due to solids & liquids	1 (<1)	1 (<1)	0
	Pneumothorax	1 (<1)	0	1 (<1)
	Status asthmaticus	1 (<1)	1 (<1)	0
Skin & Subcutaneous Tissue	Pruritus	18 (1)	10 (1)	8 (1)
	Other dermatitis	9 (1)	6 (1)	3 (<1)
	Other erythematous conditions	8 (<1)	5 (1)	3 (<1)
	Urticaria	4 (<1)	3 (<1)	1 (<1)
	Allergic contact dermatitis	3 (<1)	2 (<1)	1 (<1)
	Lichen simplex chronicus & prurigo	3 (<1)	1 (<1)	2 (<1)
	Other nonscarring hair loss	3 (<1)	1 (<1)	2 (<1)
	Psoriasis	3 (<1)	2 (<1)	1 (<1)
	Cutaneous abscess, furuncle & carbuncle	2 (<1)	1 (<1)	1 (<1)
	Other local infections of skin & subcutaneous tissue	2 (<1)	0	2 (<1)
	Other papulosquamous disorders	2 (<1)	1 (<1)	1 (<1)
	Ulcer of lower limb, NEC	2 (<1)	1 (<1)	1 (<1)
	Acanthosis nigricans	1 (<1)	1 (<1)	0
	Atrophic disorders of skin	1 (<1)	1 (<1)	0
	Cellulitis	1 (<1)	1 (<1)	0
	Dermatitis due to substances taken internally	1 (<1)	0	1 (<1)
	Erythema nodosum	1 (<1)	0	1 (<1)
	Follicular cysts of skin & subcutaneous tissue	1 (<1)	0	1 (<1)
	Granulomatous disorders of skin & subcutaneous tissue	1 (<1)	1 (<1)	0
	Other disorders of pigmentation	1 (<1)	1 (<1)	0
	Other disorders of skin & subcutaneous tissue related to radiation	1 (<1)	1 (<1)	0
	Pemphigus	1 (<1)	1 (<1)	0
	Radiodermatitis	1 (<1)	1 (<1)	0
	Rosacea	1 (<1)	0	1 (<1)
	Unspecified contact dermatitis	59 (4)	10 (1)	49 (6)
Endocrine, Nutritional & Metabolic	Disorders of lipoprotein metabolism & other lipidemias	13 (1)	5 (1)	8 (1)
	Unspecified diabetes mellitus	4 (<1)	2 (<1)	2 (<1)
	Non-insulin-dependent diabetes mellitus			

Table 53: LIPS All Adverse Events

			Treatment	
		All	Fluvastatin	Placebo
	Thyrotoxicosis [hyperthyroidism]	4 (<1)	2 (<1)	2 (<1)
	Obesity	3 (<1)	3 (<1)	0
	Other disorders of amino-acid metabolism	3 (<1)	3 (<1)	0
	Other disorders of pancreatic internal secretion	3 (<1)	1 (<1)	2 (<1)
	Other hypothyroidism	3 (<1)	0	3 (<1)
	Disorders of mineral metabolism	1 (<1)	1 (<1)	0
	Disorders of porphyrin & bilirubin metabolism	1 (<1)	1 (<1)	0
	Insulin-dependent diabetes mellitus	1 (<1)	0	1 (<1)
	Other disorders of fluid, electrolyte & acid-base balance	1 (<1)	0	1 (<1)
	Other metabolic disorders	1 (<1)	0	1 (<1)
	Volume depletion	1 (<1)	1 (<1)	0
External Causes of Morbidity & Mortality	Fall on & from ladder	2 (<1)	0	2 (<1)
	Motor- or nonmotor-vehicle accident, type of vehicle unspecified	2 (<1)	1 (<1)	1 (<1)
	Accidental poisoning by & exposure to other drugs acting on the autonomic nervous system	1 (<1)	0	1 (<1)
	Fall on & from stairs & steps	1 (<1)	1 (<1)	0
	Intentional self-harm by unspecified means	1 (<1)	1 (<1)	0
	Other & unspecified firearm discharge, undetermined intent	1 (<1)	0	1 (<1)
	Work-related condition	1 (<1)	0	1 (<1)
Factors Influencing Health Status & Contact with Health Services	Adjustment & management of implanted device	10 (1)	3 (<1)	7 (1)
	Follow-up examination after treatment for conditions other than malignant neoplasms	3 (<1)	3 (<1)	0
	Medical observation & evaluation for suspected diseases & conditions	2 (<1)	1 (<1)	1 (<1)
	Contraceptive management	1 (<1)	1 (<1)	0
	Other surgical follow-up care	1 (<1)	0	1 (<1)
	Problems related to life-management difficulty	1 (<1)	0	1 (<1)
	Special screening examination for other diseases & disorders	1 (<1)	1 (<1)	0
Injury, Poisoning & Other External Causes	Other complications of surgical & medical care, NEC	15 (1)	4 (<1)	11 (1)
	Injury of unspecified of body	14 (1)	7 (1)	7 (1)
	Adverse effects, NEC	7 (<1)	1 (<1)	6 (1)
	Fracture of lower leg, including ankle	5 (<1)	1 (<1)	4 (<1)
	Fracture of shoulder & upper arm	5 (<1)	3 (<1)	2 (<1)
	Complications of cardiac & vascular prosthetic devices, implants & grafts	4 (<1)	0	4 (<1)
	Complications of procedures, NEC	4 (<1)	1 (<1)	3 (<1)
	Dislocation, sprain & strain of joints & ligaments at ankle & foot level	4 (<1)	2 (<1)	2 (<1)
	Fracture of femur	4 (<1)	2 (<1)	2 (<1)
	Fracture of foot, except ankle	4 (<1)	2 (<1)	2 (<1)

Table 53: LIPS All Adverse Events

			Treatment	
		All	Fluvastatin	Placebo
	Dislocation, sprain & strain of joint & ligaments of hip	3 (<1)	0	3 (<1)
	Dislocation, sprain & strain of joints & ligaments of knee	3 (<1)	-0	3 (<1)
	Complications of other internal prosthetic devices, implants & grafts	2 (<1)	1 (<1)	1 (<1)
	Fracture of forearm	2 (<1)	1 (<1)	1 (<1)
	Injury of muscle & tendon at lower leg level	2 (<1)	2 (<1)	0
	Other & unspecified injuries of thorax	2 (<1)	0	2 (<1)
	Superficial injury of thorax	2 (<1)	0	2 (<1)
	Burn & corrosion of hip & lower limb, except ankle & foot	1 (<1)	1 (<1)	0
	Certain early complications of trauma, not elsewhere classified	1 (<1)	1 (<1)	0
	Complications of internal orthopaedic prosthetic devices, implants & grafts	1 (<1)	0	1 (<1)
	Dislocation, sprain & strain of joints & ligaments at neck level	1 (<1)	0	1 (<1)
	Dislocation, sprain & strain of joints & ligaments of shoulder girdle	1 (<1)	0	1 (<1)
	Effects of other external causes	1 (<1)	0	1 (<1)
	Fracture at wrist & hand level	1 (<1)	1 (<1)	0
	Fracture of lumbar spine & pelvis	1 (<1)	1 (<1)	0
	Fracture of rib(s), sternum & thoracic spine	1 (<1)	1 (<1)	0
	Fracture of skull & facial bones	1 (<1)	1 (<1)	0
	Fracture of spine, level unspecified	1 (<1)	1 (<1)	0
	Injury of eye & orbit	1 (<1)	1 (<1)	0
	Injury of muscle & tendon at hip & thigh level	1 (<1)	1 (<1)	0
	Injury of muscle & tendon at shoulder & upper arm level	1 (<1)	0	1 (<1)
	Intracranial injury	1 (<1)	1 (<1)	0
	Other & unspecified injuries of head	1 (<1)	0	1 (<1)
	Other & unspecified injuries of wrist & hand	1 (<1)	0	1 (<1)
	Other injuries of spine & trunk, level unspecified	1 (<1)	0	1 (<1)
	Superficial injuries involving multiple body regions	1 (<1)	1 (<1)	0
	Superficial injury of abdomen, lower back & pelvis	1 (<1)	1 (<1)	0
	Toxic effect of contact with venomous animals	1 (<1)	1 (<1)	0
	Traumatic amputation of wrist & hand	1 (<1)	0	1 (<1)
Mental & Behavioral	Depressive episodes	25 (2)	13 (2)	12 (1)
	Other anxiety disorders	19 (1)	7 (1)	12 (1)
	Somatoform disorders	4 (<1)	3 (<1)	1 (<1)
	Mental & behavioral disorders due to use of alcohol	3 (<1)	1 (<1)	2 (<1)
	Delirium, not induced by alcohol & other	1 (<1)	0	1 (<1)

Table 53: LIPS All Adverse Events

			Treatment	
		All	Fluvastatin	Placebo
	psychoactive substances			
	Eating disorders	1 (<1)	0	1 (<1)
	Mental disorder, NOS	1 (<1)	1	0
	Phobic anxiety disorders	1 (<1)	0	1 (<1)
	Recurrent depressive disorder	1 (<1)	1 (<1)	0
	Sexual dysfunction, not caused by organic disorder or disease	1 (<1)	0	1 (<1)
	Unspecified mental retardation	1 (<1)	0	1 (<1)
Neoplasms	Malignant neoplasm of prostate	12 (1)	10 (1)	2 (<1)
	Malignant neoplasm of bronchus & lung	8 (<1)	6 (1)	2 (<1)
	Malignant neoplasm of colon	7 (<1)	2 (<1)	5 (1)
	Malignant neoplasm of larynx	7 (<1)	0	7 (1)
	Neoplasm of uncertain or unknown behavior of oral cavity & digestive organs	4 (<1)	0	4 (<1)
	Malignant neoplasm of breast	3 (<1)	1 (<1)	2 (<1)
	Neoplasm of uncertain or unknown behavior of middle ear & respiratory & intrathoracic organs	3 (<1)	3 (<1)	0
	Neoplasm of uncertain or unknown behavior of other & unspecified sites	3 (<1)	3 (<1)	0
	Neoplasm of uncertain or unknown behavior of urinary organs	3 (<1)	2 (<1)	1 (<1)
	Other & unspecified types of non-Hodgkin's lymphoma	3 (<1)	2 (<1)	1 (<1)
	Other malignant neoplasms of skin	3 (<1)	1 (<1)	2 (<1)
	Secondary malignant neoplasm of other sites	3 (<1)	3 (<1)	0
	Benign neoplasm of colon, rectum, anus & anal canal	2 (<1)	1 (<1)	1 (<1)
	Malignant neoplasm of brain	2 (<1)	0	2 (<1)
	Malignant neoplasm of kidney, except renal pelvis	2 (<1)	1 (<1)	1 (<1)
	Malignant neoplasm of pancreas	2 (<1)	2 (<1)	0
	Malignant neoplasm of rectum	2 (<1)	0	2 (<1)
	Malignant neoplasm of stomach	2 (<1)	1 (<1)	1 (<1)
	Multiple myeloma & malignant plasma cell neoplasms	2 (<1)	1 (<1)	1 (<1)
	Neoplasm of uncertain or unknown behavior of brain & central nervous system	2 (<1)	0	2 (<1)
	Secondary malignant neoplasm of respiratory & digestive organs	2 (<1)	0	2 (<1)
	Benign lipomatous neoplasm	1 (<1)	0	1 (<1)
	Benign neoplasm of bone & articular cartilage	1 (<1)	0	1 (<1)
	Benign neoplasm of meninges	1 (<1)	0	1 (<1)
	Benign neoplasm of middle ear & respiratory system	1 (<1)	0	1 (<1)
	Benign neoplasm of other & ill-defined parts of digestive system	1 (<1)	1 (<1)	0
	Benign neoplasm of other & unspecified	1 (<1)	1 (<1)	0

Table 53: LIPS All Adverse Events

		Treatment		
		All	Fluvastatin	Placebo
	sites	1 (<1)	0	1 (<1)
	Malignant neoplasm of anus & anal canal	1 (<1)	0	1 (<1)
	Malignant neoplasm of bladder	1 (<1)	1 (<1)	0
	Malignant neoplasm of corpus uteri	1 (<1)	0	1 (<1)
	Malignant neoplasm of heart, mediastinum & pleura	1 (<1)	0	1 (<1)
	Malignant neoplasm of liver & intrahepatic bile ducts	1 (<1)	1 (<1)	0
	Malignant neoplasm of oesophagus	1 (<1)	0	1 (<1)
	Malignant neoplasm of other & ill-defined digestive organs	1 (<1)	1 (<1)	0
	Malignant neoplasm of other & ill-defined sites	1 (<1)	0	1 (<1)
	Malignant neoplasm of other & unspecified parts of mouth	1 (<1)	0	1 (<1)
	Malignant neoplasm of other & unspecified parts of tongue	1 (<1)	1 (<1)	0
	Malignant neoplasm of other & unspecified urinary organs	1 (<1)	0	1 (<1)
	Malignant neoplasm of other connective & soft tissue	1 (<1)	1 (<1)	0
	Malignant neoplasm of ovary	1 (<1)	0	1 (<1)
	Malignant neoplasm of rectosigmoid junction	1 (<1)	0	1 (<1)
	Malignant neoplasm of spinal cord, cranial nerves & other parts of central nervous system	1 (<1)	0	1 (<1)
	Malignant neoplasm of thymus	1 (<1)	1 (<1)	0
	Malignant neoplasm of tonsil	1 (<1)	1 (<1)	0
	Malignant neoplasm without specification of site	1 (<1)	0	1 (<1)
	Melanocytic nevi	1 (<1)	1 (<1)	0
	Neoplasm of uncertain or unknown behavior of endocrine glands	1 (<1)	0	1 (<1)
	Other benign neoplasms of connective & other soft tissue	1 (<1)	0	1 (<1)
	Other benign neoplasms of uterus	53 (3)	23 (3)	30 (4)
Surgical Procedures	Surgery - Cardiac - TCT	41 (3)	19 (2)	22 (3)
	Surgery - Cardiac - other cardiac procedures	21 (1)	7 (1)	14 (2)
	Surgery - Cardiac - CABG	14 (1)	4 (<1)	10 (2)
	Surgery - Digestive system	11 (1)	5 (1)	6 (1)
	Surgery - Genitourinary system	11 (1)	6 (1)	5 (1)
	Surgery - Musculoskeletal system & connective tissue	7 (<1)	4 (<1)	3 (<1)
	Surgery - Vascular (extracardiac) system	2 (<1)	0	2 (<1)
	Surgery - Endocrine, nutritional & metabolic diseases	2 (<1)	1 (<1)	1 (<1)
	Surgery - Eye & adnexa	2 (<1)	1 (<1)	1 (<1)
	Surgery - Respiratory system	2 (<1)	1 (<1)	1 (<1)
	Surgery - Skin & subcutaneous tissue			

Table 53: LIPS All Adverse Events

			Treatment	
		All	Fluvastatin	Placebo
	Surgery - Ear & mastoid process	1 (<1)	1 (<1)	0
Symptoms, Signs & Abnormal Clinical & Laboratory Findings, NEC	Pain in throat & chest	321 (20)	161 (20)	160 (20)
	Abnormalities of breathing	147 (9)	69 (8)	78 (10)
	Abdominal & pelvic pain	123 (8)	70 (9)	53 (6)
	Malaise & fatigue	94 (6)	56 (7)	38 (5)
	Dizziness & giddiness	80 (5)	40 (5)	40 (5)
	Other symptoms & signs involving the digestive system & abdomen	74 (5)	41 (5)	33 (4)
	Edema, NEC	63 (4)	37 (5)	26 (3)
	Abnormalities of heart beat	61 (4)	33 (4)	28 (3)
	Headache	50 (3)	23 (3)	27 (3)
	Nausea & vomiting	49 (3)	27 (3)	22 (3)
	Other ill-defined & unspecified causes of mortality	44 (3)	16 (2)	28 (3)
	Syncope & collapse	43 (3)	22 (3)	21 (3)
	Abnormal serum enzyme levels	42 (3)	25 (3)	17 (2)
	Rash & other nonspecific skin eruption	29 (2)	14 (2)	15 (2)
	Heartburn	28 (2)	17 (2)	11 (1)
	Disturbances of skin sensation	27 (2)	13 (2)	14 (2)
	Symptoms & signs concerning food & fluid intake	19 (1)	12 (1)	7 (1)
	Cough	18 (1)	12 (1)	6 (1)
	Symptoms & signs involving emotional state	14 (1)	9 (1)	5 (1)
	Other general symptoms & signs	13 (1)	10 (1)	3 (<1)
	Other skin changes	13 (1)	9 (1)	4 (<1)
	Abnormal blood-pressure reading, without diagnosis	12 (1)	8 (1)	4 (<1)
	Abnormal involuntary movements	12 (1)	5 (1)	7 (1)
	Elevated blood glucose level	12 (1)	9 (1)	3 (<1)
	Fever of unknown origin	12 (1)	6 (1)	6 (1)
	Flatulence & related conditions	12 (1)	6 (1)	6 (1)
	Unspecified hematuria	12 (1)	4 (<1)	8 (1)
	Hemorrhage from respiratory passages	9 (1)	3 (<1)	6 (1)
	Other sudden death, cause unknown	8 (<1)	5 (1)	3 (<1)
	Other symptoms & signs involving cognitive functions & awareness	8 (<1)	1 (<1)	7 (1)
	Other symptoms & signs involving the circulatory & respiratory systems	8 (<1)	2 (<1)	6 (1)
	Unknown & unspecified causes of morbidity	6 (<1)	3 (<1)	3 (<1)
	Hyperhidrosis	5 (<1)	2 (<1)	3 (<1)
	Abnormal results of function studies	4 (<1)	1 (<1)	3 (<1)
	Hemorrhage, not elsewhere classified	4 (<1)	3 (<1)	1 (<1)
	Somnolence, stupor & coma	4 (<1)	1 (<1)	3 (<1)
	Voice disturbances	4 (<1)	2 (<1)	2 (<1)
	Disturbances of smell & taste	3 (<1)	3 (<1)	0
	Other abnormal findings of blood chemistry	3 (<1)	3 (<1)	0
	Unspecified urinary incontinence	3 (<1)	3 (<1)	0

