

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021192Orig1s019

Trade Name: Lescol/Lescol XL

Generic Name: fluvastatin sodium

Sponsor: Novartis Pharmaceuticals Corporation

Approval Date: 02/28/2012

Indications: LESCOL/LESCOL XL is an HMG-CoA reductase inhibitor (statin) indicated as an adjunctive therapy to diet to: Reduce elevated TC, LDL-C, Apo B, and TG, and to increase HDL-C in adult patients with primary hypercholesterolemia and mixed dyslipidemia; Reduce elevated TC, LDL-C, and Apo B levels in boys and post-menarchal girls, 10 to 16 years of age, with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy; Reduce the risk of undergoing revascularization procedures in patients with clinically evident CHD; Slow the progression of atherosclerosis in patients with CHD.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021192Orig1s019

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	X
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	X
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021192Orig1s019

APPROVAL LETTER



NDA 20261/S-046
NDA 21192/S-019

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Raffy H. Chilingirian, DMH
Global Drug Regulatory Affairs
One Health Plaza
East Hanover, New Jersey 07636-1080

Dear Dr. Chilingirian:

Please refer to your Supplemental New Drug Application (sNDA) dated September 1, 2011, received September 2, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lescol (fluvastatin sodium) Capsules 20 mg and 40 mg (NDA 20-261) and Lescol XL (fluvastatin sodium) Extended-Release Tablets 80 mg (NDA 21-192).

We acknowledge receipt of your amendments dated October 5, 2011, and January 5, and February 8, 2011.

We also refer to our letter dated August 11, 2011, requesting that sponsors of HMG-CoA reductase inhibitor (statin) drugs, modify their labeling based on our comprehensive review of clinical trial data, Adverse Event Reporting System (AERS) reports, the published literature, and the labels of other approved drugs containing information on statin coadministration.

This "Prior Approval" supplemental new drug application provides for revisions to the **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS** sections of the Highlights of Prescribing Information section and changes to the **WARNINGS AND PRECAUTIONS**, **ADVERSE REACTIONS**, **DRUG INTERACTIONS**, **CLINICAL PHARMACOLOGY**, and **PATIENT COUNSELING INFORMATION** sections of the Full Prescribing Information sections of the Lescol/Lescol XL package insert, and corresponding revisions to the Lescol/Lescol XL patient package insert.

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA

automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

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

If you have any questions, call Margaret Simoneau, M.S., R.Ph., Regulatory Project Manager, at (301) 796-1295.

Sincerely,

{See appended electronic signature page}

Amy G. Egan, M.D., M.P.H.
Deputy Director for Safety
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

AMY G EGAN
02/28/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
021192Orig1s019

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Lescol®/ Lescol® XL safely and effectively. See full prescribing information for Lescol®/ Lescol® XL.

Lescol® (fluvastatin sodium) capsules/ Lescol® XL (fluvastatin sodium) extended-release tablets for oral use

Initial U.S. Approval: 1993/ 2000

INDICATIONS AND USAGE

LESCOL/LESCOL XL is an HMG-CoA reductase inhibitor (statin) indicated as an adjunctive therapy to diet to:

- Reduce elevated TC, LDL-C, Apo B, and TG, and to increase HDL-C in adult patients with primary hypercholesterolemia and mixed dyslipidemia (1.1)
- Reduce elevated TC, LDL-C, and Apo B levels in boys and post-menarchal girls, 10 to 16 years of age, with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy (1.1)
- Reduce the risk of undergoing revascularization procedures in patients with clinically evident CHD (1.2)
- Slow the progression of atherosclerosis in patients with CHD (1.2)

Limitations of Use:

- 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) (1.3)

DOSAGE AND ADMINISTRATION

- Dose range: 20 mg to 80 mg/ day (2.1)
- LESCOL/LESCOL XL can be taken with or without food. Only LESCOL XL may be taken at any time of the day (2.1)
- Do not break, crush or chew LESCOL XL tablets or open LESCOL capsules prior to administration (2.1)
- Adults: the recommended starting dose is 40 mg to 80 mg (administered as one LESCOL 40 mg capsule twice daily, or one 80 mg LESCOL XL once daily) (2.2)
- Do not take two LESCOL 40 mg capsules at one time
- Children with heterozygous familial hypercholesterolemia (ages 10 to 16, inclusive): the recommended starting dose is LESCOL capsule 20 mg once daily (2.3)

DOSAGE FORMS AND STRENGTHS

LESCOL Capsules: 20 mg, 40 mg;

LESCOL XL Tablets: 80 mg (3)

CONTRAINDICATIONS

- Hypersensitivity to any component of this medication (4) Active liver disease or unexplained, persistent elevations in serum transaminases (4, 5.2)

- Women who are pregnant or may become pregnant (4, 8.1)
- Nursing mothers (4, 8.3)

WARNINGS AND PRECAUTIONS

- **Skeletal muscle effects (e.g. myopathy and rhabdomyolysis):** Risks increase with advanced age (≥ 65), uncontrolled hypothyroidism, renal impairment, and combination use with cyclosporine, or gemfibrozil (5.1, 8.5, 8.7)
- Patients should be advised to report promptly any symptoms of myopathy. LESCOL/LESCOL XL therapy should be discontinued if myopathy is diagnosed or suspected (5.1)
- **Liver enzyme abnormalities:** Persistent elevations in hepatic transaminases can occur. Check liver enzyme tests before initiating therapy and as clinically indicated thereafter (5.2)

ADVERSE REACTIONS

Most frequent adverse reactions (rate $\geq 2\%$ and $>$ placebo) are: headache, dyspepsia, myalgia, abdominal pain and nausea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- **Cyclosporine:** Combination increases fluvastatin exposure. Limit LESCOL dose to 20 mg (2.4, 7.1)
- **Fluconazole:** Combination increases fluvastatin exposure. Limit LESCOL dose to 20 mg (2.5, 7.2)
- **Concomitant lipid-lowering therapies:** Use with fibrates or lipid-modifying doses (≥ 1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with LESCOL/LESCOL XL (5.1, 7.3, 7.4)
- **Glyburide:** Monitor blood glucose levels when fluvastatin dose is changed (7)
- **Phenytoin:** Monitor plasma phenytoin levels when fluvastatin treatment is initiated or when the dosage is changed (7)
- **Warfarin and coumarin derivatives:** Monitor prothrombin times when fluvastatin co-administration is initiated, discontinued, or the dosage changed (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 02/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia
- 1.2 Secondary Prevention of Cardiovascular Disease
- 1.3 Limitations of Use

2 DOSAGE AND ADMINISTRATION

- 2.1 General Dosing Information
- 2.2 Adult Patients with Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia
- 2.3 Pediatric Patients (10-16 years of age) with Heterozygous Familial Hypercholesterolemia
- 2.4 Use with Cyclosporine
- 2.5 Use with Fluconazole

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

- 4.1 Hypersensitivity to any Component of this Medication
- 4.2 Active Liver Disease
- 4.3 Pregnancy
- 4.4 Nursing Mothers

5 WARNINGS AND PRECAUTIONS

- 5.1 Skeletal Muscle
- 5.2 Liver Enzymes
- 5.3 Endocrine Effects
- 5.4 CNS Toxicity

6 ADVERSE REACTIONS

- 6.1 Clinical Studies Experience in Adult Patients
- 6.2 Clinical Studies Experience in Pediatric Patients
- 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Cyclosporine
- 7.2 Fluconazole
- 7.3 Gemfibrozil
- 7.4 Other Fibrates

- 7.5 Niacin
- 7.6 Glyburide
- 7.7 Phenytoin
- 7.8 Warfarin
- 7.9 Colchicine

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment
- 8.7 Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia
- 14.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients
- 14.3 Secondary Prevention of Cardiovascular Disease

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

- 17.1 Muscle Pain
- 17.2 Liver Enzymes
- 17.3 Pregnancy
- 17.4 Breastfeeding

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Drug therapy is indicated as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other non-pharmacologic measures alone has been inadequate.

1.1 Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia

LESCOL and LESCOL XL are indicated

- as an adjunct to diet to reduce elevated total cholesterol (Total-C), 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).
- as an adjunct to diet to reduce Total-C, LDL-C, and Apo B levels in adolescent boys and adolescent girls who are at least one year post-menarche, 10-16 years of age, with heterozygous familial hypercholesterolemia and the following findings are present:
 - LDL-C remains ≥ 190 mg/dL or
 - LDL-C remains ≥ 160 mg/dL and:
 - there is a positive family history of premature cardiovascular disease or
 - two or more other cardiovascular disease risk factors are present

The NCEP classification of cholesterol levels in pediatric patients with a familial history of hypercholesterolemia or premature CVD is summarized below.

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

Children treated with fluvastatin in adolescence should be re-evaluated in adulthood and appropriate changes made to their cholesterol-lowering regimen to achieve adult treatment goals.

1.2 Secondary Prevention of Cardiovascular Disease

In patients with clinically evident CHD, LESCOL and LESCOL XL are indicated to:

- reduce the risk of undergoing coronary revascularization procedures
- slow the progression of coronary atherosclerosis

1.3 Limitations of Use

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).

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

Dose range: 20 mg to 80 mg/ day.

LESCOL/LESCOL XL can be administered orally as a single dose, with or without food.

Do not break, crush or chew LESCOL XL tablets or open LESCOL capsules prior to administration.

Do not take two LESCOL 40 mg capsules at one time.

Since the maximal effect of a given dose is seen within 4 weeks, periodic lipid determinations should be performed at this time and dosage adjusted according to the patient's response to therapy and established treatment guidelines.

For patients requiring LDL-C reduction to a goal of $\geq 25\%$, the recommended starting dose is 40 mg as one capsule in the evening, 80 mg as one LESCOL XL tablet administered as a single dose at any time of the day 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.

2.2 Adult Patients with Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia

Adult patients can be started on either LESCOL or LESCOL XL. The recommended starting dose for LESCOL is one 40 mg capsule in the evening, or one LESCOL 40 mg capsule twice daily. Do not take two LESCOL 40 mg capsules at one time.

The recommended starting dose for LESCOL XL is one 80 mg tablet administered as a single dose at any time of the day.

2.3 Pediatric Patients (10-16 years of age) with Heterozygous Familial Hypercholesterolemia

The recommended starting dose is one 20 mg LESCOL capsule. Dose adjustments, up to a maximum daily dose administered either as LESCOL capsules 40 mg twice daily or one LESCOL XL 80 mg tablet once daily should be made at 6 week intervals. Doses should be individualized according to the goal of therapy [see *NCEP Pediatric Panel Guidelines* and *CLINICAL STUDIES (14)*]¹.

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

2.4 Use with Cyclosporine

Do not exceed a dose of 20 mg b.i.d. LESCOL in patients taking cyclosporine [see *Drug Interactions 7.1*].

2.5 Use with Fluconazole

Do not exceed a dose of 20 mg b.i.d. LESCOL in patients taking fluconazole [see *Drug Interactions 7.2*].

3 DOSAGE FORMS AND STRENGTHS

- LESCOL 20 mg capsules are 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.
- LESCOL 40 mg capsules are 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.
- LESCOL XL 80 mg tablets are yellow, round, slightly biconvex film-coated tablet with beveled edges debossed with “LESCOL XL” on one side and “80” on the other.

4 CONTRAINDICATIONS

4.1 Hypersensitivity to any Component of this Medication

LESCOL and LESCOL XL are contraindicated in patients with hypersensitivity to any component of this medication.

4.2 Active Liver Disease

LESCOL and LESCOL XL are contraindicated in patients with active liver disease or unexplained, persistent elevations in serum transaminases [see *Warnings and Precautions (5.2)*].

4.3 Pregnancy

LESCOL and LESCOL XL are contraindicated in women who are pregnant or may become pregnant. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. LESCOL and LESCOL XL may cause fetal harm when administered to pregnant women. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia.

LESCOL and LESCOL XL should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking this drug, LESCOL and LESCOL XL should be discontinued and the patient should be apprised of the potential hazard to the fetus [see *Use In Specific Populations (8.1)*].

4.4 Nursing Mothers

Fluvastatin is secreted into the breast milk of animals and because HMG-CoA reductase inhibitors have the potential to cause serious adverse reactions in nursing infants, women who require treatment with LESCOL or LESCOL XL should be advised not to breastfeed their infants [see *Use In Specific Populations (8.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle

Rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with LESCOL/LESCOL XL and other drugs in this class.

LESCOL/LESCOL XL should be prescribed with caution in patients with predisposing factors for myopathy. These factors include advanced age (>65 years), renal impairment, and inadequately treated hypothyroidism.

The risk of myopathy and/or rhabdomyolysis with statins is increased with concurrent therapy with cyclosporine, erythromycin, fibrates or niacin. Myopathy was not observed in a clinical trial in 74 patients involving patients who were treated with LESCOL/LESCOL XL together with niacin. Isolated cases of myopathy have been reported during post-marketing experience with concomitant administration of LESCOL/LESCOL XL and colchicine. No information is available on the pharmacokinetic interaction between LESCOL/LESCOL XL and colchicine.

Uncomplicated myalgia has also been reported in LESCOL-treated patients [see *Adverse Reactions* (6)]. In clinical trials, uncomplicated myalgia has been observed infrequently in patients treated with LESCOL at rates indistinguishable from placebo. Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in CPK values to greater than 10 times the upper limit of normal, was <0.1% in fluvastatin clinical trials. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

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

5.2 Liver Enzymes

Increases in serum transaminases (aspartate aminotransferase [AST]/serum glutamic-oxaloacetic transaminase, or alanine aminotransferase [ALT]/serum glutamic-pyruvic transaminase) have been reported with HMG-CoA reductase inhibitors, including LESCOL/LESCOL XL. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy.

Approximately 1.1% of patients treated with LESCOL capsules in worldwide trials developed dose-related, persistent elevations of serum 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 LESCOL 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 daily doses of 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 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 enzyme tests be performed prior to the initiation of LESCOL/LESCOL XL, and if signs or symptoms of liver injury occur.

There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including fluvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with LESCOL/LESCOL XL, promptly interrupt therapy. If an alternate etiology is not found do not restart LESCOL/LESCOL XL.

In very rare cases, possibly drug-related hepatitis was observed that resolved upon discontinuation of treatment.¹ Active liver disease or unexplained serum transaminase elevations are contraindications to the use of LESCOL and LESCOL XL [see *Contraindications (4)* and *Warnings and Precautions (5.2)*]. Caution should be exercised when LESCOL is administered to patients with a history of liver disease or heavy alcohol ingestion [see *Clinical Pharmacology (12.4)*]. Such patients should be closely monitored.

5.3 Endocrine Effects

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including LESCOL/LESCOL XL.

Statins interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production.

LESCOL/LESCOL XL exhibited no effect upon non-stimulated cortisol levels and demonstrated no effect upon thyroid metabolism as assessed by measurement of thyroid stimulating hormone (TSH). Small declines in total serum 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 LESCOL/LESCOL XL 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 LESCOL 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 LESCOL or placebo.

Patients treated with LESCOL/LESCOL XL who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if a statin or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g. ketoconazole, spironolactone, cimetidine) that may decrease the levels of endogenous steroid hormones.

5.4 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 rats) 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 drug 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.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Rhabdomyolysis with myoglobinuria and acute renal failure and myopathy (including myositis) [see *Warnings and Precautions (5.1)*].
- Liver Enzyme Abnormalities [see *Warnings and Precautions (5.2)*].

6.1 Clinical Studies Experience in Adult Patients

Because clinical studies on LESCOL/LESCOL XL are conducted in varying study populations and study designs, the frequency of adverse reactions observed in the clinical studies of LESCOL/LESCOL XL cannot be directly compared with that in the clinical studies of other statins and may not reflect the frequency of adverse reactions observed in clinical practice.