Table 53: LIPS All Adverse Events

	All	Treatment	
		Fluvastatin	Placebo
Abnormality of white blood cells, NEC	2 (<1)	2 (<1)	0
Dysphagia	2 (<1)	2 (<1)	0
Elevated erythrocyte sedimentation rate & abnormality of plasma viscosity	2 (<1)	2 (<1)	0
Localized swelling, mass & lump of skin & subcutaneous tissue	2 (<1)	0	2 (<1)
Other abnormal immunological findings in serum	2 (<1)	1 (<1)	1 (<1)
Pain associated with micturition	2 (<1)	2 (<1)	0
Retention of urine	2 (<1)	0	2 (<1)
Shock, not elsewhere classified	2 (<1)	0	2 (<1)
Unspecified jaundice	2 (<1)	1 (<1)	1 (<1)
Abnormalities of gait & mobility	1 (<1)	1 (<1)	0
Abnormality of red blood cells	1 (<1)	1 (<1)	0
Cardiac murmurs & other cardiac sounds	1 (<1)	1 (<1)	0
Fecal incontinence	1 (<1)	0	1 (<1)
Gangrene, not elsewhere classified	1 (<1)	1 (<1)	0
Isolated proteinuria	1 (<1)	1 (<1)	0
Other lack of coordination	1 (<1)	0	1 (<1)
Other symptoms & signs involving general sensations & perceptions	1 (<1)	1 (<1)	0
Other symptoms & signs involving the urinary system	1 (<1)	0	1 (<1)
Pain, NEC	1 (<1)	0	1 (<1)

C. Discontinuations for Adverse Events

All discontinuations for AEs, including MACE are summarized in the following table

Table 54: LIPS Adverse Events Resulting in Study Drug Discontinuation (including MACE)

			Treatment	
		All	Fluvastatin	Placebo
Safety Population, n =		1640	822	817
Body System	**AE Preferred Term**	n (%)	n (%)	n (%)
Certain infectious and parasitic diseases	Diarrhea and gastroenteritis of presumed infectious origin	13 (1)	7 (1)	6 (1)
	Aspergillosis	1 (<1)	0	1 (<1)
	Other and unspecified infectious diseases	1 (<1)	0	1 (<1)
	Other septicemia	1 (<1)	1 (<1)	0
Diseases of blood & blood-forming organs & certain disorders involving the immune mechanism	Other anemias	2 (<1)	2 (<1)	0
	Purpura and other hemorrhagic conditions	1 (<1)	0	1 (<1)
Diseases of the circulatory system	Angina pectoris	75 (5)	33 (4)	42 (5)
	Chronic ischemic heart disease	17 (1)	4 (<1)	13
	Acute myocardial infarction	15 (1)	7 (1)	8 (1)
	Stroke, not specified as hemorrhage or infarction	6 (<1)	3 (<1)	3 (<1)
	Cardiac arrest	4 (<1)	2 (<1)	2 (<1)
	Essential (primary) hypertension	4 (<1)	4 (<1)	0
	Heart failure	4 (<1)	1 (<1)	3 (<1)
	Other peripheral vascular diseases	4 (<1)	2 (<1)	2 (<1)
	Atrioventricular and left bundle-branch block	3 (<1)	2 (<1)	1 (<1)
	Other cardiac arrhythmias	3 (<1)	0	3 (<1)
	Aortic aneurysm and dissection	2 (<1)	1 (<1)	1 (<1)
	Other disorders of arteries and arterioles	2 (<1)	1 (<1)	1 (<1)
	Paroxysmal tachycardia	2 (<1)	2 (<1)	0
	Atrial fibrillation and flutter	1 (<1)	1 (<1)	0
	Cerebral infarction	1 (<1)	1 (<1)	0
	Haemorrhoids	1 (<1)	0	1 (<1)
	Other cerebrovascular diseases	1 (<1)	0	1 (<1)
	Other nontraumatic intracranial haemorrhage	1 (<1)	0	1 (<1)
	Other venous embolism and thrombosis	1 (<1)	0	1 (<1)
	Phlebitis and thrombophlebitis	1 (<1)	1 (<1)	0
	Pulmonary embolism	1 (<1)	1 (<1)	0
Diseases of the digestive system	Gastritis and duodenitis	11 (1)	6 (1)	5 (1)
	Dyspepsia	9 (1)	4 (<1)	5 (1)
	Other diseases of digestive system	9 (1)	3 (<1)	6 (1)
	Other functional intestinal disorders	7 (<1)	4 (<1)	3 (<1)
	Oesophagitis	3 (<1)	2 (<1)	1 (<1)
	Gastro-oesophageal reflux disease	2 (<1)	1 (<1)	1 (<1)
	Inguinal hernia	2 (<1)	0	2 (<1)
	Other diseases of liver	2 (<1)	2 (<1)	0
	Other inflammatory liver diseases	2 (<1)	1 (<1)	1 (<1)
	Unspecified hernia of abdominal cavity	2 (<1)	1 (<1)	1 (<1)
	Cholelithiasis	1 (<1)	0	1 (<1)
	Crohn's disease [regional enteritis]	1 (<1)	0	1 (<1)
	Diaphragmatic hernia	1 (<1)	0	1 (<1)

Table 54: LIPS Adverse Events Resulting in Study Drug Discontinuation (including MACE)

			Treatment	
		All	Fluvastatin	Placebo
	Diseases of tongue	1 (<1)	1 (<1)	0
	Diverticular disease of intestine	1 (<1)	0	1 (<1)
	Gastric ulcer	1 (<1)	0	1 (<1)
	Irritable bowel syndrome	1 (<1)	0	1 (<1)
	Other diseases of pancreas	1 (<1)	0	1 (<1)
	Other diseases of stomach and duodenum	1 (<1)	0	1 (<1)
	Other disorders of teeth and supporting structures	1 (<1)	1 (<1)	0
	Peptic ulcer, site unspecified	1 (<1)	0	1 (<1)
Diseases of the ear and mastoid process	Disorders of vestibular function	2 (<1)	2 (<1)	0
Diseases of the eye and adnexa	Other cataract	3 (<1)	1 (<1)	2 (<1)
	Conjunctivitis	1 (<1)	1 (<1)	0
	Disorders of lacrimal system	1 (<1)	0	1 (<1)
	Other disorders of conjunctiva	1 (<1)	0	1 (<1)
	Visual disturbances	1 (<1)	1 (<1)	0
Diseases of the genitourinary system	Other disorders of penis	4 (<1)	1 (<1)	3 (<1)
	Hyperplasia of prostate	2 (<1)	0	2 (<1)
	Acute renal failure	1 (<1)	0	1 (<1)
	Calculus of kidney and ureter	1 (<1)	0	1 (<1)
	Excessive, frequent and irregular menstruation	1 (<1)	1 (<1)	0
	Hypertrophy of breast	1 (<1)	0	1 (<1)
	Obstructive and reflux uropathy	1 (<1)	0	1 (<1)
	Other disorders of urinary system	1 (<1)	1 (<1)	0
	Unspecified renal failure	1 (<1)	0	1 (<1)
Diseases of the musculoskeletal system and connective tissue	Other soft tissue disorders, NEC	14 (1)	9 (1)	5 (1)
	Dorsalgia	5 (<1)	0	5 (1)
	Other arthritis	3 (<1)	1 (<1)	2 (<1)
	Other joint disorders, NEC	3 (<1)	3 (<1)	0
	Gonarthrosis [arthrosis of knee]	2 (<1)	2 (<1)	0
	Other disorders of muscle	2 (<1)	2 (<1)	0
	Shoulder lesions	2 (<1)	0	2 (<1)
	Enthesopathies of lower limb, excluding foot	1 (<1)	1 (<1)	0
	Osteomyelitis	1 (<1)	1 (<1)	0
	Other arthrosis	1 (<1)	0	1 (<1)
	Other enthesopathies	1 (<1)	0	1 (<1)
	Pyogenic arthritis	1 (<1)	1 (<1)	0
Diseases of the nervous system	Disorders of autonomic nervous system	1 (<1)	0	1 (<1)
	Epilepsy	1 (<1)	1 (<1)	0
	Hemiplegia	1 (<1)	0	1 (<1)
	Hydrocephalus	1 (<1)	1 (<1)	0
	Multiple sclerosis	1 (<1)	0	1 (<1)
	Myasthenia gravis and other myoneural disorders	1 (<1)	1 (<1)	0
	Other extrapyramidal and movement disorders	1 (<1)	0	1 (<1)
	Other paralytic syndromes	1 (<1)	0	1 (<1)
	Sleep disorders	1 (<1)	1 (<1)	0
	Spinal muscular atrophy and related syndromes	1 (<1)	1 (<1)	0
	Transient cerebral ischaemic attacks and related syndromes	1 (<1)	0	1 (<1)
Diseases of the respiratory	Pneumonia, organism unspecified	7 (<1)	3 (<1)	4 (<1)

Table 54: LIPS Adverse Events Resulting in Study Drug Discontinuation (including MACE)

		Treatment		
		All	Fluvastatin	Placebo
system	Pulmonary edema	3 (<1)	1 (<1)	2 (<1)
	Acute nasopharyngitis [common cold]	2 (<1)	0	2 (<1)
	Bacterial pneumonia, NEC	1 (<1)	0	1 (<1)
	Bronchitis, not specified as acute or chronic	1 (<1)	0	1 (<1)
	Influenza, virus not identified	1 (<1)	0	1 (<1)
	Other chronic obstructive pulmonary disease	1 (<1)	0	1 (<1)
	Other diseases of upper respiratory tract	1 (<1)	0	1 (<1)
	Other interstitial pulmonary diseases	1 (<1)	0	1 (<1)
	Respiratory failure, NEC	1 (<1)	1 (<1)	0
Diseases of the skin and subcutaneous tissue	Other dermatitis	3 (<1)	3 (<1)	0
	Other nonscarring hair loss	2 (<1)	1 (<1)	1 (<1)
	Pruritus	2 (<1)	0	2 (<1)
	Other disorders of pigmentation	1 (<1)	1 (<1)	0
	Other erythematous conditions	1 (<1)	1 (<1)	0
	Other papulosquamous disorders	1 (<1)	0	1 (<1)
	Pemphigus	1 (<1)	1 (<1)	0
	Psoriasis	1 (<1)	1 (<1)	0
Endocrine, nutritional and metabolic diseases	Disorders of lipoprotein metabolism and other lipidemias	46 (3)	5 (1)	41 (5)
	Other disorders of pancreatic internal secretion	3 (<1)	1 (<1)	2 (<1)
	Unspecified diabetes mellitus	2 (<1)	1 (<1)	1 (<1)
	Disorders of mineral metabolism	1 (<1)	1 (<1)	0
	Non-insulin-dependent diabetes mellitus	1 (<1)	0	1 (<1)
External causes of morbidity and mortality	Intentional self-harm by unspecified means	1 (<1)	1 (<1)	0
	Motor- or nonmotor-vehicle accident, type of vehicle unspecified	1 (<1)	1 (<1)	0
Factors influencing health status and contact with health services	Adjustment and management of implanted device	2 (<1)	2 (<1)	0
	Other surgical follow-up care	1 (<1)	0	1 (<1)
Injury, poisoning and certain other consequences of external causes	Adverse effects, NEC	4 (<1)	0	4 (<1)
	Fracture of lower leg, including ankle	3 (<1)	1 (<1)	2 (<1)
	Other complications of surgical and medical care, NEC	2 (<1)	1 (<1)	1 (<1)
	Certain early complications of trauma, NEC	1 (<1)	1 (<1)	0
	Complications of cardiac and vascular prosthetic devices, implants and grafts	1 (<1)	0	1 (<1)
	Complications of other internal prosthetic devices, implants and grafts	1 (<1)	1 (<1)	0
	Fracture of foot, except ankle	1 (<1)	0	1 (<1)
	Fracture of forearm	1 (<1)	1 (<1)	0
	Fracture of lumbar spine and pelvis	1 (<1)	1 (<1)	0
	Injury of unspecified of body	1 (<1)	1 (<1)	0
Mental and behavioural disorders	Depressive episodes	5 (<1)	3 (<1)	2 (<1)
	Other anxiety disorders	4 (<1)	0	4 (<1)
	Mental & behavioral disorders due to use of alcohol	1 (<1)	1 (<1)	0
	Unspecified mental retardation	1 (<1)	0	1 (<1)
Neoplasms	Malignant neoplasm of bronchus and lung	5 (<1)	5 (1)	0
	Malignant neoplasm of prostate	3 (<1)	2 (<1)	1 (<1)
	Malignant neoplasm of colon	2 (<1)	1 (<1)	1 (<1)

Table 54: LIPS Adverse Events Resulting in Study Drug Discontinuation (including MACE)

		Treatment		
		All	Fluvastatin	Placebo
	Neoplasm of uncertain or unknown behaviour of oral cavity and digestive organs	2 (<1)	0	2 (<1)
	Benign neoplasm of other and unspecified sites	1 (<1)	1 (<1)	0
	Malignant neoplasm of brain	1 (<1)	0	1 (<1)
	Malignant neoplasm of heart, mediastinum & pleura	1 (<1)	0	1 (<1)
	Malignant neoplasm of kidney, except renal pelvis	1 (<1)	0	1 (<1)
	Malignant neoplasm of larynx	1 (<1)	0	1 (<1)
	Malignant neoplasm of oesophagus	1 (<1)	1 (<1)	0
	Malignant neoplasm of other and ill-defined digestive organs	1 (<1)	0	1 (<1)
	Malignant neoplasm of other and ill-defined sites	1 (<1)	1 (<1)	0
	Malignant neoplasm of other & unspec. Parts of tongue	1 (<1)	0	1 (<1)
	Malignant neoplasm of other connective & soft tissue	1 (<1)	0	1 (<1)
	Malignant neoplasm of pancreas	1 (<1)	1 (<1)	0
	Malignant neoplasm of rectosigmoid junction	1 (<1)	0	1 (<1)
	Malignant neoplasm of rectum	1 (<1)	0	1 (<1)
	Malignant neoplasm of stomach	1 (<1)	0	1 (<1)
	Malignant neoplasm of thymus	1 (<1)	0	1 (<1)
	Malignant neoplasm without specification of site	1 (<1)	1 (<1)	0
	Multiple myeloma and malignant plasma cell neoplasms	1 (<1)	1 (<1)	0
	Neoplasm of uncertain or unknown behaviour of brain and central nervous system	1 (<1)	0	1 (<1)
	Neoplasm of uncertain or unknown behaviour of endocrine glands	1 (<1)	1 (<1)	0
	Neoplasm of uncertain or unknown behaviour of middle ear and respiratory and intrathoracic organs	1 (<1)	1 (<1)	0
	Neoplasm of uncertain or unknown behaviour of urinary organs	1 (<1)	0	1 (<1)
	Secondary malignant neoplasm of other sites	1 (<1)	1 (<1)	0
	Secondary malignant neoplasm of respiratory and digestive organs	1 (<1)	0	1 (<1)
Surgical procedures	Surgery - Cardiac - TCT	7 (<1)	3 (<1)	4 (<1)
	Surgery - Cardiac - CABG	6 (<1)	2 (<1)	4 (<1)
	Surgery - Cardiac - other cardiac procedures	4 (<1)	0	4 (<1)
	Surgery - Musculoskeletal system & connective tissue	3 (<1)	2 (<1)	1 (<1)
	Surgery - Digestive system	1 (<1)	1 (<1)	0
	Surgery - Respiratory system	1 (<1)	1 (<1)	0
	Surgery - Vascular (extracardiac) system	1 (<1)	1 (<1)	0
Symptoms, signs and abnormal clinical and laboratory findings, NEC	Other symptoms and signs involving the digestive system and abdomen	32 (2)	21 (3)	11 (1)
	Pain in throat and chest	32 (2)	14 (2)	18 (2)
	Abdominal and pelvic pain	28 (2)	17 (2)	11 (1)
	Abnormal serum enzyme levels	23 (1)	15 (2)	8 (1)
	Other ill-defined and unspecified causes of mortality	22 (1)	9 (1)	13 (2)