In the LESCOL placebo-controlled clinical trials database of 2326 patients treated with LESCOL¹ (age range 18-75 years, 44% women, 94% Caucasians, 4% Blacks, 2% other ethnicities) with a median treatment duration of 24 weeks, 3.4% of patients on LESCOL and 2.3% patients on placebo discontinued due to adverse reactions regardless of causality. The most common adverse reactions that led to treatment discontinuation and occurred at an incidence greater than placebo were: transaminase increased (0.8%), upper abdominal pain (0.3%), dyspepsia (0.3%), fatigue (0.2%) and diarrhea (0.2%).

In the LESCOL XL database of controlled clinical trials of 912 patients treated with LESCOL XL (age range 21-87 years, 52% women, 91% Caucasians, 4% Blacks, 5% other ethnicities) with a median treatment duration of 24 weeks, 3.9% of patients on LESCOL XL discontinued due to adverse reactions regardless of causality. The most common adverse reactions that led to treatment discontinuation were abdominal pain (0.7%), diarrhea (0.5%), nausea (0.4%), dyspepsia (0.4%) and chest pain (0.3%).

Clinically relevant adverse experiences occurring in the LESCOL and LESCOL XL controlled studies with a frequency $\geq 2\%$, regardless of causality, included the following:

Table 1 Clinical adverse events reported in $>2\%$ in patients treated with LESCOL/LESCOL XL and at an incidence greater than placebo in placebo-controlled trials regardless of causality (% of patients) Pooled Dosages

		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
	Tooth disorder	2.1	1.7	1.4
	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) compared to placebo

² Controlled trials with LESCOL XL 80 mg Tablets as compared to LESCOL Capsules

LESCOL Intervention Prevention Study

In the LESCOL Intervention Prevention Study (LIPS), the effect of LESCOL 40 mg, administered twice daily on the risk of recurrent cardiac events was assessed in 1677 patients with CHD who had undergone a percutaneous coronary intervention (PCI) procedure. This was a 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 [see *Clinical Studies* (14.3)].

Table 2 Clinical adverse events reported in $\geq 2\%$ in patients treated with LESCOL/LESCOL XL and at an incidence greater than placebo in the LIPS Trial regardless of causality (% of patients)

	LESCOL 40 mg b.i.d. N=822 (%)	Placebo N=818 (%)
--	--	-------------------------

		LESCOL 40 mg b.i.d. N=822 (%)	Placebo N=818 (%)
Cardiac disorders	Atrial fibrillation	2.4	2.0
Gastrointestinal disorders	Abdominal pain upper	6.3	4.5
	Constipation	3.3	2.1
	Dyspepsia	4.5	4.0
	Gastric disorder	2.7	2.1
	Nausea	2.7	2.3
General disorders	Fatigue	4.7	3.8
	Edema peripheral	4.4	2.9
Infections and infestations	Bronchitis	2.3	2.0
	Nasopharyngitis	2.8	2.1
Musculoskeletal and connective tissue disorders	Arthralgia	2.1	1.8
	Myalgia	2.2	1.6
	Pain in extremity	4.1	2.7
Nervous system disorders	Dizziness	3.9	3.5
	Syncope	2.4	2.2
Respiratory disorders	Dyspnea exertional	2.8	2.4
Vascular disorders	Hypertension	5.8	4.2
	Intermittent claudication	2.3	2.1

6.2 Clinical Studies Experience in Pediatric Patients

In patients aged <18 years, efficacy and safety have not been studied for treatment periods longer than two years.

In two open-label, uncontrolled studies, 66 boys and 48 girls with heterozygous familial hypercholesterolemia (9-16 years of age, 80% Caucasian, 19% Other [mixed ethnicity], 1% Asians) were treated with fluvastatin sodium administered as LESCOL capsules 20 mg -40 mg twice daily, or LESCOL XL 80 mg extended-release tablet [see *Clinical Studies (14.2)* and *Use In Specific Populations (8.4)*].

6.3 Postmarketing Experience

Because adverse reactions from spontaneous reports are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. 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.

Musculoskeletal: muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias, muscle spasms, muscle weakness, myositis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, vertigo, paresthesia, hypoesthesia, dysesthesia, peripheral neuropathy, peripheral nerve palsy.

There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Psychiatric: anxiety, insomnia, depression, psychic disturbances

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 (erythrocyte sedimentation rate) increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity reaction, 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, cirrhosis, fulminant hepatic necrosis, hepatoma, anorexia, vomiting, fatal and non-fatal hepatic failure.

Skin: rash, dermatitis, including bullous dermatitis, eczema, alopecia, pruritus, a variety of skin changes (e.g. nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails).

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

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

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

7 DRUG INTERACTIONS

7.1 Cyclosporine

Cyclosporine coadministration increases fluvastatin exposure. Therefore, in patients taking cyclosporine, therapy should be limited to LESCOL 20 mg twice daily [see *Warnings and Precautions* (5.1) and *Clinical Pharmacology* (12.3)].

7.2 Fluconazole

Administration of fluvastatin 40 mg single dose to healthy volunteers pre-treated with fluconazole for 4 days results in an increase of fluvastatin exposure. Therefore, in patients taking fluconazole, therapy should be limited to LESCOL 20 mg twice daily [see *Clinical Pharmacology* (12.3)].

7.3 Gemfibrozil

Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are coadministered with gemfibrozil, concomitant administration of LESCOL/LESCOL XL with gemfibrozil should be avoided.

7.4 Other Fibrates

Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of other fibrates, LESCOL/LESCOL XL should be administered with caution when used concomitantly with other fibrates [see *Warnings and Precautions* (5.1) and *Clinical Pharmacology* (12.3)].

7.5 Niacin

The risk of skeletal muscle effects may be enhanced when LESCOL is used in combination with lipid-modifying doses (≥ 1 g/day) of niacin; a reduction in LESCOL dosage should be considered in this setting [see *Warnings and Precautions* (5.1)].

7.6 Glyburide

Concomitant administration of fluvastatin and glyburide increased glyburide exposures. Patients on concomitant therapy of glyburide and fluvastatin should continue to be monitored appropriately [see *Clinical Pharmacology* (12.3)].

7.7 Phenytoin

Concomitant administration of fluvastatin and phenytoin increased phenytoin exposures. Patients should continue to be monitored appropriately when fluvastatin therapy is initiated or when fluvastatin dose is changed [see *Clinical Pharmacology* (12.3)].

7.8 Warfarin

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.

7.9 Colchicine

Cases of myopathy, including rhabdomyolysis, have been reported with fluvastatin coadministered with colchicine, and caution should be exercised when prescribing fluvastatin with colchicine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

LESCOL/LESCOL XL is contraindicated in women who are or may become pregnant [see *Contraindications (4)*].

Lipid lowering drugs are contraindicated during pregnancy, because cholesterol and cholesterol derivatives are needed for normal fetal development. Serum cholesterol and triglycerides increase during normal pregnancy. Atherosclerosis is a chronic process, and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hypercholesterolemia therapy

There are no adequate and well-controlled studies of use with LESCOL/LESCOL XL during pregnancy. Rare reports of congenital anomalies have been received following intrauterine exposure to other statins. In a review² of about 100 prospectively followed pregnancies in women exposed to other statins, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed the rate expected in the general population. The number of cases is adequate only to exclude a 3- to 4-fold increase in congenital anomalies over background incidence. In 89% of prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified.

Teratology studies with fluvastatin in rats and rabbits showed maternal toxicity at high dose levels, but there was no evidence of embryotoxic or teratogenic potential [see *Non-Clinical Toxicology (13)*].

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.

8.3 Nursing Mothers

Based on animal data, fluvastatin 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 (4)*].

8.4 Pediatric Use

The safety and efficacy of LESCOL and LESCOL XL in children and adolescent patients 9-16 years of age with heterozygous familial hypercholesterolemia have been evaluated in open-label, uncontrolled clinical trials for a duration of two years. The most common adverse events observed were influenza and infections. In these limited uncontrolled studies, there was no detectable effect on growth or sexual maturation in the adolescent boys or on menstrual cycle length in girls [see *Clinical Studies (14.2)*, *Adverse Reactions (6.3)* and *Dosage And Administration (2.2)*]. Adolescent females should be counseled on appropriate contraceptive methods while on LESCOL therapy [see *Contraindications (4)*].

8.5 Geriatric Use

Fluvastatin exposures were not significantly different between the nonelderly and elderly populations (age ≥ 65 years) [see *Clinical Pharmacology (12.3)*]. Since advanced age (≥ 65 years) is a predisposing factor for myopathy, LESCOL/LESCOL XL should be prescribed with caution in the elderly.

8.6 Hepatic Impairment

LESCOL and LESCOL XL are contraindicated in patients with active liver disease or unexplained, persistent elevations in serum transaminases [see *Clinical Pharmacology (12.3)*].

8.7 Renal Impairment

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 [see *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

To date, there has been limited experience with overdosage of fluvastatin. If an overdose occurs, it should be treated symptomatically with laboratory monitoring and supportive measures should be instituted as required. The dialyzability of fluvastatin sodium and of its metabolites in humans is not known at present [see *Warnings and Precautions (5)*].

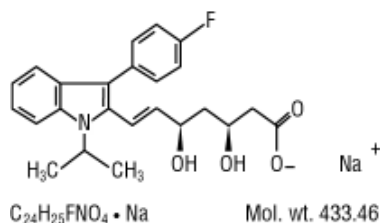
In the pediatric population, there have been reports of overdose with fluvastatin sodium in children including a 2 year-old and the other 3 years of age, either of whom may have possibly ingested fluvastatin sodium. The maximum amount of fluvastatin sodium that could have been ingested was 80 mg (4 x 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.

In the postmarketing experience there have been reports of accidental ingestion of LESCOL tablets in infants up to 3 years of age. In one case, increased serum CPK values were noted. There have been reports of intentional overdose in adolescents with the development of hepatic enzyme elevations, convulsions and gastroenteritis/vomiting/diarrhea. One case of intentional overdose as suicide attempt in a 15 year-old female reported ingestion of 2,800 mg LESCOL XL with hepatic enzyme elevation.

11 DESCRIPTION

LESCOL 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 C₂₄H₂₅FNO₄•Na, its molecular weight is 433.46 and its structural formula is:



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 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: calcium carbonate, gelatin, magnesium stearate, microcrystalline cellulose, pregelatinized starch (corn), red iron oxide, sodium bicarbonate, 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, sodium lauryl sulfate, and sodium propionate.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

LESCOL is a competitive inhibitor of HMG-CoA reductase, the rate limiting enzyme that converts 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.

12.3 Pharmacokinetics

Absorption:

Following oral administration of the capsule, fluvastatin reaches peak concentrations in less than 1 hour. The absolute bioavailability is 24% (range 9%-50%) after administration of a 10 mg dose.

At steady state, administration of fluvastatin with the evening meal results in a 50% decrease in C_{max} , a 11% decrease in AUC, and a more than two-fold increase in t_{max} as compared to administration 4 hours after the evening meal. No significant differences 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 more than dose proportional plasma fluvastatin concentrations.

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%. However, the maximum concentration of LESCOL XL seen after a high-fat meal is less than the peak concentration following a single dose or twice daily dose of the 40 mg LESCOL capsule.

Distribution:

Fluvastatin is 98% bound to plasma proteins. The mean volume of distribution (VD_{ss}) is estimated at 0.35 L/kg. 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. Fluvastatin has two enantiomers. Both enantiomers of fluvastatin are metabolized in a similar manner.

In vitro data indicate that fluvastatin metabolism involves multiple Cytochrome P450 (CYP) isozymes. CYP2C9 isoenzyme is primarily involved in the metabolism of fluvastatin (approximately 75%), while CYP2C8 and CYP3A4 isoenzymes are involved to a much less extent, i.e. approximately 5% and approximately 20%, respectively.

Excretion:

Following oral administration, fluvastatin is primarily (about 90%) excreted in the feces as metabolites, with less than 2% present as unchanged drug. Approximately 5% of a radiolabeled oral dose were recovered in urine. The elimination half-life ($t_{1/2}$) of fluvastatin is approximately 3 hours.

Specific Populations

Renal Impairment:

In patients with moderate to severe renal impairment (CL_{Cr} 10-40 mL/min), AUC and C_{max} increased approximately 1.2-fold after administration of a single dose of 40 mg fluvastatin compared to healthy volunteers. In patients with end-stage renal disease on hemodialysis, the AUC increased by approximately 1.5-fold. LESCOL XL was not evaluated in patients with renal impairment. However, systemic exposures after administration of LESCOL XL are lower than after the 40 mg immediate release capsule.

Hepatic Impairment:

In patients with hepatic impairment due to liver cirrhosis, fluvastatin AUC and C_{max} increased approximately 2.5-fold compared to healthy subjects after administration of a single 40 mg dose. The enantiomer ratios of the two isomers of fluvastatin in hepatic impairment patients were comparable to those observed in healthy subjects.

Geriatric:

Plasma levels of fluvastatin are not significantly different in patients age > 65 years compared to patients age 21 to 49 years.

Gender:

In a study evaluating the effect of age and gender on fluvastatin pharmacokinetics, there was no significant differences in fluvastatin exposures between males and females, except between younger females and younger males (both ages 21-49 years), where there was an approximate 30% increase in AUC in females. Adjusting for body weight decreases the magnitude of the differences seen. For LESCOL XL, the AUC increases 67% and 77% for women compared to men under fasted and high-fat meal fed conditions, respectively.

Pediatric:

Pharmacokinetic data in the pediatric population are not available.

Drug-Drug Interactions:

Data from drug-drug interactions studies involving coadministration of gemfibrozil, niacin, itraconazole, erythromycin, tolbutamide or clopidogrel indicate that the PK disposition of fluvastatin is not significantly altered when fluvastatin is coadministered with any of these drugs.

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

Table 3 Effect of Co-administered Drugs on Fluvastatin Systemic Exposure

Co-administered drug and dosing regimen	Fluvastatin		
	Dose (mg)*	Change in AUC**	Change in Cmax**
Cyclosporine – stable dose (b.i.d.) [†]	20 mg QD for 14 weeks	↑ 90%	↑ 30%
Fluconazole 400 mg QD day 1, 200 mg b.i.d. day 2- 4 [†]	40 mg QD	↑ 84%	↑ 44%
Cholestyramine 8 g QD	20 mg QD administered 4 hrs after a meal plus cholestyramine	↓ 51%	↓ 83%
Rifampicin 600 mg QD for 6 days	20 mg QD	↓ 53%	↓ 42%
Cimetidine 400 mg b.i.d. for 5 days, QD on Day 6	20 mg QD	↑ 30%	↑ 40%
Ranitidine 150 mg b.i.d. for 5 days, QD on Day 6	20 mg QD	↑ 10%	↑ 50%
Omeprazole 40 mg QD for 6 days	20 mg QD	↑ 20%	↑ 37%
Phenytoin 300 mg QD	40 mg b.i.d. for 5 days	↑ 40 %	↑ 27%
Propranolol 40 mg b.i.d. for 3.5 days	40 mg QD	↓ 5%	No change
Digoxin 0.1 – 0.5 mg QD for 3 weeks	40 mg QD	No change	↑ 11%
Diclofenac 25 mg QD	40 mg QD for 8 days	↑50 %	↑ 80%
Glyburide 5 – 20 mg QD for 22 days	40 mg b.i.d for 14 days	↑ 51%	↑ 44%
Warfarin 30 mg QD	40 mg QD for 8 days	↑ 30%	↑ 67%
Clopidogrel 300 mg loading dose on day 10, 75 mg QD on days 11-19	80 mg XL QD for 19 days	↓ 2%	↑ 27%

*Single dose unless otherwise noted

**Mean ratio (with/without coadministered drug and no change = 1-fold) or % change (with/without coadministered drug and no change = 0%); symbols of ↑ and ↓ indicate the exposure increase and decrease, respectively.