Table 54: LIPS Adverse Events Resulting in Study Drug Discontinuation (including MACE)

		Treatment		
		All	Fluvastatin	Placebo
	Malaise and fatigue	16 (1)	11 (1)	5 (1)
	Nausea and vomiting	15 (1)	9 (1)	6 (1)
	Abnormalities of breathing	14 (1)	5 1)	9 (1)
	Dizziness and giddiness	8 (<1)	4 (<1)	4 (<1)
	Symptoms & signs concerning food & fluid intake	7 (<1)	4 (<1)	3 (<1)
	Other sudden death, cause unknown	6 (<1)	4 (<1)	2 (<1)
	Headache	5 (<1)	1 (<1)	4 (<1)
	Rash and other nonspecific skin eruption	5 (<1)	1 (<1)	4 (<1)
	Syncope and collapse	5 (<1)	3 (<1)	2 (<1)
	Heartburn	4 (<1)	3 (<1)	1 (<1)
	Abnormalities of heart beat	3 (<1)	1 (<1)	2 (<1)
	Disturbances of smell and taste	3 (<1)	3 (<1)	0
	Oedema, NEC	3 (<1)	1 (<1)	2 (<1)
	Other symptoms and signs involving the circulatory and respiratory systems	3 (<1)	0	3 (<1)
	Abnormal blood-pressure reading, w/o diagnosis	2 (<1)	1 (<1)	1 (<1)
	Elevated blood glucose level	2 (<1)	2 (<1)	0
	Fever of unknown origin	2 (<1)	2 (<1)	0
	Shock, NEC	2 (<1)	0	2 (<1)
	Symptoms and signs involving emotional state	2 (<1)	2 (<1)	0
	Abnormal involuntary movements	1 (<1)	1 (<1)	0
	Abnormal results of function studies	1 (<1)	1 (<1)	0
	Abnormality of red blood cells	1 (<1)	1 (<1)	0
	Dysphagia	1 (<1)	1 (<1)	0
	Elevated erythrocyte sedimentation rate and abnormality of plasma viscosity	1 (<1)	1 (<1)	0
	Flatulence and related conditions	1 (<1)	0	1 (<1)
	Gangrene, NEC	1 (<1)	1 (<1)	0
	Haemorrhage from respiratory passages	1 (<1)	0	1 (<1)
	Hyperhidrosis	1 (<1)	0	1 (<1)
	Other general symptoms and signs	1 (<1)	0	1 (<1)
	Somnolence, stupor and coma	1 (<1)	0	1 (<1)
	Unknown and unspecified causes of morbidity	1 (<1)	1 (<1)	0
	Unspecified haematuria	1 (<1)	0	1 (<1)
	Unspecified jaundice	1 (<1)	1 (<1)	0
	Unspecified urinary incontinence	1 (<1)	1 (<1)	0
	Voice disturbances	1 (<1)	0	1 (<1)

D. Serious Adverse Events

All Serious Adverse Events are summarized in the following table

Table 55: LIPS All Serious Adverse Events

			Treatment	
		All	Fluvastatin	Placebo
Safety Population, n =		1640	822	817
Body System	**AE Preferred Term**	**n (%)**	**n (%)**	**n (%)**
Infectious and parasitic diseases	Diarrhea and gastroenteritis of presumed infectious origin	8 (<1)	4 (<1)	4 (<1)
	Other septicaemia	3 (<1)	2 (<1)	1 (<1)
	Aspergillosis	2 (<1)	0	2 (<1)
	Bacterial infection of unspecified site	1 (<1)	0	1 (<1)
	Other and unspecified infectious diseases	1 (<1)	0	1 (<1)
	Other rickettsioses	1 (<1)	0	1 (<1)
	Other salmonella infections	1 (<1)	0	1 (<1)
	Strongyloidiasis	1 (<1)	0	1 (<1)
	Unspecified malaria	1 (<1)	0	1 (<1)
Blood, Blood-forming organs, & Immune Mechanism	Iron deficiency anemia	3 (<1)	2 (<1)	1 (<1)
	Other anemias	3 (<1)	2 (<1)	1 (<1)
	Purpura and other haemorrhagic conditions	2 (<1)	0	2 (<1)
	Vitamin B12 deficiency anemia	1 (<1)	1 (<1)	0
Circulatory System	Angina pectoris	323 (20)	149 (18)	174 (21)
	Acute myocardial infarction	70 (4)	29 (4)	41 (5)
	Chronic ischaemic heart disease	70 (4)	27 (4)	43 (5)
	Other peripheral vascular diseases	17 (1)	8(1)	9 (1)
	Atrial fibrillation and flutter	15 (1)	9 (1)	6 (1)
	Heart failure	15 (1)	6 (1)	9 (1)
	Stroke, not specified as haemorrhage or infarction	14 (1)	5 (1)	9 (1)
	Cardiac arrest	10 (1)	4 (<1)	6 (1)
	Essential (primary) hypertension	8 (<1)	4 (<1)	4 (<1)
	Aortic aneurysm and dissection	6 (<1)	2 (<1)	4 (<1)
	Other cardiac arrhythmias	6 (<1)	0	6 (1)
	Pulmonary embolism	6 (<1)	4 (<1)	2 (<1)
	Atrioventricular and left bundle-branch block	5 (<1)	3 (<1)	2 (<1)
	Other diseases of pericardium	5 (<1)	2 (<1)	3 (<1)
	Phlebitis and thrombophlebitis	5 (<1)	3 (<1)	2 (<1)
	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction	4 (<1)	3 (<1)	1 (<1)
	Haemorrhoids	3 (<1)	1 (<1)	2 (<1)
	Other disorders of arteries and arterioles	3 (<1)	2 (<1)	1 (<1)
	Atherosclerosis	2 (<1)	0	2 (<1)
	Hypotension	2 (<1)	2 (<1)	0
	Other aneurysm	2 (<1)	1 (<1)	1 (<1)
	Paroxysmal tachycardia	2 (<1)	2 (<1)	0
	Arterial embolism and thrombosis	1 (<1)	1 (<1)	0
	Cerebral infarction	1 (<1)	1 (<1)	0
	Hypertensive heart disease	1 (<1)	1 (<1)	0
	Hypertensive renal disease	1 (<1)	0	1 (<1)
	Nonrheumatic aortic valve disorders	1 (<1)	1 (<1)	0

Table 55: LIPS All Serious Adverse Events

		All	Treatment	
			Fluvastatin	Placebo
	Other cerebrovascular diseases	1 (<1)	0	1 (<1)
	Other conduction disorders	1 (<1)	0	1 (<1)
	Other nontraumatic intracranial haemorrhage	1 (<1)	0	1 (<1)
	Other venous embolism and thrombosis	1 (<1)	0	1 (<1)
Digestive System	Other diseases of digestive system	14 (1)	6 (1)	8 (1)
	Inguinal hernia	11 (1)	2 (<1)	9 (1)
	Cholelithiasis	7 (<1)	2 (<1)	5 (1)
	Gastritis and duodenitis	6 (<1)	3 (<1)	3 (<1)
	Gastric ulcer	4 (<1)	4 (<1)	0
	Other noninfective gastroenteritis and colitis	4 (<1)	3 (<1)	1 (<1)
	Cholecystitis	3 (<1)	1 (<1)	2 (<1)
	Diverticular disease of intestine	3 (<1)	1 (<1)	2 (<1)
	Esophagitis	3 (<1)	2 (<1)	1 (<1)
	Unspecified appendicitis	3 (<1)	1 (<1)	2 (<1)
	Diseases of salivary glands	2 (<1)	2 (<1)	0
	Fissure and fistula of anal and rectal regions	2 (<1)	1 (<1)	1 (<1)
	Other inflammatory liver diseases	2 (<1)	1 (<1)	1 (<1)
	Paralytic ileus & intestinal obstruction w/o hernia	2 (<1)	1 (<1)	1 (<1)
	Unspecified hernia of abdominal cavity	2 (<1)	1 (<1)	1 (<1)
	Ventral hernia	2 (<1)	1 (<1)	1 (<1)
	Acute appendicitis	1 (<1)	0	1 (<1)
	Acute pancreatitis	1 (<1)	0	1 (<1)
	Diaphragmatic hernia	1 (<1)	0	1 (<1)
	Duodenal ulcer	1 (<1)	0	1 (<1)
	Gastro-oesophageal reflux disease	1 (<1)	0	1 (<1)
	Other diseases of anus and rectum	1 (<1)	1 (<1)	0
	Other diseases of intestine	1 (<1)	1 (<1)	0
	Other diseases of pancreas	1 (<1)	0	1 (<1)
	Other diseases of stomach and duodenum	1 (<1)	1 (<1)	0
	Other functional intestinal disorders	1 (<1)	0	1 (<1)
	Peptic ulcer, site unspecified	1 (<1)	0	1 (<1)
	Ulcerative colitis	1 (<1)	1 (<1)	0
	Vascular disorders of intestine	1 (<1)	1 (<1)	0
Ear and Mastoid Process	Cholesteatoma of middle ear	1 (<1)	1 (<1)	0
	Disorders of vestibular function	1 (<1)	1 (<1)	0
	Otalgia and effusion of ear	1 (<1)	0	1 (<1)
Eye and Adnexa	Other cataract	6 (<1)	2 (<1)	4 (<1)
	Disorders of globe	1 (<1)	0	1 (<1)
	Paralytic strabismus	1 (<1)	0	1 (<1)
	Retinal vascular occlusions	1 (<1)	0	1 (<1)
Genitourinary System	Hyperplasia of prostate	10 (1)	2 (<1)	8 (1)
	Other disorders of urinary system	7 (<1)	4 (<1)	3 (<1)
	Calculus of kidney and ureter	3 (<1)	1 (<1)	2 (<1)
	Unspecified renal failure	3 (<1)	1 (<1)	2 (<1)
	Hydrocele and spermatocele	2 (<1)	0	2 (<1)
	Inflammatory diseases of prostate	2 (<1)	0	2 (<1)
	Orchitis and epididymitis	2 (<1)	2 (<1)	0
	Tubulo-interstitial nephritis, not specified as acute or chronic	2 (<1)	2 (<1)	0

Table 55: LIPS All Serious Adverse Events

			Treatment	
		All	Fluvastatin	Placebo
	Acute renal failure	1 (<1)	0	1 (<1)
	Calculus of lower urinary tract	1 (<1)	1 (<1)	0
	Chronic renal failure	1 (<1)	1 (<1)	0
	Obstructive and reflux uropathy	1 (<1)	0	1 (<1)
	Other disorders of male genital organs	1 (<1)	0	1 (<1)
	Other disorders of penis	1 (<1)	1 (<1)	0
	Unspecified renal colic	1 (<1)	1 (<1)	0
	Urethral stricture	1 (<1)	0	1 (<1)
Musculoskeletal System & Connective Tissue	Dorsalgia	4 (<1)	0	4 (<1)
	Other intervertebral disc disorders	4 (<1)	2 (<1)	2 (<1)
	Coxarthrosis [arthrosis of hip]	2 (<1)	1 (<1)	1 (<1)
	Gonarthrosis [arthrosis of knee]	2 (<1)	2 (<1)	0
	Other joint disorders, not elsewhere classified	2 (<1)	1 (<1)	1 (<1)
	Other rheumatoid arthritis	2 (<1)	1 (<1)	1 (<1)
	Pyogenic arthritis	2 (<1)	1 (<1)	1 (<1)
	Shoulder lesions	2 (<1)	1 (<1)	1 (<1)
	Osteomyelitis	1 (<1)	1 (<1)	0
	Other arthritis	1 (<1)	1 (<1)	0
	Other arthrosis	1 (<1)	0	1 (<1)
	Other disorders of cartilage	1 (<1)	1 (<1)	0
	Other disorders of muscle	1 (<1)	1 (<1)	0
	Other dorsopathies, NEC	1 (<1)	1 (<1)	0
	Other enthesopathies	1 (<1)	0	1 (<1)
	Other inflammatory spondylopathies	1 (<1)	1 (<1)	0
	Other soft tissue disorders, NEC	1 (<1)	1 (<1)	0
	Spondylosis	1 (<1)	1 (<1)	0
Nervous System	Transient cerebral ischemic attacks and related syndromes	10 (1)	8 (1)	2 (<1)
	Epilepsy	2 (<1)	1 (<1)	1 (<1)
	Hemiplegia	2 (<1)	0	2 (<1)
	Disorders of autonomic nervous system	1 (<1)	0	1 (<1)
	Hydrocephalus	1 (<1)	1 (<1)	0
	Other degenerative diseases of nervous system, NEC	1 (<1)	0	1 (<1)
	Other myopathies	1 (<1)	1 (<1)	0
	Spinal muscular atrophy and related syndromes	1 (<1)	1 (<1)	0
Respiratory System	Pneumonia, organism unspecified	22	10 (1)	12 (1)
	Pulmonary edema	7 (<1)	1 (<1)	6 (1)
	Other chronic obstructive pulmonary disease	5 (<1)	2 (<1)	3 (<1)
	Other respiratory disorders	5 (<1)	1 (<1)	4 (<1)
	Unspecified acute lower respiratory infection	5 (<1)	1 (<1)	4 (<1)
	Acute bronchitis	4 (<1)	1 (<1)	3 (<1)
	Bronchitis, not specified as acute or chronic	2 (<1)	2 (<1)	0
	Respiratory failure, NEC	2 (<1)	2 (<1)	0
	Asthma	1 (<1)	0	1 (<1)
	Bacterial pneumonia, NEC	1 (<1)	0	1 (<1)
	Chronic laryngitis and laryngotracheitis	1 (<1)	1 (<1)	0
	Influenza due to identified influenza virus	1 (<1)	0	1 (<1)
	Other interstitial pulmonary diseases	1 (<1)	0	1 (<1)

Table 55: LIPS All Serious Adverse Events

			Treatment	
		All	Fluvastatin	Placebo
	Other pleural conditions	1 (<1)	0	1 (<1)
	Pleural effusion, not elsewhere classified	1 (<1)	0	1 (<1)
	Pneumothorax	1 (<1)	0	1 (<1)
Skin and Subcutaneous Tissue	Pemphigus	1 (<1)	1 (<1)	0
Endocrine, nutritional and metabolic diseases	Other disorders of pancreatic internal secretion	3 (<1)	1 (<1)	2 (<1)
	Unspecified diabetes mellitus	3 (<1)	1 (<1)	2 (<1)
	Disorders of lipoprotein metabolism & other lipidemias	1 (<1)	0	1 (<1)
	Insulin-dependent diabetes mellitus	1 (<1)	0	1 (<1)
	Other disorders of fluid, electrolyte and acid-base balance	1 (<1)	0	1 (<1)
	Other metabolic disorders	1 (<1)	0	1 (<1)
	Thyrotoxicosis [hyperthyroidism]	1 (<1)	0	1 (<1)
	Volume depletion	1 (<1)	1 (<1)	0
External causes of morbidity and mortality	Intentional self-harm by unspecified means	1 (<1)	1 (<1)	0
	Motor- or nonmotor-vehicle accident, type of vehicle unspecified	1 (<1)	1 (<1)	0
	Other and unspecified firearm discharge, undetermined intent	1 (<1)	0	1 (<1)
Factors influencing health status and contact with health services	Adjustment and management of implanted device	7 (<1)	1 (<1)	6 (1)
	Follow-up examination after treatment for conditions other than malignant neoplasms	3 (<1)	3 (<1)	0
	Contraceptive management	1 (<1)	1 (<1)	0
	Medical observation and evaluation for suspected diseases and conditions	1 (<1)	1 (<1)	0
	Other surgical follow-up care	1 (<1)	0	1 (<1)
Injury, poisoning and certain other consequences of external causes	Fracture of femur	4 (<1)	2 (<1)	2 (<1)
	Dislocation, sprain and strain of joint and ligaments of hip	3 (<1)	0	3 (<1)
	Fracture of shoulder and upper arm	3 (<1)	1 (<1)	2 (<1)
	Complications of other internal prosthetic devices, implants and grafts	2 (<1)	1 (<1)	1 (<1)
	Fracture of foot, except ankle	2 (<1)	1 (<1)	1 (<1)
	Fracture of lower leg, including ankle	2 (<1)	0	2 (<1)
	Injury of unspecified of body	2 (<1)	1 (<1)	1 (<1)
	Other complications of surgical & medical care, NEC	2 (<1)	0	2 (<1)
	Adverse effects, NEC	1 (<1)	0	1 (<1)
	Certain early complications of trauma, NEC	1 (<1)	1 (<1)	0
	Complications of cardiac and vascular prosthetic devices, implants and grafts	1 (<1)	0	1 (<1)
	Complications of internal orthopedic prosthetic devices, implants and grafts	1 (<1)	0	1 (<1)
	Complications of procedures, NEC	1 (<1)	0	1 (<1)
	Dislocation, sprain and strain of joints and ligaments of shoulder girdle	1 (<1)	0	1 (<1)
	Fracture of forearm	1 (<1)	1 (<1)	0
	Fracture of lumbar spine and pelvis	1 (<1)	1 (<1)	0
	Fracture of skull and facial bones	1 (<1)	1 (<1)	0