† Considered clinically significant [see *Dosage And Administration (2)* and *Drug Interactions (7)*]

Data from drug-drug interaction studies involving fluvastatin and coadministration of either gemfibrozil, tolbutamide or losartan indicate that the PK disposition of either gemfibrozil, tolbutamide or losartan is not significantly altered when coadministered with fluvastatin.

Table 4 Effect of Fluvastatin Co-Administration on Systemic Exposure of Other Drugs

Fluvastatin dosage regimen	Co-administered drug		
	Name and Dose (mg) *	Change in AUC **	Change in Cmax **
40 mg QD for 5 days	Phenytoin 300 mg QD [†]	↑ 20%	↑ 5%
40 mg b.i.d. for 21 days	Glyburide 5 – 20 mg QD for 22 days [†]	↑ 70%	↑ 50%
40 mg QD for 8 days	Diclofenac 25 mg QD	↑ 25%	↑ 60%
40 mg QD for 8 days	Warfarin 30 mg QD	S-warfarin: ↑7%	S-warfarin: ↑ 10%
		R-warfarin: no change	R-warfarin: ↑ 6%

*Single dose unless otherwise noted

**Mean ratio (with/without coadministered drug and no change = 1-fold) or % change (with/without coadministered drug and no change = 0%); symbols of ↑ and ↓ indicate the exposure increase and decrease, respectively.

† Considered clinically significant [see *Dosage And Administration (2)* and *Drug Interactions (7)*]

13 NONCLINICAL TOXICOLOGY

13.1 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 mg human daily dose based on surface area, mg/m²). 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 mg daily dose).

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/m² 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.

14 CLINICAL STUDIES

14.1 Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia

In 12 placebo-controlled studies in patients with primary hypercholesterolemia and mixed dyslipidemia, LESCOL 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 (Table 5). After 24 weeks of treatment, treatment with LESCOL resulted in significantly reduced plasma LDL-C, TC, TG, and Apo B compared to placebo and was associated with variable increases in HDL-C across the dose range.

LESCOL XL has been studied in five controlled studies of patients with primary hypercholesterolemia and mixed dyslipidemia. 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 and resulted in increases in HDL-C (Table 5).

In patients with primary mixed dyslipidemia as defined by baseline plasma TG levels ≥200 mg/dL and <400 mg/dL, treatment with LESCOL/LESCOL XL produced significant decreases in Total-C, LDL-C, TG and Apo B and variable increases in HDL-C (Table 5).

**Table 5 Median Percent Change in Lipid Parameters from Baseline to Week 24 Endpoint
All Placebo-Controlled Studies (LESCOL) and Active Controlled Trials (LESCOL XL)**

Dose	Total Chol		TG		LDL		Apo B		HDL	
	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

14.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients

LESCOL was studied in two open-label, uncontrolled, dose-titration studies. The first study enrolled 29 pre-pubertal boys, 9-12 years of age, who had an LDL-C level >90th percentile for age and one parent with primary hypercholesterolemia and either a family history of premature ischemic heart disease or tendon xanthomas. The mean baseline LDL-C was 226 mg/dL (range: 137-354 mg/dL). All patients were started on LESCOL capsules 20 mg daily with dose adjustments every

6 weeks to 40 mg daily then 80 mg daily (40 mg b.i.d.) to achieve an LDL-C goal between 96.7 – 123.7 mg/dL. Endpoint analyses were performed at Year 2. LESCOL decreased plasma levels of Total-C and LDL-C by 21% and 27%, respectively. The mean achieved LDL-C was 161 mg/dL (range: 74-336 mg/dL).

The second study enrolled 85 male and female patients, 10 to 16 years of age, who had an LDL-C >190 mg/dL or LDL-C >160 mg/dL and one or more risk factors for coronary heart disease, or LDL-C >160 mg/dL and a proven LDL-receptor defect. The mean baseline LDL-C was 225 mg/dL (range: 148-343 mg/dL). All patients were started on LESCOL capsules 20 mg daily with dose adjustments every 6 weeks to 40 mg daily then 80 mg daily (LESCOL 80 mg XL tablet) to achieve an LDL-C goal of <130 mg/dL. Endpoint analyses were performed at Week 114. LESCOL decreased plasma levels of Total-C and LDL-C by 22% and 28%, respectively. The mean achieved LDL-C was 159 mg/dL (range: 90-295 mg/dL).

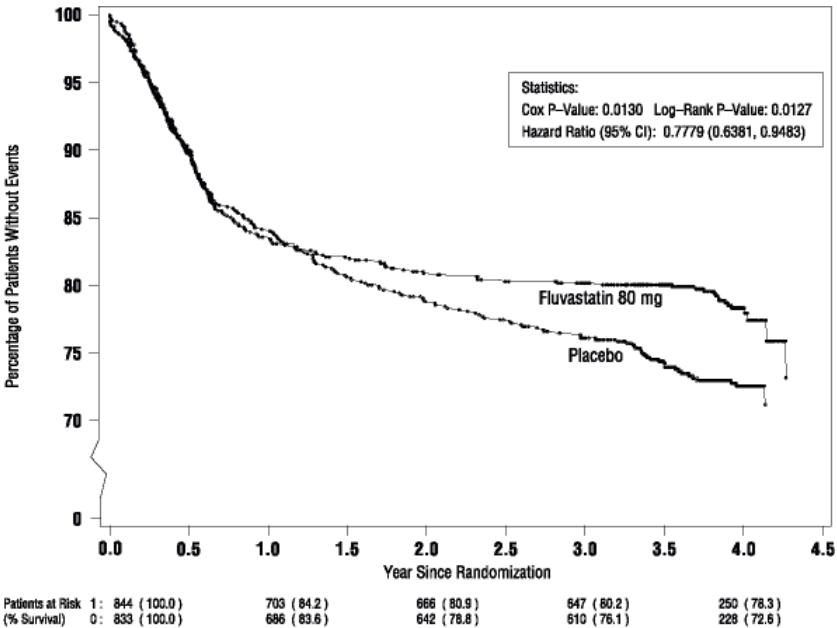
The majority of patients in both studies (83% in the first study and 89% in the second study) were titrated to the maximum daily dose of 80 mg. At study endpoint, 26% to 30% of patients in both studies achieved a targeted LDL-C goal of <130 mg/dL. The long-term efficacy of LESCOL or LESCOL XL therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

14.3 Secondary Prevention of Cardiovascular Disease

In the LESCOL Intervention Prevention Study (LIPS), 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 CHD 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. Mean baseline lipid concentrations were: total cholesterol 201 mg/dL, LDL-C 132 mg/dL, triglycerides 70 mg/dL and HDL-C 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.