Table 55: LIPS All Serious Adverse Events

			Treatment	
		All	Fluvastatin	Placebo
	Fracture of spine, level unspecified	1 (<1)	1 (<1)	0
	Injury of muscle and tendon at hip and thigh level	1 (<1)	1 (<1)	0
	Intracranial injury	1 (<1)	1 (<1)	0
	Other and unspecified injuries of head	1 (<1)	0	1 (<1)
	Other and unspecified injuries of wrist and hand	1 (<1)	0	1 (<1)
	Toxic effect of contact with venomous animals	1 (<1)	1 (<1)	0
Mental and behavioural disorders	Mental and behavioural disorders due to use of alcohol	2 (<1)	1 (<1)	1 (<1)
	Other anxiety disorders	2 (<1)	0	2 (<1)
	Depressive episodes	1 (<1)	1 (<1)	0
	Recurrent depressive disorder	1 (<1)	1 (<1)	0
Neoplasms	Malignant neoplasm of prostate	11 (1)	9 (1)	2 (<1)
	Malignant neoplasm of bronchus and lung	8 (<1)	6 (1)	2 (<1)
	Malignant neoplasm of colon	7 (<1)	2 (<1)	5 (1)
	Malignant neoplasm of larynx	5 (<1)	0	5 (1)
	Malignant neoplasm of breast	3 (<1)	1 (<1)	2 (<1)
	Neoplasm of uncertain or unknown behaviour of middle ear and respiratory and intrathoracic organs	3 (<1)	3 (<1)	0
	Neoplasm of uncertain or unknown behaviour of urinary organs	3 (<1)	2 (<1)	1 (<1)
	Other and unspecified types of non-Hodgkin's lymphoma	3 (<1)	2 (<1)	1 (<1)
	Secondary malignant neoplasm of other sites	3 (<1)	3 (<1)	0
	Malignant neoplasm of brain	2 (<1)	0	2 (<1)
	Malignant neoplasm of kidney, except renal pelvis	2 (<1)	1 (<1)	1 (<1)
	Malignant neoplasm of pancreas	2 (<1)	2 (<1)	0
	Malignant neoplasm of rectum	2 (<1)	0	2 (<1)
	Malignant neoplasm of stomach	2 (<1)	1 (<1)	1 (<1)
	Neoplasm of uncertain or unknown behaviour of brain and central nervous system	2 (<1)	0	2 (<1)
	Other malignant neoplasms of skin	2 (<1)	0	2 (<1)
	Secondary malignant neoplasm of respiratory and digestive organs	2 (<1)	0	2 (<1)
	Benign neoplasm of other and ill-defined parts of digestive system	1 (<1)	1 (<1)	0
	Benign neoplasm of other and unspecified sites	1 (<1)	1 (<1)	0
	Malignant neoplasm of anus and anal canal	1 (<1)	0	1 (<1)
	Malignant neoplasm of bladder	1 (<1)	0	1 (<1)
	Malignant neoplasm of corpus uteri	1 (<1)	1 (<1)	0
	Malignant neoplasm of heart, mediastinum and pleura	1 (<1)	0	1 (<1)
	Malignant neoplasm of liver and intrahepatic bile ducts	1 (<1)	0	1 (<1)
	Malignant neoplasm of esophagus	1 (<1)	1 (<1)	0
	Malignant neoplasm of other and ill-defined digestive organs	1 (<1)	0	1 (<1)
	Malignant neoplasm of other and ill-defined sites	1 (<1)	1 (<1)	0
	Malignant neoplasm of other and unspecified parts of mouth	1 (<1)	0	1 (<1)
	Malignant neoplasm of other and unspecified parts	1 (<1)	0	1 (<1)

Table 55: LIPS All Serious Adverse Events

		All	Treatment	
			Fluvastatin	Placebo
	of tongue			
	Malignant neoplasm of other and unspecified urinary organs	1 (<1)	1 (<1)	0
	Malignant neoplasm of other connective and soft tissue	1 (<1)	0	1 (<1)
	Malignant neoplasm of ovary	1 (<1)	1 (<1)	0
	Malignant neoplasm of rectosigmoid junction	1 (<1)	0	1 (<1)
	Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system	1 (<1)	0	1 (<1)
	Malignant neoplasm of thymus	1 (<1)	0	1 (<1)
	Malignant neoplasm without specification of site	1 (<1)	1 (<1)	0
	Multiple myeloma and malignant plasma cell neoplasms	1 (<1)	1 (<1)	0
	Neoplasm of uncertain or unknown behaviour of endocrine glands	1 (<1)	1 (<1)	0
	Neoplasm of uncertain or unknown behaviour of oral cavity and digestive organs	1 (<1)	0	1 (<1)
	Neoplasm of uncertain or unknown behaviour of other and unspecified sites	1 (<1)	1 (<1)	0
Surgical procedures	Surgery - Cardiac - TCT	53 (3)	23 (3)	30 (4)
	Surgery - Cardiac – other cardiac procedures	31 (2)	14 (2)	17 (2)
	Surgery - Cardiac – CABG	21 (1)	7 (<1)	14 (2)
	Surgery - Digestive system	9 (1)	4 (<1)	5 (1)
	Surgery – Genitourinary system	8 (<1)	5 (1)	3 (<1)
	Surgery – Musculoskeletal system and connective tissue	7 (<1)	4 (<1)	3 (<1)
	Surgery - Vascular (extracardiac) system	5 (<1)	2 (<1)	3 (<1)
	Surgery - Endocrine, nutritional and metabolic diseases	2 (<1)	0	2 (<1)
	Surgery - Respiratory system	1 (<1)	0	1 (<1)
	Surgery - Skin and subcutaneous tissue	1 (<1)	0	1 (<1)
Symptoms, signs and abnormal clinical and laboratory findings, NEC	Pain in throat and chest	141 (9)	70 (9)	71 (9)
	Other ill-defined and unspecified causes of mortality	43 (3)	16 (2)	27 (3)
	Syncope and collapse	23 (1)	12 (1)	11 (1)
	Abnormalities of breathing	22 (1)	10 (1)	12 (1)
	Abdominal and pelvic pain	21 (1)	10 (1)	11 (1)
	Abnormalities of heart beat	11 (1)	6 (1)	5 (1)
	Malaise and fatigue	9 (1)	6 (1)	3 (<1)
	Other sudden death, cause unknown	8 (<1)	5 (1)	3 (<1)
	Nausea and vomiting	6 (<1)	5 (1)	1 (<1)
	Fever of unknown origin	5 (<1)	3 (<1)	2 (<1)
	Other symptoms and signs involving the circulatory and respiratory systems	5 (<1)	1 (<1)	4 (<1)
	Abnormal serum enzyme levels	4 (<1)	3 (<1)	1 (<1)
	Dizziness and giddiness	4 (<1)	2 (<1)	2 (<1)
	Abnormal results of function studies	3 (<1)	1 (<1)	2 (<1)
	Shock, not elsewhere classified	2 (<1)	0	2 (<1)
	Abnormal blood-pressure reading, without diagnosis	1 (<1)	1 (<1)	0

Table 55: LIPS All Serious Adverse Events

			Treatment	
		All	Fluvastatin	Placebo
	Abnormal involuntary movements	1 (<1)	0	1 (<1)
	Cough	1 (<1)	1 (<1)	0
	Dysphagia	1 (<1)	1 (<1)	0
	Elevated blood glucose level	1 (<1)	1 (<1)	0
	Elevated erythrocyte sedimentation rate and abnormality of plasma viscosity	1 (<1)	1 (<1)	0
	Gangrene, not elsewhere classified	1 (<1)	1 (<1)	0
	Hemorrhage from respiratory passages	1 (<1)	0	1 (<1)
	Hyperhidrosis	1 (<1)	0	1 (<1)
	Other abnormal findings of blood chemistry	1 (<1)	1 (<1)	0
	Other lack of coordination	1 (<1)	0	1 (<1)
	Other symptoms and signs involving the digestive system and abdomen	1 (<1)	0	1 (<1)
	Rash and other nonspecific skin eruption	1 (<1)	0	1 (<1)
	Retention of urine	1 (<1)	0	1 (<1)
	Somnolence, stupor and coma	1 (<1)	0	1 (<1)
	Symptoms and signs concerning food and fluid intake	1 (<1)	1 (<1)	0
	Unknown and unspecified causes of morbidity	1 (<1)	1 (<1)	0
	Unspecified urinary incontinence	1 (<1)	1 (<1)	0

E. Laboratory Abnormalities

1. Patients with Notable ALT Elevations

Table 56: LIPS Patients with Notable ALT Elevations**

Patient #	Treatment	Sex M/F	Visit	ALT Result (U/L)	X ULN*
	Fluvastatin			69	1.53
				52	1.16
				155	3.44
	Fluvastatin			60	1.33
				200	4.44
				170	3.78
	Fluvastatin			57	1.27
				45	1.00
				52	1.16
				95	2.11
				94	2.09
				73	1.62
				106	2.36
				138	3.07
				177	3.93
				162	3.60
				131	2.91
				90	2.00
	Fluvastatin			32	0.71
				97	2.16
				46	1.02
				212	4.71
				169	3.76
				139	3.09
				153	3.40
	Fluvastatin			22	0.49
				137	3.04
				214	4.76
				91	2.02
				30	0.67
	Fluvastatin			52	1.16
				24	0.53
				492	10.93
				278	6.18
				32	0.71
				17	0.38
	Placebo			12	0.27
				283	6.29
	Placebo			39	0.87
				41	0.91
				78	1.73
				165	3.67
	Placebo			98	2.18
				80	1.78

	47	1.04
	63	1.40
	63	1.40
	68	1.51
	90	2.00
	68	1.51
	152	3.38
	144	3.20
Placebo	46	1.02
	33	0.73
	22	0.49
	32	0.71
	42	0.93
	71	1.58
	105	2.33
	113	2.51
	70	1.56
	138	3.07
Placebo	117	2.60
	146	3.24
	99	2.20
	77	1.71
	95	2.11
	158	3.51
Fluvastatin	35	0.78
	121	2.69
	342	7.60
	297	6.60
	34	0.76
Fluvastatin	91	2.02
	251	5.58
Fluvastatin	69	1.53
	24	0.53
	277	6.16
	466	10.36
Fluvastatin	76	1.69
	32	0.71
	76	1.69
	153	3.40
Placebo	27	0.60
	57	1.27
	146	3.24
	142	3.16
	110	2.44
	163	3.62
	123	2.73
	73	1.62
	45	1.00
	42	0.93
	38	0.84
	49	1.09
	64	1.42

Fluvastatin	53	1.18
	49	1.09
	54	1.20
	39	0.87
	151	3.36
	164	3.64
	47	1.04
	39	0.87
Fluvastatin	12	0.27
	20	0.44
	200	4.44
	185	4.11
	74	1.64
	60	1.33
	67	1.49
	41	0.91
	128	2.84
	-	-
	22	0.49
Placebo	15	0.33
	22	0.49
	174	3.87
Fluvastatin	50	1.11
	48	1.07
	49	1.09
	42	0.93
	55	1.22
	35	0.78
	42	0.93
	77	1.71
	43	0.96
	163	3.62
Fluvastatin	21	0.47
	17	0.38
	20	0.44
	25	0.56
	155	3.44
	147	3.27
	173	3.84
	53	1.18
	38	0.84
Fluvastatin	57	1.27
	47	1.04
	23	0.51
	26	0.58
	43	0.96
	72	1.60
	47	1.04
	89	1.98
	147	3.27

*Notable defined as 3 X ULN on 2 occasions (or 1 occasion if no f/u available)
**ULN = 45 U/L

2. Patients with Notable AST Elevations

Table 57: LIPS Patients with Notable AST Elevations

Patient #	Treatment	Sex M/F	Visit	AST Result (U/L)	X ULN*
	Fluvastatin			44	1.07
				59	1.44
				145	3.54
	Fluvastatin			37	0.90
				29	0.71
				345	8.41
				192	4.68
				39	0.95
				31	0.76
	Placebo			18	0.44
				190	4.63
	Placebo			106	2.59
				125	3.05
				83	2.02
				77	1.88
				108	2.63
				211	5.15
	Fluvastatin			27	0.66
				64	1.56
				180	4.39
				134	3.27
				30	0.73
	Fluvastatin			53	1.29
				134	3.27
	Fluvastatin			40	0.98
				20	0.49
				132	3.22
				213	5.20
	Placebo			15	0.37
				16	0.39
				18	0.44
				10	0.24
				18	0.44
				22	0.54
				341	8.32
				152	3.71
				92	2.24
				176	4.29
				106	2.59
	Fluvastatin			14	0.34
				22	0.54
				190	4.63
				144	3.51
				47	1.15
				115	2.80
				67	1.63
				33	0.80
				147	3.59

					0.46

*ULN = 41 U/L

3. Patients with Notable CK Elevations

Table 58: LIPS Patients with Notable CK Elevations**

Patient #	Treatment	Sex M/F	Visit	CK Result (U/L)	X ULN*
	Placebo			20	0.09
				106	0.46
				34	0.15
				36	0.16
				28	0.12
				2498	10.77
				37	0.16
	Placebo			59	0.25
				138	0.59
				239	1.03
				325	1.40
				328	1.41
				259	1.12
				332	1.43
				9240	39.83
				214	0.92
				243	1.05
	Placebo			46	0.20
				64	0.28
				119	0.51
				156	0.67
				3868	16.67
				1973	8.50
				113	0.49
				151	0.65
				111	0.48

*Notable defined as 10 X ULN
**ULN = 232 U/L

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/s/

Anne Pariser
5/12/03 03:28:36 PM
MEDICAL OFFICER

Mary Parks
5/13/03 12:11:35 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-261/S-033
NDA 21-192/S-005

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

1. ORGANIZATION CDER/HFD-510 Division of Metabolism and Endocrine Drug Products	**2. NDA #** 21-192 Original NDA approved: 06-OCT-2000
3. NAME AND ADDRESS OF APPLICANT Novartis Pharmaceuticals Corp. 59 Route 10 East Hanover, NJ 07936 (Phone): 973-781-7500	**4. SUPPLEMENT** SE1-005 31-JUL-2002 (Rec. 01-AUG-2002)
	5. Name of the Drug Lescol™ XL Tablets
	6. Nonproprietary Name Fluvastatin sodium
7. SUPPLEMENT PROVIDES for a label change to include risk reduction of major adverse cardiac events in patients with coronary heart disease	**8. AMENDMENT** --

9. PHARMACOLOGICAL CATEGORY	**10. HOW DISPENSED**	**11. RELATED**
Lipid-lowering agent	Oral	-N. A. -
12. DOSAGE FORM Tablet	**13. POTENCY** 10mg, 20mg and 40mg	

14. CHEMICAL NAME AND STRUCTURE

[*R*
*
,*S**-(*E*)] -(±)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1*H*-
-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid, monosodium salt.
$C_{24}H_{25}FNO4 \cdot Na$, MW = 433.46

15. COMMENTS No additional CMC information is provided for by this supplement. A categorical exclusion to prepare an Environmental Assessment is requested. The information provided for in this supplement also applies to NDA 20-261 S-033 Lescol Capsules.

16. CONCLUSIONS AND RECOMMENDATIONS From the Chemistry point of view, the waiver to prepare an Environmental Assessment is acceptable and this supplement can be approved. Issue Approval letter.