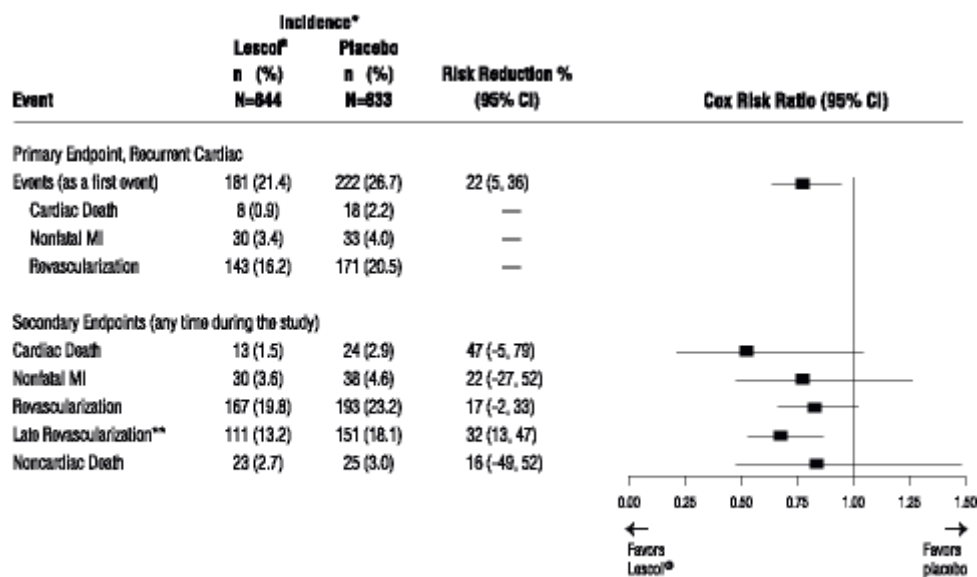
Figure 1 Primary Endpoint – Recurrent Cardiac Events (Cardiac Death, Nonfatal MI or Revascularization Procedure) (ITT Population)



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

instrumental 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



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 CAD 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 which 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.

Compared to placebo, LESCOL significantly slowed the progression of coronary atherosclerosis as measured by within-patient per-lesion change in minimum lumen diameter (MLD), the primary endpoint (Figure 3 below), percent diameter stenosis (Figure 4), and the formation of new lesions (13% of all fluvastatin patients versus 22% of all placebo patients). 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 Change in Minimum Lumen Diameter (mm)

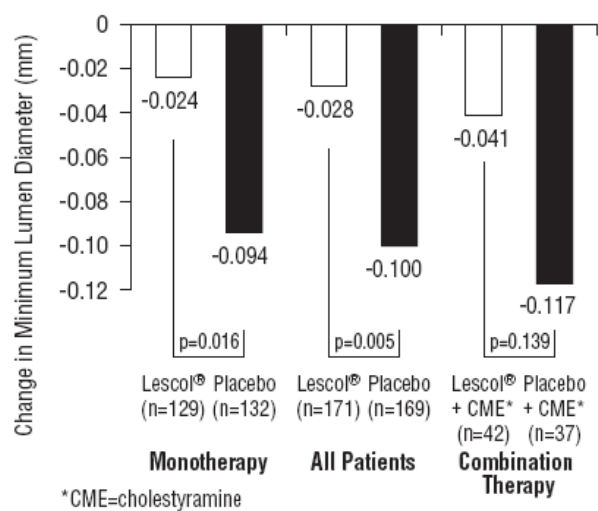
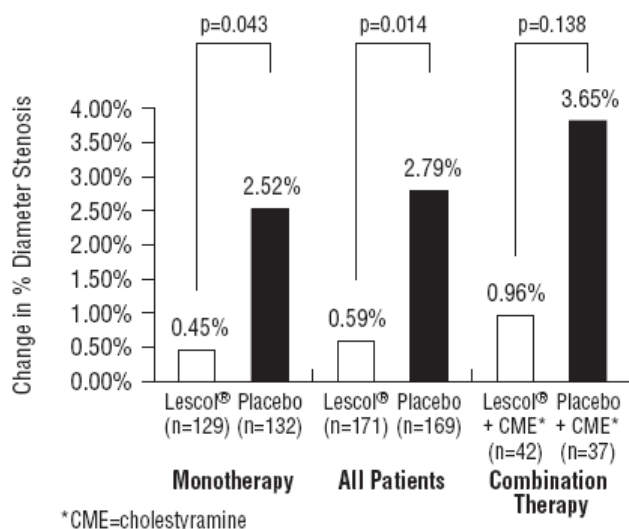


Figure 4 Change in % Diameter Stenosis



15 REFERENCES

1. National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics*. 89(3):495-501.1992.
2. Manson, J.M., Freyssinges, C., Ducrocq, M.B., Stephenson, W.P., Postmarketing Surveillance of Lovastatin and Simvastatin Exposure During Pregnancy, *Reproductive Toxicology*, 10(6): 439-446, 1996.

16 HOW SUPPLIED/STORAGE AND HANDLING

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 -30°C (59 -86°F) [see USP Controlled Room Temperature]. Dispense in a tight container. Protect from light.

17 PATIENT COUNSELING INFORMATION

Information for Patients

Patients taking LESCOL/LESCOL XL should be advised that high cholesterol is a chronic condition and they should adhere to their medication along with their National Cholesterol Education Program (NCEP)-recommended diet, a regular exercise program, and periodic testing of a fasting lipid panel to determine goal attainment.

Patients should be advised about substances they should not take concomitantly with LESCOL/LESCOL XL [see *Warnings and Precautions (5.1)*]. Patients should also be advised to inform other healthcare professionals prescribing a new medication that they are taking LESCOL/LESCOL XL.

17.1 Muscle Pain

Patients starting therapy with LESCOL/LESCOL XL should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

17.2 Liver Enzymes

It is recommended that liver enzyme tests be performed before the initiation of LESCOL/LESCOL XL and if signs or symptoms of liver injury occur. All patients treated with LESCOL/LESCOL XL should be advised to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice.

17.3 Pregnancy

Women of childbearing age should be advised to use an effective method of birth control to prevent pregnancy while using LESCOL/LESCOL XL. Discuss future pregnancy plans with your patients, and discuss when to stop taking LESCOL/LESCOL XL if they are trying to conceive. Patients should be advised that if they become pregnant they should stop taking LESCOL/LESCOL XL and call their healthcare professional.

17.4 Breastfeeding

Women who are breastfeeding should not use LESCOL/LESCOL XL. Patients who have a lipid disorder and are breastfeeding should be advised to discuss the options with their healthcare professional.

T2012-XX

FDA-Approved Patient Labeling

LESCOL[®] (fluvastatin sodium) Capsules

20 mg, 40 mg

LESCOL[®] XL (fluvastatin sodium) Extended-Release Tablets

80 mg

Rx Only

You must read and follow all instructions before using LESCOL or LESCOL XL.

Read the Patient Information every time you or a family member gets LESCOL or LESCOL XL. There may be new information. This Patient Information does not take the place of talking with your doctor about your medical condition or treatment. If you have any questions about LESCOL or LESCOL XL, ask your doctor or pharmacist.

What are LESCOL and LESCOL XL?

LESCOL and LESCOL XL are prescription medicines called "statins" that lower cholesterol in your blood. They lower the "bad" cholesterol and triglycerides in your blood. They can raise your "good" cholesterol as well.

LESCOL and LESCOL XL are for people whose cholesterol does not come down enough with exercise and a low-fat diet alone.

LESCOL and LESCOL XL may be used in patients with heart disease (coronary artery disease) to:

- lower the chances of heart problems which would require procedures to help restore blood flow to the heart.
- slow the buildup of too much cholesterol in the arteries of the heart.

Treatment with LESCOL or LESCOL XL has not been shown to prevent heart attacks or stroke.

LESCOL and LESCOL XL have the same active ingredient, fluvastatin. However, LESCOL is a capsule that is taken one or two times a day and LESCOL XL is an extended-release tablet that is only taken one time a day.

Who should not take LESCOL or LESCOL XL?

Do not take LESCOL or LESCOL XL if you:

- are pregnant or think you may be pregnant, or are planning to become pregnant. LESCOL and LESCOL XL may harm your unborn baby. If you get pregnant, stop taking LESCOL or LESCOL XL and call your doctor right away.
- are breast-feeding. LESCOL and LESCOL XL can pass into your breast milk and may harm your baby
- have liver problems
- are allergic to LESCOL or LESCOL XL or any of its ingredients. The active ingredient in LESCOL and LESCOL XL is fluvastatin. See the end of this leaflet for a complete list of ingredients in LESCOL and LESCOL XL.

LESCOL and LESCOL XL have not been studied in children under 9 years of age.