17. REVIEWER NAME (AND SIGNATURE) **DATE**
COMPLETED 25-SEPT-2002
Sharon Kelly, PhD
R/D INITIATED BY

filename: 21192#005 NDA

DISTRIBUTION: Original: sNDA 21-192 cc: HFD-510 Division File CSO Reviewer

AP

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/s/

Sharon Kelly
9/25/02 01:17:58 PM
CHEMIST

Stephen Moore
9/25/02 01:24:29 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-261/S-033
NDA 21-192/S-005

PHARMACOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY EVALUATION

NDA number: 20-261
Review number: 1
Sequence number/date/type of submission: SE1 033; 8/2/02
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Novartis
Manufacturer for drug substance : Novartis

Reviewer name: Karen Davis-Bruno; Ph.D.
Division name: DMEDP
HFD #: 510
Review completion date: 8/12/02

Drug:
Trade name: Lescol
Generic name (list alphabetically): fluvastatin sodium

Drug class: HMG reductase inhibitor (statin)

Indication: hypercholesterolemia (approved), indicated to reduce cardiovascular events

Clinical formulation: capsules

Route of administration: oral

This supplemental NDA is submitted to support the safe and effective use of Lescol and Lescol XL to reduce the risk of maior adverse cardiac events in patients with The data contained within the application are based on the results of the Lescol Intervention prevention Study (LIPS). Patients receive Lescol capsules 80 mg/day (40 mg BID) or placebo following their first PCI. The primary endpoint is to evaluate the time to first major adverse cardiac events; cardiovascular death, non-fatal MI, re-intervention defined as CABG surgery or repeated PCI. Since this application contains only clinical study data without any additional non-clinical data, a pharmacology/toxicology review is not needed. This proposed change in indication does not affect the Carcinogenicity, Reproductive (fertility, pregnancy) or Mutagenicity sections of the label.

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/s/

Karen Davis-Bruno
8/12/02 03:50:04 PM
PHARMACOLOGIST

PHARMACOLOGY/TOXICOLOGY EVALUATION

NDA number: 21192
Review number: 1
Sequence number/date/type of submission: SE1 005; 8/2/02
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Novartis
Manufacturer for drug substance : Novartis

Reviewer name: Karen Davis-Bruno; Ph.D.
Division name: DMEDP
HFD #: 510
Review completion date: 8/12/02

Drug:

Trade name: Lescol XL
Generic name (list alphabetically): fluvastatin sodium extended release

Drug class: HMG reductase inhibitor (statin)

Indication: hypercholesterolemia (approved), indicated to reduce cardiovascular events

Clinical formulation: capsules

Route of administration: oral

This supplemental NDA is submitted to support the safe and effective use of Lescol and Lescol XL to reduce the risk of major adverse cardiac events in patients with

The data contained within the application are based on the results of the Lescol Intervention prevention Study (LIPS). Patients receive Lescol capsules 80 mg/day (40 mg BID) or placebo following their first PCI. The primary endpoint is to evaluate the time to first major adverse cardiac events; cardiovascular death, non-fatal MI, re-intervention defined as CABG surgery or repeated PCI. Since this application contains only clinical study data without any additional non-clinical data, a pharmacology/toxicology review is not needed. This proposed change in indication does not affect the Carcinogenicity, Reproductive (fertility, pregnancy) or Mutagenicity sections of the label.

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/s/

Karen Davis-Bruno
8/12/02 03:45:29 PM
PHARMACOLOGIST
P/T review NN

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-261/S-033
NDA 21-192/S-005

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	20-261/SE1-033 and 21-192/SE1-005
Name of drug:	Lescol/Lescol XL 40 mg bid
Applicant:	Novartis Pharmaceuticals Corporation
Indication:	Risk reduction of major adverse cardiac effects
Documents reviewed	Statistical Volume 1 of 18
Project manager:	Margaret Simoneau (HFD-510)
Clinical reviewer:	Anne Pariser, M.D. (HFD-510)
Dates:	Received 02 August 2002
Statistical reviewer:	David Hoberman, Ph.D. (HFD-715)
Statistics team leader and secondary reviewer:	Todd Sahlroot, Ph.D. (HFD-715).
Biometrics division director:	S. Edward Nevius, Ph.D. (HFD-715)

Keywords: clinical studies, NDA review, one study application, multiple endpoints

Background

The sponsor has submitted one randomized, placebo-controlled, double-blind, multi-center trial.

The LIPS trial (Lescol Intervention Prevention Study) enrolled a total of 1677 patients in 57 interventional centers from 10 countries, all in Western Europe except for Canada and Brazil.

Design

The *primary clinical endpoint* was MACE-free survival where MACE was a *composite* of 1) cardiac death, 2) non-fatal MI, or 3) revascularization or repeat PCI of index legion(s) or new lesions, or CABG. Eligible patients were those with 1) a total cholesterol between 135 and 240 mg/dL with fasting TG level <400 mg/dL and 2) any type of recent PCI. **Patients with prior interventions were excluded**. The planned patient accrual period was 1 year with a follow up period of 3 years. Thus patients were to be treated for up to 4 years.

The sample size of 850 patients/group was based on 90% power with 5% Type I error, assuming a 25% MACE incidence at 3 years in the placebo group and an 18.75% MACE incidence in the Lescol group.

The primary analysis of time to first MACE was tested using the stratified logrank test with interventional center as the stratification variable. Cox regression models were used in supplementary analyses within specified subgroups and for assessing the influence of demographic and various risk factors on time to first MACE. Covariates were age, ejection fraction, multiple vs single vessel disease, presence of diabetes, previous MI or not, and baseline total cholesterol.

Interim analyses were conducted at 1 and 2 years after the last patient was enrolled using the O'Brien-Fleming rule. The final analysis was to be done at approximately 3 years after the last patient was enrolled. As a result the final nominal alpha level is .046.

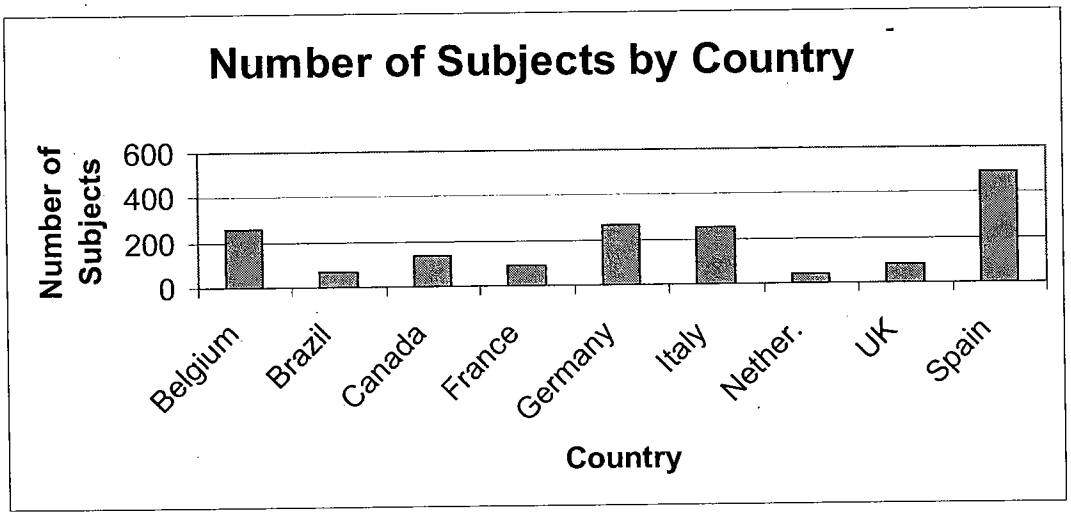
Results

A total of 1677 patients were randomized to the two treatment groups: N=844 Lescol, N=833 placebo. The mean age was 60 and 84% of the patients were male. According to the sponsor, 14.7% took non-study statin treatment in the Lescol group *at some time during the study*, while 31.3% did so in the placebo group.

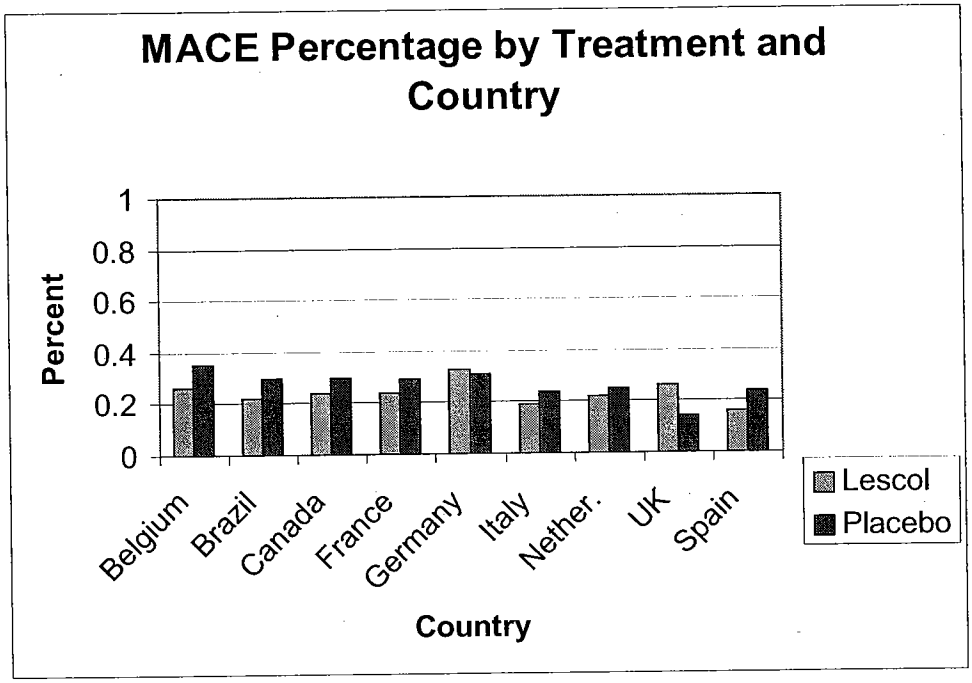
The primary analysis p-value for time to first MACE (stratified logrank) was .0127. The Cox regression using the specified covariates resulted in a p-value of .004. In addition, the sponsor computed p-values using Mantel-Haenszel tests for the various components of the MACE endpoint (See Medical Officer review).

Discussion

The figure below displays the number of enrolled subjects by country.



The treatment differences in the various countries were mostly consistent. The figure below displays the percentage of MACE in each group within countries:



In the UK and Germany, there was a reversal in the direction of treatment difference. We may regard a patient's outcome as one of possibly eight potential outcomes, each having 3 components: re-intervention or not, cardiac death or not, and non-fatal MI or not. Any subset of these 3 outcomes is possible. Obviously, the temporal order of some subsets is not free. Formally, let (C,R,M) be a vector standing for (cardiac death, re-intervention, non-fatal MI) where each symbol can be 0 or 1. Then we may examine the distribution of these vectors within each treatment group. For convenience, we can produce a table whose columns list only the events which the patient experienced.

Counts of combined events

	No Event	CRM	CR	RM	R	CM	C	M
Lescol	663	0	4	24	**139**	1	8	5
Placebo	611	2	4	25	**162**	0	18	11

Percentages of combined events

	No Event	CRM	CR	RM	R	CM	C	M
Lescol	78.6	0.0	0.5	2.8	**16.5**	0.1	1.0	0.5
Placebo	73.4	0.2	0.5	3.0	**19.5**	0.0	2.2	1.2

The table suggests that the overall p-value of .0127 is due to the **bolded** difference in patients who experienced *only* a re-intervention.

One of the uncontrolled features of the study was that patients could have interventions shortly after randomization. From previous studies, the sponsor concluded that re-interventions of the index lesion performed within 6 months would not be related to study medication. Of the 167 Lescol patients who received a re-intervention *at any time*, 56 (34%) were excluded by the 6 month 'rule'. In the placebo group, of the 193 patients who received a re-intervention *at any time*, 42 (22%) were excluded by the 6 month rule. Since the percentage of Lescol early re-interventions of the index lesion was 50% greater than the percentage of early re-interventions in the placebo group, excluding them from the analysis of MACE lowered the p-value to .0004.

Conclusion

The sponsor's analysis rejects the null hypothesis of no treatment difference at the .05 level. Since the endpoint is composite, the interpretation is not straightforward; but apparently, if there is indeed a benefit, it is due to a lower rate of re-interventions for those who take Lescol.

David Hoberman, Ph.D.
Mathematical Statistician

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/s/

Todd Sahlroot
5/27/03 10:08:23 AM
BIOMETRICS
Submitted for David Hoberman, the primary statistics reviewer

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-261/S-033
NDA 21-192/S-005

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

Time Sensitive Patent Information
Pursuant to 21 CFR 314.53
for
NDA 20-261 and NDA 21-192

The following is provided in accordance with the Drug Price Competition and Patent term Restoration Act of 1984:

Trade Name:	Lescol®	Lescol® XL
Active Ingredient:	Fluvastatin sodium	Fluvastatin sodium
Strengths:	20 mg, 40 mg	80 mg
Dosage form:	Capsules	Extended-release Tablet

US Patent Number	Expiration Date	Type of Patent	Name of Patent Owner
5,354,772	October 11, 2001	Composition/Use	Novartis Pharmaceuticals Corporation
5,356,896	December 12, 2011	Formulation	
6,242,003	April 13, 2020	Sustained Release Tablet Formulation	

The undersigned declares that the above stated US patent numbers cover the composition, formulation and/or method of use for Lescol capsules and Lescol XL extended-release tablets. These products are the subject of this application for which approval is being sought.

Signed _____ Date 7/31/02

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 8300

NOVARTIS

November 4, 2002

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

NDA 21-192
Lescol® XL (fluvastatin sodium)
Extended-Release Tablets

General Correspondence

Dear Dr. Orloff:

Reference is made to NDA 21-192 for Lescol® XL (fluvastatin sodium) extended-release tablets which was approved October 6, 2000.

The purpose of this submission is to supplement Section 13 of the Application, Patent information on any patent that claims the drug, with the following information:

United States Patent 6,242,003 issued June 5, 2001 and which will expire April 13, 2020.

This patent covers the sustained release tablet formulation for Lescol XL.

If you have any questions or comments, please contact me at (973) 781-3279.

Sincerely,

Lisa N. Pitt, PharmD
Associate Director
Drug Regulatory Affairs

Desk copies: Ms. Margaret Simoneau, HFD-510
Ms. Mary Ann Holovac, HFD-615 (via fax)

EXCLUSIVITY SUMMARY for NDA # 20-261/S-033 Lescol (fluvastatin sodium) Capsules and 21-192/S-005 Lescol XL (fluvastatin sodium) Extended-Release Tablets

Applicant Name Novartis Pharmaceuticals Corporation **HFD-510**

Approval Date May 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_x_/

   b) Is it an effectiveness supplement? YES /_x_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE-1

   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 /_ __/ NO /_x _/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_x_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /x/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 # 20-261 Lescol

NDA # 21-192 Lescol XL

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 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 9:**

(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 /__/ NO /_x__/

(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:

Investigation #1, Study # LIPS

Investigation #2, Study #

Investigation #3, Study #

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 /_ _/
Investigation #3	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:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(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 /_ _/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(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"):

Investigation #_1_, Study # _LIPS

Investigation #___, Study #

Investigation #__, Study #

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?

Please note: Studies were conducted under the NDA not IND.

Investigation #1	
IND # _____ YES /_ _/	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: _____

_____

_____

Margaret Simoneau
Signature of Preparer
Title: Reg Project Manager

May 20,2003
Date

Mary Parks, MD
Deputy Director, Medical Team Leader

May 21, 2003

Signature of Office or Division Director

Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

David Orloff
5/27/03 06:20:48 PM

Debarment Certification

NOVARTIS PHARMACEUTICALS CORPORATION certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.

Signed _____ Date 7/31/02

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See attached list which includes all	
	Principal Investigators	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Martin Bedigian MD	Sr Clinical Physician
FIRM/ORGANIZATION: Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936	
SIGNATURE: Martin Bedigian MD	DATE: 31-July-02

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

Created by Electronic Document Services/USDHHS: (301) 443-2454 EF

1. Financial Disclosure (FD) FDA Forms

- FDA Form 3454: Included with attached list of principal investigators

The following process was used to collect information:

- Letters were sent out to principal investigators of all "covered studies" requesting financial disclosure information. A synopsis of the Financial Disclosure Regulation and certification/disclosure forms was included with the letter. Principal investigators were instructed to provide information for themselves.
- A follow-up letter was sent to principal investigators. if no reply was received
- A signed financial disclosure form received from an investigator with none of the information boxes checked has been interpreted by Novartis to indicate that the investigator had no financial information to disclose
- At study close out and/or as part of retrospective collection the principal investigators were told to update Novartis for one year from last patient last visit. if the status of their financial disclosure changed
- Retrospective collection of financial disclosure information was applied for studies on going on 2/2/99

2. Description of Spreadsheets

The listing provided with this document detail all the principal investigators participating in studies conducted at non-US sites. The information is presented by country. center. principal investigator. study facility and address.

3. Summary of Findings

No principal investigators are full or part-time employees of Novartis Pharmaceuticals Corporation. No disclosable financial information was reported by any of the investigators participating in the trials on the attached listings.

Any bias resulting from these arrangements is minimized by independent data monitoring by Novartis: multiple investigators used in the studies and double-blind placebo controlled trials.

Retrospective collection of financial disclosure information was applied for studies LES EUR 01 because they were ongoing on 2/2/99.

Percent of Investigators who responded:)

- Study LES EUR 01 (Europe) 54% of investigators responded (54 PIs out of a total of 73)

16 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative-_____

Meeting Minutes

Division of Metabolic and Endocrine Drug Products

NDA 20-261/S-033 and NDA 21-192/S-005

Date: Tuesday, September 24, 2002
Location: Parklawn 14B45
Time: 2 to 3 PM
FDA Attendees:

Drs. Mary Parks and Anne Pariser, Todd Sahlroot, David Hoberman, Karen Davis-Bruno, Sang Chung, and Margaret Simoneau.

This was an efficacy supplement **filing meeting** for Lescol (fluvastatin sodium) capsules (NDA 20-261, S-033) and Lescol XL Extended-Release (fluvastatin sodium) tablets (NDA 21-192, S-005), submissions dated July 31, 2002. These supplements propose to add additional information to various sections of the Package Insert from the Lescol Intervention Prevention Study (LIPS).

- **Clinical**- Dr. Pariser is the primary medical reviewer. There were no filing issues and financial disclosure information was submitted.
- **Pharmacology**- Not needed.
- **Chemistry**- Sponsor requested a categorical exclusion from the requirements to prepare an Environmental Assessment.
- **Biopharm**- Not needed.
- **Biostatistics**- David Hoberman is the statistician for these supplements. There were no filing issues.
- **DSI**- No audit would be required.
- **Advisory Committee**- Not needed.
- Review Goal Date with labeling-

The file date for these supplements were September 30, 2002. The application will receive a **standard** review. The user fee goal date is June 1, 2003. Primary reviews are due in DFS by April 30, 2003.

Minutes preparer: Margaret Simoneau, R.Ph.
Regulatory Project Manager
(*See appended signature page*)

Concurrence Chairman: Mary Parks, M.D./10.25.02
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/

Margaret Simoneau
10/29/02 09:21:49 AM

Division of Metabolic & Endocrine Drug Products

Labeling Review

Application Number: NDA 20-261/S-033

NDA 21-192/S-005

Name of Drug: Lescol (fluvastatin sodium) Capsules, 20 mg, 40 mg

Lescol XL (fluvastatin sodium) Extended-Release Tablets, 80 mg

Sponsor: Novartis Pharmaceuticals Corporation

Submission Date: May 20, 2003 submission

Background and Summary:

Lescol is indicated in:

- Hypercholesterolemia (heterozygous familial and non familial) and Mixed Dyslipidemia
- Atherosclerosis

The last approved labeling for NDA 20-261/S-032 (Lescol Capsules) and NDA 21-192/S-004 (Lescol XL Extended-Release Tablets), were approved on September 6, 2002, (Package Identifier #T2002-76, 89011105, Rev. August 2002). The final draft labeling for NDA 20-261/S-033 and NDA 21-192/S-005, submitted on May 20, 2003, (Package Identifier # T2003340, 89011106) was compared to the last approved labeling.

Review:

These supplemental new drug applications provide for a new indication, based on the results of the Lescol Intervention Prevention Study (LIPS), for the use of fluvastatin in patients with coronary heart disease to reduce the risk of undergoing coronary revascularization procedures.

In addition, these supplemental applications provide for changes to the **CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE,** and **ADVERSE REACTIONS** sections of the LESCOL and LESCOL XL package insert. The specific changes are as follows:

1. In the **CLINICAL PHARMACOLOGY** section, the third paragraph, last sentence,

   The effect of Lescol or Lescol XL induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular mortality has not been determined.

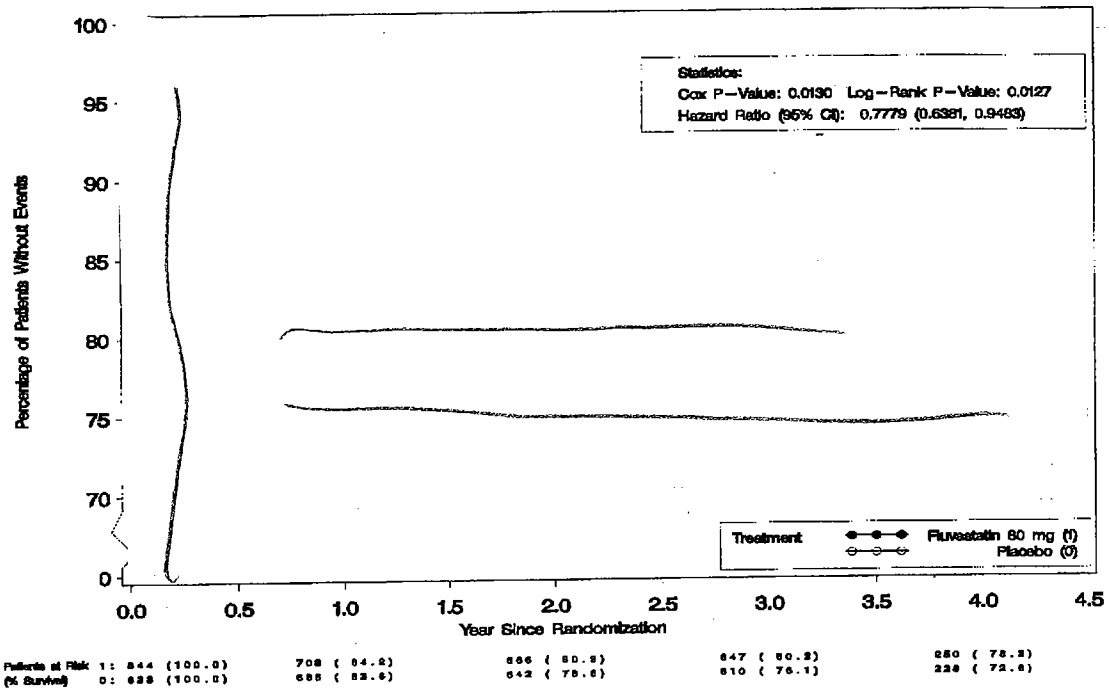
2. In **CLINICAL STUDIES**, a new subsection including Figures 1 and 2 have been added to read:

   Reduction in the Risk of Recurrent Cardiac Events

   In the Lescol Intervention Prevention Study, the effect of Lescol 40 mg administered twice daily on the risk of recurrent cardiac events (time to first occurrence of cardiac death, nonfatal myocardial infarction, or revascularization) was assessed in 1677 patients with coronary heart disease who had undergone a percutaneous coronary intervention (PCI) procedure (mean time from PCI to randomization = 3 days). In this multicenter, randomized, double-blind, placebo-controlled study, patients were treated with dietary/lifestyle counseling and either Lescol 40 mg (n = 844) or placebo (n = 833) given twice daily for a median of 3.9 years. The study population was 84% male, 98% Caucasian, with 37% >65 years of age. At baseline patients had total cholesterol between 100 and 367 mg/dL (mean 201 mg/dL), LDL-C between 42 and 243 mg/dL (mean 132 mg/dL), triglycerides between 15 and 270 mg/dL (mean 70 mg/dL) and HDL-C between 8 and 174 mg/dL (mean 39 mg/dL).

   Lescol significantly reduced the risk of recurrent cardiac events (Figure 1) by 22% (p=0.013, 181 patients in the Lescol group vs 222 patients in the placebo group). Revascularization procedures comprised the majority of the initial recurrent cardiac events (143 revascularization procedures in the Lescol group and 171 in the placebo group). Consistent trends in risk reduction were observed in patients > 65 years of age.

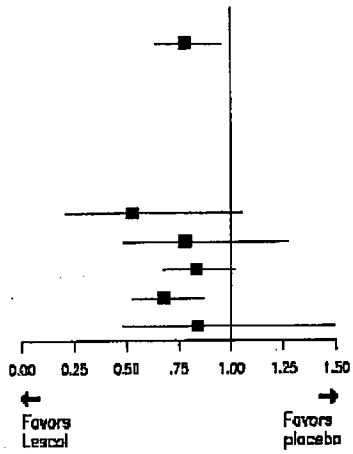
Figure 1. Primary Endpoint – Recurrent Cardiac Events (Cardiac Death, Nonfatal MI or Revascularization Procedure) (ITT Population)



Outcome data for the Lescol Intervention Prevention Study are shown in Figure 2. After exclusion of revascularization procedures (CABG and repeat PCI) occurring within the first 6 months of the initial procedure involving the originally instrumented site, treatment with Lescol was associated with a 32% (p= 0.002) reduction in risk of late revascularization procedures (CABG or PCI occurring at the original site > 6 months after the initial procedure, or at another site).

Figure 2. Lescol Intervention Prevention Study – Primary and Secondary Endpoints

Event	Incidence* Lescol n (%) N=844	Placebo n (%) N=833	Risk Reduction % (95% CI)
Primary Endpoint, Recurrent Cardiac Events (as a first event)	181 (21.4)	222 (26.7)	22 (5 , 36)
Cardiac Death	8 (0.9)	18 (2.2)	–
Nonfatal MI	30 (3.4)	33 (4.0)	–
Revascularization	143 (16.2)	171 (20.5)	–
Secondary Endpoints (any time during the study)			
Cardiac Death	13 (1.5)	24 (2.9)	47 (−5 , 79)
Nonfatal MI	30 (3.6)	38 (4.6)	22 (−27 , 52)
Revascularization	167 (19.8)	193 (23.2)	17 (−2 , 33)
Late Revascularization††	111 (13.2)	151 (18.1)	32 (13 , 47)
Noncardiac Death	23 (2.7)	25 (3.0)	16 (−49 , 52)



*Number of patients with events

††Excludes revascularization procedures of the target lesion within the first 6 months of the initial procedure

3. **INDICATIONS AND USAGE** section has been changed to read:

   Therapy with lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol (see National Cholesterol Education Program (NCEP) Treatment Guidelines, below).

4. **INDICATIONS AND USAGE**, *Hypercholesterolemia (heterozygous familial and non familial) and Mixed Dyslipidemia*

5. In **INDICATIONS AND USAGE**, *Secondary Prevention of Coronary Events*, a new subsection has been added to read:

   Secondary Prevention of Coronary Events

   In patients with coronary heart disease, Lescol and Lescol XL are indicated to reduce the risk of undergoing coronary revascularization procedures.

6. In **ADVERSE REACTIONS**, [illegible] added to the description of adverse experiences. The new section should read:

Clinically relevant adverse experiences occurring in the Lescol and Lescol XL controlled studies with a frequency >2%, regardless of causality, include the following:

Table 5
Clinically relevant adverse experiences occurring in >2% patients in Lescol and Lescol XL controlled studies

Adverse Event	Lescol[1] (%) (N=2326)	Placebo[1] (%) (N=960)	Lescol XL[2] (%) (N = 912)
Musculoskeletal			
Myalgia	5.0	4.5	3.8
Arthritis	2.1	2.0	1.3
Arthropathy	NA	NA	3.2
Respiratory			
Sinusitis	2.6	1.9	3.5
Bronchitis	1.8	1.0	2.6
Gastrointestinal			
Dyspepsia	7.9	3.2	3.5
Diarrhea	4.9	4.2	3.3
Abdominal Pain	4.9	3.8	3.7
Nausea	3.2	2.0	2.5
Flatulence	2.6	2.5	1.4
Psychiatric Disorders			
Insomnia	2.7	1.4	0.8
Genitourinary			
Urinary Tract Infection	1.6	1.1	2.7
Miscellaneous			
Headache	8.9	7.8	4.7
Influenza-Like Symptoms	5.1	5.7	7.1
Accidental Trauma	5.1	4.8	4.2
Fatigue	2.7	2.3	1.6
Allergy	2.3	2.2	1.0

[1] Controlled trials with Lescol Capsules (20 and 40 mg daily and 40 mg twice daily)

[2] Controlled trials with Lescol XL 80 mg Tablets

Conclusion:

The proposed draft label (Package Identifier #T2003340, 89011106), submitted May 20, 2003, was found acceptable by the reviewing team. The Agency will issue an approval action on these efficacy supplements.

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
5/27/03 02:17:51 PM
CSO

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Tel 862 778 8300

NOVARTIS

May 20, 2003

Previously submitted via email May 20, 2003 at 11:34AM

David Orloff, MD
Director
Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 8B45
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-261/S-033
Lescol® (fluvastatin sodium)
Capsules

NDA 21-192/S-005
Lescol® XL (fluvastatin sodium)
Extended-Release Tablets

Draft Final Printed Labeling

Dear Dr. Orloff:

Reference is made to NDA 20-261/S-033 for Lescol® (fluvastatin sodium) capsules and NDA 21-192/S-005 for Lescol® XL (fluvastatin sodium) extended-release tablets. Enclosed please find the draft final printed labeling as agreed to during our teleconference on May 16, 2003.

Please contact me at (862) 778-3279 should you have comments or questions regarding this submission.

Sincerely,

Lisa N. Pitt, PharmD
Associate Director
Drug Regulatory Affairs

Attachment
Submitted in duplicate
Desk Copy: Margaret Simoneau, MS, RPh

NOVARTIS

T2003340
89011106

Lescol®
(fluvastatin sodium)
Capsules

Lescol® XL
(fluvastatin sodium)
Extended-Release Tablets

Rx only

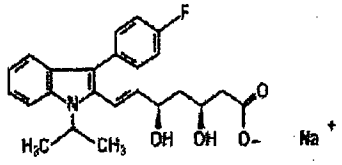
Approved Paper Labeling
5/27/03

Prescribing Information

DESCRIPTION

Lescol® (fluvastatin sodium), is a water-soluble cholesterol lowering agent which acts through the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase.

Fluvastatin sodium is [*R**,*S**-(*E*)]-(±)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1*H*-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid, monosodium salt. The empirical formula of fluvastatin sodium is $C_{24}H_{25}FNO_4$•Na, its molecular weight is 433.46 and its structural formula is:



$C_{24}H_{25}FNO_4$ • Na Mol. wt. 433.46

This molecular entity is the first entirely synthetic HMG-CoA reductase inhibitor, and is in part structurally distinct from the fungal derivatives of this therapeutic class.

Fluvastatin sodium is a white to pale yellow, hygroscopic powder soluble in water, ethanol and methanol. Lescol is supplied as capsules containing fluvastatin sodium, equivalent to 20 mg or 40 mg of fluvastatin, for oral administration. Lescol® XL (fluvastatin sodium) is supplied as extended-release tablets containing fluvastatin sodium, equivalent to 80 mg of fluvastatin, for oral administration.

Active Ingredient: fluvastatin sodium

Inactive Ingredients in capsules: gelatin, magnesium stearate, microcrystalline cellulose, pregelatinized starch (corn), red iron oxide, sodium lauryl sulfate, talc, titanium dioxide, yellow iron oxide, and other ingredients.

Capsules may also include: benzyl alcohol, black iron oxide, butylparaben, carboxymethylcellulose sodium, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide and sodium propionate.

5/20/03

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Tel 862 778 8300

NOVARTIS

DUPLICATE

RECEIVED
MAY 15 2003
FDR/CDER

May 9, 2003

Previously Submitted via E-Mail

SL 103 (NL)

NDA 20-261/S-033 NDA SUPPL AMENDMENT
Lescol® (fluvastatin sodium) Capsules

NDA 21-192/S-005
Lescol® XL (fluvastatin sodium)
Extended-Release Tablets

Labeling Counter-proposal

David Orloff, MD
Director
Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Orloff:

Reference is made to our pending supplements for Lescol® (fluvastatin sodium) capsules (NDA 20-261/S-033) and Lescol® XL (fluvastatin sodium) extended-release tablets (NDA 21-192/S-005) which provide for a new indication pertaining to the secondary prevention of coronary events. We are in receipt of the revised draft labeling you sent us on April 29, 2003, and at this time we are providing you with our perspectives concerning the revisions you made. It is our understanding that we will discuss these issues in a telephone conference which will begin at 11:30am on May 12th.

An underlying issue in our discussions involves what a sponsor should be able to include in labeling when positive results are achieved with respect to pre-specified endpoints and analyses. In our situation this has relevance to the indication and patient subsets.

Regarding the indication, the primary endpoint in the LIPS study was a pre-specified composite consisting of cardiac death, MI, and revascularization procedures. We realize that the trial generated more revascularizations than other events. However, the trial was successful overall, with all components contributing to the results

We have edited the Clinical Trials section.

Figure 2 has been restructured generally consistent with your requests. Please note that we have substituted Risk Reduction for Risk Ratio, which is again conceptually similar to presentations in the Zocor PI. We feel this is reasonable in that it conveys the same basic information, and it is in a context perhaps more familiar to physicians who prescribe statins.