Before taking LESCOL or LESCOL XL, tell your doctor if you:

- have muscle aches or weakness
- drink more than 2 glasses of alcohol daily
- have diabetes
- have a thyroid problem
- have kidney problems

Some medicines should not be taken with LESCOL or LESCOL XL. Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. LESCOL and LESCOL XL and certain other medicines can interact causing serious side effects. Especially tell your doctor if you take medicines for:

- your immune system
- cholesterol
- infections
- heart failure
- seizures
- diabetes
- heartburn or stomach ulcers

Know all the medicines you take. Keep a list of all the medicines you take with you to show your doctor and pharmacist.

How should I take LESCOL or LESCOL XL?

- Your doctor will prescribe the medicine that is right for you. Take LESCOL or LESCOL XL exactly as prescribed. Do not change your dose or stop LESCOL or LESCOL XL without talking to your doctor. Your doctor may do blood tests to check your cholesterol levels during treatment with LESCOL and LESCOL XL. Your dose of LESCOL or LESCOL XL may be changed based on these blood test results.
- LESCOL XL tablets may be taken at any time of the day. Take LESCOL capsules at the same time every evening. When LESCOL capsules are taken twice daily, the capsules may be taken once in the morning and once in the evening. LESCOL and LESCOL XL can be taken with or without food.
- LESCOL XL tablets must be swallowed whole with a liquid. Do not break, crush or chew LESCOL XL tablets or open LESCOL capsules. Tell your doctor if you cannot swallow tablets whole. You may need LESCOL capsules or a different medicine instead of LESCOL XL tablets.
- Your doctor should start you on a low-fat and low-cholesterol diet before giving you LESCOL or LESCOL XL. Stay on this low-fat and low-cholesterol diet while taking LESCOL or LESCOL XL.
- If you miss a dose of LESCOL or LESCOL XL, take it as soon as you remember. Do not take LESCOL or LESCOL XL if it has been more than 12 hours since your last dose. Wait and take the next dose at your regular time. Do not take 2 doses of LESCOL or LESCOL XL at the same time.
- If you take too much LESCOL or LESCOL XL or overdose, call your doctor or Poison Control Center right away. Or, go to the nearest emergency room.

What should I avoid while taking LESCOL or LESCOL XL?

- Talk to your doctor before you start any new medicines. This includes prescription and nonprescription medicines, vitamins and herbal supplements. LESCOL and LESCOL XL and certain other medicines can interact causing serious side effects.
- Do not get pregnant. If you get pregnant, stop taking LESCOL or LESCOL XL right away and call your doctor.

What are the possible side effects of LESCOL and LESCOL XL?

When taking LESCOL and LESCOL XL, some patients may develop serious side effects, including:

muscle problems. These serious muscle problems can sometimes lead to kidney problems, including kidney failure. You have a higher chance for muscle problems if you are taking certain other medicines with LESCOL or LESCOL XL. Call your doctor right away if you have:

- muscle problems like weakness, tenderness, or pain that happen without a good reason, especially if you also have a fever or feel more tired than usual

liver problems. Your doctor should do blood tests to check your liver before you start taking LESCOL or LESCOL XL, and if you have symptoms of liver problems while you take LESCOL or LESCOL XL. Call your doctor right away if you have the following symptoms of liver problems:

- feel tired or weak
- loss of appetite
- upper belly pain

- dark amber colored urine
- yellowing of your skin or the whites of your eyes

The most common side effects of LESCOL or LESCOL XL are headache, upset stomach and stomach pain, diarrhea, flu-like symptoms, muscle pain, sinus infection, tiredness, or trouble sleeping. These side effects are usually mild and may go away. The following additional side effects have been reported with LESCOL/LESCOL XL: memory loss, and confusion.

Talk to your doctor or pharmacist if you have side effects that bother you or that will not go away.

These are not all the side effects of LESCOL and LESCOL XL. Ask your doctor or pharmacist for a complete list.

How should I store LESCOL and LESCOL XL?

- Store LESCOL and LESCOL XL at room temperature, 59° to 86° F (15° to 30° C). Protect from light.
- Do not keep medicine that is out of date or that you no longer need.
- Keep LESCOL and LESCOL XL out of the reach of children. Be sure that if you throw medicines away, it is out of the reach of children.

General information about LESCOL and LESCOL XL

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use LESCOL or LESCOL XL for a condition for which it was not prescribed. Do not give LESCOL or LESCOL XL to other people, even if they have the same problem you have; it may harm them.

For more information, you can also visit the Novartis Internet site at www.LESCOLXL.com or call the Novartis help line at 1-888-669-6682.

What are the ingredients in LESCOL and LESCOL XL?

Active Ingredient: fluvastatin sodium

Inactive Ingredients:

LESCOL Capsules: calcium carbonate, gelatin, magnesium stearate, microcrystalline cellulose, pregelatinized starch (corn), red iron oxide, sodium bicarbonate, talc, titanium dioxide, yellow iron oxide, and other ingredients. The capsules may also contain benzyl alcohol, black iron oxide, butylparaben, carboxymethylcellulose sodium, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide, sodium lauryl sulfate, and sodium propionate.

LESCOL XL Tablets: microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, potassium bicarbonate, povidone, magnesium stearate, yellow iron oxide, titanium dioxide and polyethylene glycol 8000.

Distributed by:

Novartis Pharmaceuticals Corporation

East Hanover, New Jersey 07936

© Novartis

T2012-XX/T2012-XX

February 2012/ February 2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021192Orig1s019

Tracked Changes Label

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Lescol®/ Lescol® XL safely and effectively. See full prescribing information for Lescol®/ Lescol® XL.

Lescol® (fluvastatin sodium) capsules/ Lescol® XL (fluvastatin sodium) extended-release tablets for oral use

Initial U.S. Approval: 1993/ 2000

INDICATIONS AND USAGE

LESCOL/LESCOL XL is an HMG-CoA reductase inhibitor (statin) indicated as an adjunctive therapy to diet to:

- Reduce elevated TC, LDL-C, Apo B, and TG, and to increase HDL-C in adult patients with primary hypercholesterolemia and mixed dyslipidemia (1.1)
- Reduce elevated TC, LDL-C, and Apo B levels in boys and post-menarchal girls, 10 to 16 years of age, with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy (1.1)
- Reduce the risk of undergoing revascularization procedures in patients with clinically evident CHD (1.2)
- Slow the progression of atherosclerosis in patients with CHD (1.2)

Limitations of Use:

- 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) (1.3)

DOSAGE AND ADMINISTRATION

- Dose range: 20 mg to 80 mg/ day (2.1)
- LESCOL/LESCOL XL can be taken with or without food. Only LESCOL XL may be taken at any time of the day (2.1)
- Do not break, crush or chew LESCOL XL tablets or open LESCOL capsules prior to administration (2.1)
- Adults: the recommended starting dose is 40 mg to 80 mg (administered as one LESCOL 40 mg capsule twice daily, or one 80 mg LESCOL XL once daily) (2.2)
- Do not take two LESCOL 40 mg capsules at one time
- Children with heterozygous familial hypercholesterolemia (ages 10 to 16, inclusive): the recommended starting dose is LESCOL capsule 20 mg once daily (2.3)

DOSAGE FORMS AND STRENGTHS

LESCOL Capsules: 20 mg, 40 mg;

LESCOL XL Tablets: 80 mg (3)

CONTRAINDICATIONS

- Hypersensitivity to any component of this medication (4) Active liver disease or unexplained, persistent elevations in serum transaminases (4, 5.2)

- Women who are pregnant or may become pregnant (4, 8.1)
- Nursing mothers (4, 8.3)

WARNINGS AND PRECAUTIONS

- **Skeletal muscle effects (e.g. myopathy and rhabdomyolysis):** Risks increase with advanced age (≥ 65), uncontrolled hypothyroidism, renal impairment, and combination use with cyclosporine, or gemfibrozil, or niacin co-administration (5.1, 8.5, 8.7, 6.3, 7.4)
- Patients should be advised to report promptly any symptoms of myopathy. LESCOL/LESCOL XL therapy should be discontinued if myopathy is diagnosed or suspected (5.1)
- **Liver enzyme abnormalities and monitoring:** Persistent elevations in hepatic transaminases can occur. Monitor/Check liver enzymes tests before initiating therapy and during treatment as clinically indicated thereafter (5.2)