We are in general agreement with your suggested revisions to the Adverse Reactions section

We have attached our revised draft package insert with our modifications differentiated by light blue font, double underline for additions and double strikeouts for deletions.

It would be our preference to work toward a first cycle approval, and we would do whatever is necessary to support that goal. We look forward to our upcoming discussions.

Please contact me at 862 778 -3279 should you have comments or questions regarding this matter.

Sincerely,

Lisa N. Pitt, PharmD
Associate Director
Drug Regulatory Affairs

LNP/
Attachment
Submitted in duplicate

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Tel 862 778 8300

NOVARTIS

ORIGINAL

April 29, 2003

RECEIVED
MAY 0 2 2003
FDR/CDER

SE1005(BM
NDA SUPPL AMENDM

David Orloff, MD
Director
Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-261/S-033
Lescol® (fluvastatin sodium)
Capsules

NDA 21-192/S-005
Lescol® XL (fluvastatin sodium)
Extended-Release Tablets

Response to Request for Information

Dear Dr. Orloff:

Reference is made to NDA 21-192/S-005 for Lescol® XL (fluvastatin sodium) extended-release tablets and NDA 20-261/S-033 for Lescol® (fluvastatin sodium) capsules and to questions received via telephone from Margaret Simoneau and Dr. Ann Pariser on April 22, 2003.

Dr. Pariser requested an additional analysis of the re-intervention component only of the composite MACE primary endpoint. Attached, please find the requested analysis previously provided by email on April 25, 2003.

Please contact me at (862) 778-3279 should you have comments or questions regarding this matter.

Sincerely,

Lisa N. Pitt, PharmD
Associate Director
Drug Regulatory Affairs

Attachment
Submitted in duplicate

NOVARTIS

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 8300

April 2, 2003

SE1005 (BM)
NDA SUPPL AMENDMENT

David Orloff, MD
Director
Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-261/S-033
Lescol® (fluvastatin sodium)
Capsules

NDA 21-192/S-005
Lescol® XL (fluvastatin sodium)
Extended-Release Tablets

Response to Request for Information

Dear Dr. Orloff:

Reference is made to NDA 21-192/S-005 for Lescol® XL (fluvastatin sodium) extended-release tablets and NDA 20-261/S-033 for Lescol® (fluvastatin sodium) capsules and to questions received via email March 19, 2003.

Below please find responses to the questions received via email last Wednesday, March 19, 2003:

Response to Question 1:
Compliance with study medication was calculated for the entire study and not at each visit, as follows:

[redacted]

The formula below is then used to calculate a percent compliance over the entire trial duration.

[redacted]

If this calculation is <80%, then the patient is considered non-compliant. If the calculation is >80%, then the patient is considered compliant.

Response to Questions 2 & 3:
This submission is being provided in accordance with the guidance for industry titled, *Providing Regulatory Submissions in Electronic Format – NDAs* (January 1999). The relevant technical details of the electronic portions of this submission are as follows:

- **Submission size:** approximately 126 MB
- **Electronic media:** one compact disc
- **Virus scan:** Network Associates Incorporated VirusScan© version 4.5.0 (formerly known as the McAfee VirusScan). The submission is virus free.

Response to Question 4:
Screen failure information was not provided in the sNDA submission. However, monitor reports during the 27 month recruitment period indicate that all patients prospectively undergoing PCI at the investigational sites in that period, were considered for eligibility assessment. If they consented and met the eligibility criteria, they were then randomized into the study. Moreover, the selection criteria predefined in the study protocol did not favor the inclusion of subpopulations who may have been expected to respond better to or tolerate better statin treatment. In fact, baseline demographic characteristics of the LIPS population (Section 7.4, page 38 of the Clinical Study Report) did not reveal the prevalence of any specific group in the fluvastatin group as compared to the placebo group. Moreover, the only major violation to the protocol selection criteria regarded cholesterol levels at entry, which occurred in only 3 to 4% of the randomized patients (Section 7.2, page 34 of the Clinical Study Report) indicating that the patients randomized in LIPS fully represented the intended study population.

Please contact me at 862 778 -3279 should you have comments or questions regarding this matter.

Sincerely,

Lisa N. Pitt, PharmD
Associate Director
Drug Regulatory Affairs

LNP/
Attachments
Submitted in duplicate
Desk copy: Dr. Ann Pariser

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 8300

NOVARTIS

RECEIVED
JAN 22 2003
EDR/CDER

DUPLICATE

January 16, 2003

SE1-005-C

David Orloff, MD
Director
Division of Metabolic and Endocrine
Drug Products/HFD-510
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-261/S-033
Lescol® (fluvastatin sodium)
Capsules

NDA 21-192/S-005
Lescol® XL (fluvastatin sodium)
Extended-Release Tablets

General Correspondence

Dear Dr. Orloff:

Reference is made to NDA 20-261/S-033 for Lescol® (fluvastatin sodium) capsules and NDA 21-192/S-005 for Lescol® XL (fluvastatin sodium) extended-release tablets and to the December 31, 2002 e-mail correspondence to the Regulatory Project Manager Margaret Simoneau inquiring to the need for a 120-day Safety Update.

As discussed during a subsequent telephone conversation with Ms. Simoneau, it has been agreed that a 120-day Safety Update is not required for the supplemental application (NDA 20-261/S-033 and NDA 21-192/S-005) for the following reasons. This supplemental application consists of a single completed study for which there is no additional safety information to be reported. Therefore a 120-day Safety Update will not be submitted.

If you have any comments regarding this matter, please contact me at (862) 778-3279.

Sincerely,

Lisa N. Pitt, PharmD
Associate Director
Drug Regulatory Affairs

LNP/kp
Submitted in duplicate

11 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

__X__ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 20-261 5033 and 21-192 5005

Simoneau, Margaret A

From: lisa.pitt@pharma.novartis.com
Sent: Thursday, March 27, 2003 10:17 AM
To: PariserA@cder.fda.gov
Cc: SIMONEAUM@cder.fda.gov
Subject: Response to Request for LIPS Study Information


ATT657438.rtf

NOTES.CD

wssalert.txt

Dear Dr. Pariser,

Below please find responses to the questions received via email last Wednesday, March 19, 2003:

1) For compliance with study medications, it is noted that 38% of patients overall [34% in fluvastatin group and 42% of placebo group] were non-compliant (defined as compliance to study medication <80%). Can you tell me, was this compliance with study medication <80% for the entire study, or for each patient, if they had poor compliance at any study visit interval, were they counted in this number? For example, if Patient A was poorly compliant between Visit 2 and Visit 3, but overall use of study medication was >80% for the entire study, would that patient have been considered as poorly compliant or compliant?

esponse to Question 1:
mpliance with study medication was calculated for the entire study and not at each visit, as follows:

The formula below is then used to calculate a percent compliance over the entire trial duration.

If this calculation is <80%, then the patient is considered non-compliant. If the calculation is >80%, then the patient is considered compliant.

2) I was only able to locate the datasets for lab results for Baseline labs. Were the labs obtained during the study submitted to the NDA and if so, where are they? I could only find "notable" elevations and number of results in ranges (e.g. >2 to <5 X ULN) for AST, ALT, and CPK in your study report. If datasets were not submitted, need them (like-yesterday!). I would be able to live with datasets for just AST, ALT and CPK, but other

b
alues (such as GGT alk phos, etc.) would be of interest.

3) Can't locate Baseline and on-study lipid data, other than for TC and

TG
at Baseline and the lipid-data summaries in your study report. Can you tell
me where these are located, and if not submitted, please submit ASAP.

Response to Questions 2 & 3:
A complete CRT containing datasets for the lab and lipid parameters will

be provided in a separate correspondence via
express courier Thursday, April 3, 2003.

4) I am trying to find screening/screen failure information in the LIPS study
(SNDA 20-261 SE1 033 and 21-192 SE1 005; Lescol and Lescol XL) and am unable
to locate it. Could you please tell me:
1) Is this information located in the SNDA submission, and if so, where?
2) If it is not there, can you find out: How many patients were screened,
how many screen failures, and why were they screen failures? Did screen
failures differ from the randomized population? Screen failures broken down
by clinical center or, if not available, by country, or if not available -
at the very least - overall results should be submitted, as this is always
a
potential source of bias.

Response to Question 4:
Screen failure information was not provided in the sNDA submission.
However, monitor reports during the 27 month recruitment period indicate

that all patients prospectively undergoing PCI at the investigational sites in that period, were considered for eligibility assessment. If they
consented and met the eligibility criteria, they were then randomized into
the study. Moreover, the selection criteria predefined in the study
protocol did not favor the inclusion of subpopulations who may have been

expected to respond better to or tolerate better statin treatment. In
fact, baseline demographic characteristics of the LIPS population (Section
7.4, page 38 of the Clinical Study Report) did not reveal the prevalence

of any specific group in the fluvastatin group as compared to the placebo
group. Moreover, the only major violation to the protocol selection
criteria regarded cholesterol levels at entry, which occurred in only 3 to
4% of the randomized patients (Section 7.2, page 34 of the Clinical Study
Report) indicating that the patients randomized in LIPS fully represented
the intended study population.

A hard copy of information contained in this electronic transmission will
be submitted to the NDA files for Lescol (NDA 20-261/S-033) and Lescol XL
(NDA 21-192/S-005).

Please let me know if any additional information is needed.

Sincerely,

Lisa N.Pitt
Associate Director, DRA
Novartis Pharmaceuticals Corporation
862-778-3279

Dear Dr. Parlser,

Below please find responses to the questions received via email last Wednesday, March 19, 2003:

1) For compliance with study medications, it is noted that 38% of patients overall [34% in fluvastatin group and 42% of placebo group] were non-compliant (defined as compliance to study medication <80%). Can you tell me, was this compliance with study medication <80% for the entire study, or for each patient, if they had poor compliance at any study visit interval, were they counted in this number? For example, if Patient A was poorly compliant between Visit 2 and Visit 3, but overall use of study medication was >80% for the entire study, would that patient have been considered as poorly compliant or compliant?

Response to Question 1:
Compliance with study medication was calculated for the entire study and not at each visit, as follows:

The formula below is then used to calculate a percent compliance over the entire trial duration.

If this calculation is <80%, then the patient is considered non-compliant. If the calculation is >80%, then the
patient is considered compliant.

2) I was only able to locate the datasets for lab results for Baseline labs. Were the labs obtained during the study submitted to the NDA and if so, where are they? I could only find "notable" elevations and number of results in ranges (e.g. >2 to <5 X ULN) for AST, ALT, and CPK in your study report. If datasets were not submitted, need them (like-yesterday!). I would be able to live with datasets for just AST, ALT and CPK, but other lab values (such as GGT alk phos, etc.) would be of interest.

3) Can't locate Baseline and on-study lipid data, other than for TC and TG at Baseline and the lipid-data summaries in your study report. Can you tell me where these are located, and if not submitted, please submit ASAP.

Response to Questions 2 & 3:
A complete CRT containing datasets for the lab and lipid parameters will be provided in a separate correspondence via
express courier Thursday, April 3, 2003.

4) I am trying to find screening/screen failure information in the LIPS study (SNDA 20-261 SE1 033 and 21-192 SE1 005; Lescol and Lescol XL) and am unable to locate it. Could you please tell me:
1) Is this information located in the SNDA submission, and if so, where?
2) If it is not there, can you find out: How many patients were screened, how many screen failures, and why were they screen failures? Did screen failures differ from the randomized population? Screen failures broken down

by clinical center or, if not available, by country, or if not available - at the very least - overall results should be submitted, as this is always a potential source of bias.

Response to Question 4:
Screen failure information was not provided in the sNDA submission. However, monitor reports during the 27 month recruitment period indicate that all patients prospectively undergoing PCI at the investigational sites in that period, were considered for eligibility assessment. If they consented and met the eligibility criteria, they were then randomized into the study. Moreover, the selection criteria predefined in the study protocol did not favor the inclusion of subpopulations who may have been expected to respond better to or tolerate better statin treatment. In fact, baseline demographic characteristics of the LIPS population (Section 7.4, page 38 of the Clinical Study Report) did not reveal the prevalence of any specific group in the fluvastatin group as compared to the placebo group. Moreover, the only major violation to the protocol selection criteria regarded cholesterol levels at entry, which occurred in only 3 to 4% of the randomized patients (Section 7.2, page 34 of the Clinical Study Report) indicating that the patients randomized in LIPS fully represented the intended study population.

A hard copy of information contained in this electronic transmission will be submitted to the NDA files for Lescol (NDA 20-261/S-033) and Lescol XL
(NDA 21-192/S-005).

Please let me know if any additional information is needed.

Sincerely,

Lisa N.Pitt
Associate Director, DRA
Novartis Pharmaceuticals Corporation
862-778-3279

Simoneau, Margaret A

From: lisa.pitt@pharma.novartis.com
Sent: Friday, April 25, 2003 9:19 AM
To: parisera@cder.fda.gov
Cc: simoneaum@cder.fda.gov
Subject: Response to Request for Information

Dear Dr. Pariser,

Attached below please find the requested analyses for the LIPS submission. This information includes the response to the additional request received from Todd Sahlroot.

Please let me know if you need any additional information.

Regards,
Lisa
862-778-3279

Post-text Table 9.2-27
Number (%) of Re-interventions Excluding Repeat TCT and CABG on Lesions Dilated at Baseline
(Intent-to-Treat Population)

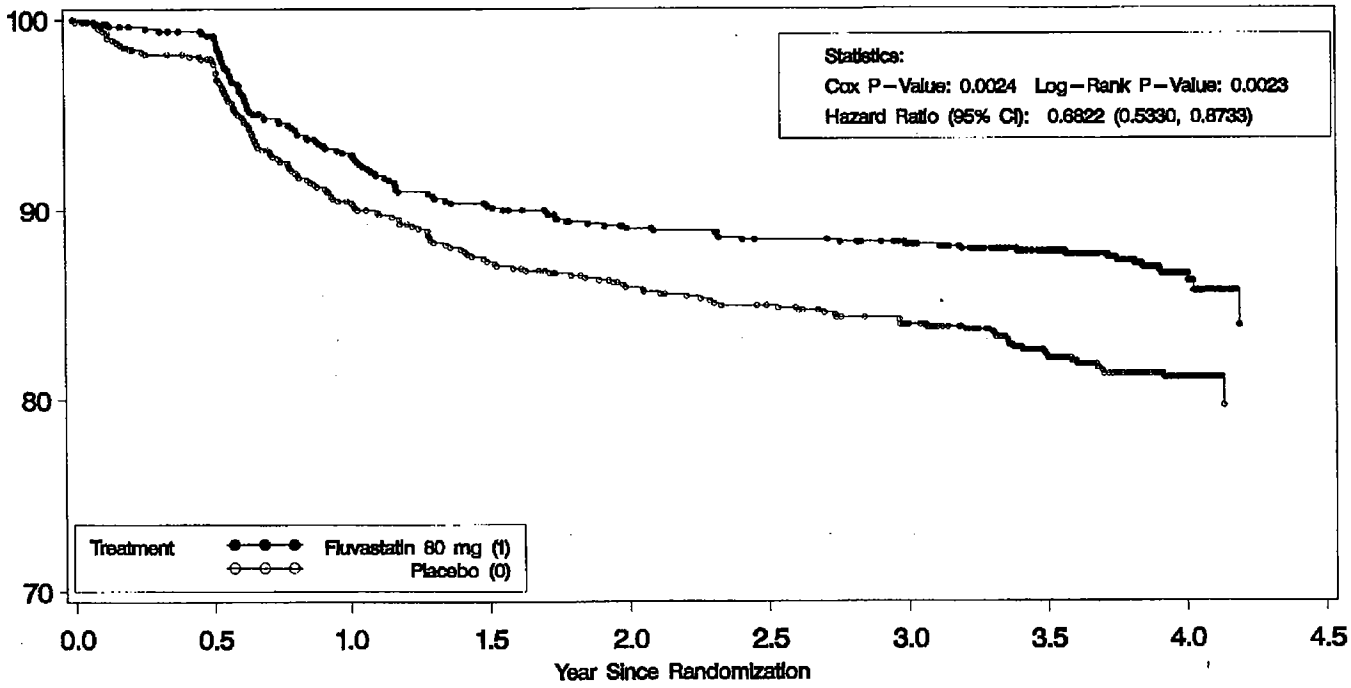
Clinical Endpoint	Fluvastatin 80 mg (N = 844)	Placebo (N = 833)	P-value
Number of patients	111 (13.2)	151 (18.1)	0.0025
Number of events (clinical endpoints)	140	192	

P-value from the Mantel-Haenzel Test with interventional centre as the stratum variable to test for differences between treatment group.

Program name: additionalanalysis2.sas Rundate: Tue, May 14, 2002 13:45:51
Dataset last modified: Mon, May 13, 2002 13:40:04

Post-text Figure 9.1-17

Time to First Revascularization Excluding Repeat TCTs and CABG on Lesions Dilated at Baseline
(Intent-to-Treat Population)



Patients at Risk (% Survival)	1: 844 (100.0)	771 (93.0)	727 (89.0)	705 (88.2)	275 (86.6)
	0: 833 (100.0)	736 (90.5)	688 (85.8)	659 (83.9)	246 (81.1)

Source: Figure.sas Rundate: Thu, Apr 24, 2003 10:13:21
Database last modified: Thu, Apr 24, 2003 9:40:46

Simoneau, Margaret A

From: Pariser, Anne
Sent: Friday, April 25, 2003 11:08 AM
To: 'lisa.pitt@pharma.novartis.com'; Pariser, Anne
Cc: Simoneau, Margaret A; Sahlroot, Jon T
Subject: RE: Response to Request for Information

Dear Lisa

Can you please clarify for me if the re-interventions numbers you sent are only for re-interventions of the target lesion within the first 6 months? We are interested in excluding only those lesions not thought to be due to atherosclerosis, that is, abrupt and subacute closures (<6 months) of the PTCA site.

Thanks

Anne Pariser

-----Original Message-----
From: lisa.pitt@pharma.novartis.com [mailto:lisa.pitt@pharma.novartis.com]
Sent: Friday, April 25, 2003 9:19 AM
To: parisera@cder.fda.gov
Cc: simoneaum@cder.fda.gov
Subject: Response to Request for Information

Dear Dr. Pariser,

Attached below please find the requested analyses for the LIPS submission. This information includes the response to the additional request received from Todd Sahlroot.

Please let me know if you need any additional information.

Regards,
Lisa
862-778-3279

Simoneau, Margaret A

From: Pariser, Anne
Sent: Friday, April 25, 2003 11:21 AM
To: Simoneau, Margaret A; Sahlroot, Jon T
Subject: FW: Response to Request for Information

Dear Peggy and Todd

The numbers for re-interventions excluding the target lesion in the attachment from Lisa Pitt at Novartis don't quite make sense to me. In the incidence table they have in the study report, they reported the following:

All Re-interventions (first event included in time to first MACE): fluva 143, placebo 171

All Re-interventions (not just first event): fluva 167, placebo 193

They then say that in the first 6 months, acute re-interventions in target lesion were: fluva 46, placebo 35

In the attachment below, they are now saying # of clinical events excluding repeat TCT and CABG on lesion dilated at Baseline were: fluva 140, placebo 192.

This just doesn't make any sense to me. Todd: any ideas?

If Lisa cannot get a satisfactory answer for us today, I suggest we set up a quick con call for Monday to clarify the situation.

Anne

-----Original Message-----
From: lisa.pitt@pharma.novartis.com [mailto:lisa.pitt@pharma.novartis.com]
Sent: Friday, April 25, 2003 9:19 AM
To: parisera@cder.fda.gov
Cc: simoneaum@cder.fda.gov
Subject: Response to Request for Information

Dear Dr. Pariser,

Attached below please find the requested analyses for the LIPS submission. This information includes the response to the additional request received from Todd Sahlroot.

Please let me know if you need any additional information.

Regards,
Lisa
862-778-3279

Simoneau, Margaret A

From: lisa.pitt@pharma.novartis.com
Sent: Friday, April 25, 2003 11:36 AM
To: Pariser, Anne
Cc: Sahlroot, Jon T; Simoneau, Margaret A
Subject: RE: Response to Request for Information

Dear Dr. Pariser,

No, essentially the opposite. The numbers presented represent interventions excluding re-interventions of the target lesion within the first six months.

Please let me know if you have any further questions.

Regards,
Lisa

"Pariser, Anne"
<PariserA@cder.fda.gov>

04/25/2003 11:07 AM

To: Lisa Pitt/PH/Novartis@PH, "Pariser, Anne" <PariserA@cder.fda.gov>
cc: "Simoneau, Margaret A" <SIMONEAUM@cder.fda.gov>, "Sahlroot, Jon T" <SAHLROOTT@cder.fda.gov>
Subject: RE: Response to Request for Information

Dear Lisa

Can you please clarify for me if the re-interventions numbers you sent are only for re-interventions of the target lesion within the first 6 months? We are interested in excluding only those lesions not thought to be due to atherosclerosis, that is, abrupt and subacute closures (<6 months) of the PTCA site.

Thanks

Anne Pariser

-----Original Message-----
From: lisa.pitt@pharma.novartis.com [mailto:lisa.pitt@pharma.novartis.com]
Sent: Friday, April 25, 2003 9:19 AM
To: parisera@cder.fda.gov
Cc: simoneaum@cder.fda.gov
Subject: Response to Request for Information

Dear Dr. Pariser,

Attached below please find the requested analyses for the LIPS submission. This information includes the response to the additional request received from Todd Sahlroot.

Please let me know if you need any additional information.

Regards,
Lisa
862-778-3279

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-261/S-033
NDA 21-192/S-005

Novartis Pharmaceuticals Corporation
Attention: Lisa N. Pitt, Pharm.D.
Associate Director, Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Dr. Pitt:

Please refer to your pending efficacy supplements submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lescol (fluvastatin sodium) capsules (NDA 20-261) and Lescol XL Extended-Release (fluvastatin sodium) tablets (NDA 21-192).

We also refer to the September 24, 2002, teleconference between you and Margaret Simoneau, regarding the drug review priority classification for this application.

Based on further consideration of your application at the filing meeting, we have concluded that this application should receive a standard review. The user fee goal date is June 1, 2003.

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

Sincerely,

{See appended electronic signature page}

Mary Parks, M.D.
Deputy Director/Medical Team Leader
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/

Mary Parks
10/2/02 10:06:20 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-261/S-033
NDA 21-192/S-005

PRIOR APPROVAL SUPPLEMENT

Novartis Pharmaceuticals Corporation
Attention: Lisa N. Pitt, PharmD
Associate Director, Drug Regulatory Affairs
59 Route 10
East Hanover, New Jersey
07936-1080

Dear Dr. Pitt:

We have received your supplemental drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA Number	Supplement Number	Drug Name
20-261	S-033	Lescol (fluvastatin sodium) Capsules
21-192	S-005	Lescol XL Extended-Release (fluvastatin sodium) Tablets

Date of Supplements: July 31, 2002

Date of Receipt: August 1, 2002

Review Priority Classification: Standard

These supplements propose to add additional information to various sections of the Package Insert from the Lescol Intervention Prevention Study (LIPS)

Unless we notify you within 60 days of our receipt date that the applications are not sufficiently complete to permit a substantive review, these applications will be filed under section 505(b) of the Act on September 30, 2002 in accordance with 21 CFR 314.101(a). If the applications are filed, the user fee goal date will be June 1, 2003.

Please cite the application numbers listed above at the top of the first page of any communications concerning these applications. All communications concerning these supplemental applications should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6411.

Sincerely,

{See appended electronic signature page}

Margaret Simoneau, M.S., R.Ph.
Regulatory Project Manager
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/

Margaret Simoneau
8/8/02 09:17:22 AM

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
Tel 973 781 8300

NOVARTIS

ORIGINAL

SE1-005 C

RECEIVED
AUG 14 2002
FDR/CDER

CDR/CDER
AUG 12 2002
RECEIVED

August 9, 2002

NDA 20-261
Lescol® (fluvastatin sodium)
Capsules
NDA 21-192
Lescol® XL (fluvastatin sodium)
Extended-Release Tablets

SUPPLEMENTAL NEW DRUG APPLICATION-
Additional Archival Copy

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

Dear Dr. Orloff,

Reference is made to NDA 20-261 for Lescol® (fluvastatin sodium) capsules and NDA 21-192 for Lescol® XL (fluvastatin sodium) extended-release tablets and the supplemental new drug application submitted on July 31, 2002. As requested by the Regulatory Project Manager via telephone August 5, 2002, we are providing an additional archival copy of the submission.

Please contact me at (973) 781-3279 should you require additional information

Sincerely,

Lisa N. Pitt, PharmD
Associate Director
Drug Regulatory Affairs

Attachments:

Item 13. Patent Information
Item 14. Patent Certification
Item 16. Debarment Certification
Sheet (Form FDA 3397)
Disclosure Certification

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 8300

NOVARTIS

ORIGINAL

SE1-033 C

RECEIVED
AUG 14 2002
FDR/CDER

CDR/CDER
AUG 12 2002
RECEIVED

August 9, 2002

NDA 20-261
Lescol® (fluvastatin sodium)
Capsules
NDA 21-192
Lescol® XL (fluvastatin sodium)
Extended-Release Tablets

SUPPLEMENTAL NEW DRUG APPLICATION-
Additional Archival Copy

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

Dear Dr. Orloff,

Reference is made to NDA 20-261 for Lescol® (fluvastatin sodium) capsules and NDA 21-192 for Lescol® XL (fluvastatin sodium) extended-release tablets and the supplemental new drug application submitted on July 31, 2002. As requested by the Regulatory Project Manager via telephone August 5, 2002, we are providing an additional archival copy of the submission.

Please contact me at (973) 781-3279 should you require additional information

Sincerely,

Lisa N. Pitt, PharmD
Associate Director
Drug Regulatory Affairs

Attachments:

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 8300

ORIGINAL

NOVARTIS

RECEIVED

AUG 0 2 2002

HFD-510 / CDER

NDA NO: 21-192 REF NO. 005
NDA SUPPL FOR SE1

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

NDA 20-261
Lescol® (fluvastatin sodium)
Capsules
NDA 21-192
Lescol® XL (fluvastatin sodium)
Extended-Release Tablets

SE1-005

SUPPLEMENTAL NEW DRUG APPLICATION 21-192

Request for Priority Review

Dear Dr. Orloff,

In accordance with 21 CFR Section 314.70, Novartis Pharmaceuticals Corporation is submitting a Supplemental New Drug Application for Lescol® (fluvastatin sodium) capsules (NDA 20-261) and Lescol® XL (fluvastatin sodium) extended-release tablets (NDA 21-192). The original New Drug Application for Lescol capsules was approved December 31, 1993, and the approval of the original New Drug Application for Lescol XL extended-release tablets occurred on October 6, 2000.

Lescol and Lescol XL are currently indicated as an adjunct to diet to reduce elevated total cholesterol (Total-C), triglycerides (TG) and Apolipoprotein B (Apo B) levels, and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIa and IIb) whose response to dietary restriction of saturated fat and cholesterol and other nonpharmacological measures has not been adequate. Lescol and Lescol XL are also indicated to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total and LDL cholesterol to target levels.

This Supplemental New Drug Application is being submitted to support the safe and effective use of Lescol and Lescol XL to reduce the risk of major adverse cardiac events in patients with coronary heart disease. The data contained in this application is based on the results of the Lescol Intervention Prevention Study (LIPS).

LIPS was a randomized, double-blind, placebo-controlled, multicenter trial in 57 centers which randomized 1677 patients to receive Lescol capsules 80 mg per day (40 mg bid) or placebo following their first percutaneous coronary intervention (PCI). The prospectively defined composite primary endpoint of the study was to evaluate the effects of fluvastatin 80 mg versus placebo on the time to the first of one of the following major adverse cardiac events (MACE):

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
Tel 973 781 8300

AUG 0 1 2002

ORIGINAL

NOVARTIS

RECEIVED
AUG 0 2 2002
HFD-510 / CDER

NDA NO. 20261 REF NO. 033 NDA 20-261
NDA SUPPL FOR SE1

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

Lescol® (fluvastatin sodium) Capsules
NDA 21-192
Lescol® XL (fluvastatin sodium) Extended-Release Tablets

SE1-033

SUPPLEMENTAL NEW DRUG APPLICATION

Request for Priority Review

Dear Dr. Orloff,

In accordance with 21 CFR Section 314.70, Novartis Pharmaceuticals Corporation is submitting a Supplemental New Drug Application for Lescol® (fluvastatin sodium) capsules (NDA 20-261) and Lescol® XL (fluvastatin sodium) extended-release tablets (NDA 21-192). The original New Drug Application for Lescol capsules was approved December 31, 1993, and the approval of the original New Drug Application for Lescol XL extended-release tablets occurred on October 6, 2000.

Lescol and Lescol XL are currently indicated as an adjunct to diet to reduce elevated total cholesterol (Total-C), triglycerides (TG) and Apolipoprotein B (Apo B) levels, and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIa and IIb) whose response to dietary restriction of saturated fat and cholesterol and other nonpharmacological measures has not been adequate. Lescol and Lescol XL are also indicated to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total and LDL cholesterol to target levels.

This Supplemental New Drug Application is being submitted to support the safe and effective use of Lescol and Lescol XL to reduce the risk of major adverse cardiac events in patients with coronary heart disease . The data contained in this application is based on the results of the Lescol Intervention Prevention Study (LIPS).

LIPS was a randomized, double-blind, placebo-controlled, multicenter trial in 57 centers which randomized 1677 patients to receive Lescol capsules 80 mg per day (40 mg bid) or placebo following their first percutaneous coronary intervention (PCI). The prospectively defined composite primary endpoint of the study was to evaluate the effects of fluvastatin 80 mg versus placebo on the time to the first of one of the following major adverse cardiac events (MACE):

- cardiovascular death
- non-fatal myocardial infarction (MI)
- re-intervention , defined as coronary artery bypass graft (CABG) surgery or repeat PCI.

The results of LIPS demonstrated that patients treated with Lescol achieved a 22% risk reduction in MACE compared to placebo (p=0.0127), indicating a statistically significant result for the composite primary endpoint. The risk reduction observed was irrespective of baseline LDL-C levels, and patients with diabetes and multivessel disease achieved greater risk reductions of 47% and 38%, respectively.

We are requesting that this application be designated for priority review as LIPS is the first trial prospectively designed to evaluate the effects of statin therapy on cardiac outcomes in the post-PCI patient population.

Items 2 (Labeling), 11 (Case Report Tabulations), and 12 (Case Report Forms) are being provided in electronic format according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format-NDA* (January 1999). The currently used labeling text, approved September 25, 2001 based on supplements NDA 20-261/S-30 and NDA 21-192/S-002, is being provided in electronic format as a PDF file on the DLT. Tape.

The size of the electronic submission is 3.4GB and will be provided on DLT Tape contained in Volume E1. The virus scanning software used for the submission is Network Associates VirusScan version 4.0.3a (formerly known as McAfee VirusScan).

The User Fee Identification number for this submission is 4389.

Novartis Pharmaceuticals Corporation considers the information contained in this application to be confidential, and its contents are not to be disclosed with express written consent.

Please contact me at (973) 781-3279 should you have any questions or comments regarding this submission.

Sincerely,

Lisa N. Pitt, PharmD
Associate Director
Drug Regulatory Affairs

Attachments: : Form FDA 356h
Form FDA 3397
Volumes 1-18 and E1

[redacted]

[redacted]

[redacted]

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, NJ

Technical R&D / CMC Documentation

Lescol® (fluvastatin sodium) 20 and 40 mg Capsules

Lescol® XL (fluvastatin sodium) 80 mg Extended-Release Tablets

Drug product
Environmental assessment information

Author(s):	D. Kapples/J. Sinno/L. Pitt
Document type:	Drug product - Environmental assessment
Document status:	Final
Date:	09-Jul-02
Number of pages:	2

[redacted]

As set forth in 21 CFR Part 25.31(b), action on a supplemental application is categorically excluded from the requirement to prepare an Environmental Assessment or an Environmental Impact Statement if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be less than 1 part per billion (ppb). "Increased use", as defined in 21 CFR Part 25.5(a), will occur if the drug is "administered at higher dosage levels, for longer duration or for different indications than were previously in effect, or if the drug is a new molecular entity."

Novartis Pharmaceuticals Corporation has filed a supplement to approved New Drug Application 20-261 for Lescol® (fluvastatin sodium) capsules and New Drug Application 21-192 for Lescol® XL (fluvastatin sodium) extended-release tablets which provides for the

disease who have undergone percutaneous

Novartis Pharmaceuticals Corporation certifies that this submission qualifies for a categorical exclusion in accordance with 21 CFR Part 25.31(b) as the concentration of the active moiety fl tin sodium will be

Further, Novartis Pharmaceuticals Corporation states that, to the best of its knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment and would thus require the preparation of at least an Environmental Assessment.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

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

Novartis Pharmaceuticals Corporation
One Health Net Plaza
East Hanover, New Jersey 07936

2. TELEPHONE NUMBER *(Include Area Code)*

(973) 781-6940

3. PRODUCT NAME

Lescol®

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

20-261

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 A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) 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 FOR THIS 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
Vera Wolsch	Director, Planning & Administration	7/18/02