ADVERSE REACTIONS

Most frequent adverse reactions (rate $\geq 2\%$ and $>$ placebo) are: headache, dyspepsia, myalgia, abdominal pain and nausea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- **Cyclosporine:** Combination increases fluvastatin exposure. Limit LESCOL dose to 20 mg (2.4, 7.1)
- **Fluconazole:** Combination increases fluvastatin exposure. Limit LESCOL dose to 20 mg (2.5, 7.2)
- **Concomitant lipid-lowering therapies:** Use with fibrates and/or lipid-modifying doses (≥ 1 g/day) of niacin products may increase the risk of adverse skeletal muscle effects. myopathy/rhabdomyolysis. Caution should be used when prescribing with LESCOL/LESCOL XL (5.1, 7.3, 7.4)
- **Glyburide/glibenclamide:** Monitor blood glucose levels when fluvastatin dose is changed (7)
- **Phenytoin:** Monitor plasma phenytoin levels when fluvastatin treatment is initiated or when the dosage is changed (7)
- **Warfarin and coumarin derivatives:** Monitor prothrombin times when fluvastatin co-administration is initiated, discontinued, or the dosage changed (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 029/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia
- 1.2 Secondary Prevention of Cardiovascular Disease
- 1.3 Limitations of Use

2 DOSAGE AND ADMINISTRATION

- 2.1 General Dosing Information
- 2.2 Adult Patients with Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia
- 2.3 Pediatric Patients (10-16 years of age) with Heterozygous Familial Hypercholesterolemia
- 2.4 Use with Cyclosporine
- 2.5 Use with Fluconazole

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

- 4.1 Hypersensitivity to any Component of this Medication
- 4.2 Active Liver Disease
- 4.3 Pregnancy
- 4.4 Nursing Mothers

5 WARNINGS AND PRECAUTIONS

- 5.1 Skeletal Muscle
- 5.2 Liver Enzymes
- 5.3 Endocrine Effects
- 5.4 CNS Toxicity

6 ADVERSE REACTIONS

- 6.1 Clinical Studies Experience in Adult Patients
- 6.2 Clinical Studies Experience in Pediatric Patients
- 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Cyclosporine
- 7.2 Fluconazole
- 7.3 Gemfibrozil
- 7.3.4 Other fibrates

- 7.4.5 Niacin
- 7.5.6 Glibenclamide Glyburide
- 7.6.7 Phenytoin
- 7.7.8 Warfarin
- 7.9 Colchicine

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment
- 8.7 Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia
- 14.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients
- 14.3 Secondary Prevention of Cardiovascular Disease

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

- 17.1 Muscle Pain
- 17.2 Liver Enzymes
- 17.3 Pregnancy
- 17.4 Breastfeeding

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Drug therapy is indicated as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other non-pharmacologic measures alone has been inadequate.

1.1 Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia

LESCOL and LESCOL XL are indicated

- as an adjunct to diet to reduce elevated total cholesterol (Total-C), 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).
- as an adjunct to diet to reduce Total-C, LDL-C, and Apo B levels in adolescent boys and adolescent girls who are at least one year post-menarche, 10-16 years of age, with heterozygous familial hypercholesterolemia and the following findings are present:
 - LDL-C remains ≥ 190 mg/dL or
 - LDL-C remains ≥ 160 mg/dL and:
 - there is a positive family history of premature cardiovascular disease or
 - two or more other cardiovascular disease risk factors are present

The NCEP classification of cholesterol levels in pediatric patients with a familial history of hypercholesterolemia or premature CVD is summarized below.

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

Children treated with fluvastatin in adolescence should be re-evaluated in adulthood and appropriate changes made to their cholesterol-lowering regimen to achieve adult treatment goals.

1.2 Secondary Prevention of Cardiovascular Disease

In patients with clinically evident CHD, LESCOL and LESCOL XL are indicated to:

- reduce the risk of undergoing coronary revascularization procedures
- slow the progression of coronary atherosclerosis

1.3 Limitations of Use

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).

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

Dose range: 20 mg to 80 mg/ day.

LESCOL/LESCOL XL can be administered orally as a single dose, with or without food.

Do not break, crush or chew LESCOL XL tablets or open LESCOL capsules prior to administration.

Do not take two LESCOL 40 mg capsules at one time.

Since the maximal effect of a given dose is seen within 4 weeks, periodic lipid determinations should be performed at this time and dosage adjusted according to the patient's response to therapy and established treatment guidelines.

For patients requiring LDL-C reduction to a goal of $\geq 25\%$, the recommended starting dose is 40 mg as one capsule in the evening, 80 mg as one LESCOL XL tablet administered as a single dose at any time of the day 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.

2.2 Adult Patients with Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia

Adult patients can be started on either LESCOL or LESCOL XL. The recommended starting dose for LESCOL is one 40 mg capsule in the evening, or one LESCOL 40 mg capsule twice daily. Do not take two LESCOL 40 mg capsules at one time.

The recommended starting dose for LESCOL XL is one 80 mg tablet administered as a single dose at any time of the day.

2.3 Pediatric Patients (10-16 years of age) with Heterozygous Familial Hypercholesterolemia

The recommended starting dose is one 20 mg LESCOL capsule. Dose adjustments, up to a maximum daily dose administered either as LESCOL capsules 40 mg twice daily or one LESCOL XL 80 mg tablet once daily should be made at 6 week intervals. Doses should be individualized according to the goal of therapy [see *NCEP Pediatric Panel Guidelines* and *CLINICAL STUDIES (14)*]¹.

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

2.4 Use with Cyclosporine

Do not exceed a dose of 20 mg b.i.d. LESCOL in patients taking cyclosporine [see *Drug Interactions 7.1*].

2.5 Use with Fluconazole

Do not exceed a dose of 20 mg b.i.d. LESCOL in patients taking fluconazole [see *Drug Interactions 7.2*].

3 DOSAGE FORMS AND STRENGTHS

- LESCOL 20 mg capsules are 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.
- LESCOL 40 mg capsules are 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.
- LESCOL XL 80 mg tablets are yellow, round, slightly biconvex film-coated tablet with beveled edges debossed with “LESCOL XL” on one side and “80” on the other.

4 CONTRAINDICATIONS

4.1 Hypersensitivity to any Component of this Medication

LESCOL and LESCOL XL are contraindicated in patients with hypersensitivity to any component of this medication.

4.2 Active Liver Disease

LESCOL and LESCOL XL are contraindicated in patients with active liver disease or unexplained, persistent elevations in serum transaminases [see *Warnings and Precautions (5.2)*].

4.3 Pregnancy

LESCOL and LESCOL XL are contraindicated in women who are pregnant or may become pregnant. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. LESCOL and LESCOL XL may cause fetal harm when administered to pregnant women. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia.

LESCOL and LESCOL XL should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking this drug, LESCOL and LESCOL XL should be discontinued and the patient should be apprised of the potential hazard to the fetus [see *Use In Specific Populations (8.1)*].

4.4 Nursing Mothers

Fluvastatin is secreted into the breast milk of animals and because HMG-CoA reductase inhibitors have the potential to cause serious adverse reactions in nursing infants, women who require treatment with LESCOL or LESCOL XL should be advised not to breastfeed their infants [see *Use In Specific Populations (8.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle

Rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with LESCOL/LESCOL XL and other drugs in this class.

LESCOL/LESCOL XL should be prescribed with caution in patients with predisposing factors for myopathy. These factors include advanced age (>65 years), renal impairment, and inadequately treated hypothyroidism.

The risk of myopathy and/or rhabdomyolysis with statins is increased with concurrent therapy with cyclosporine, erythromycin, fibrates or niacin. Myopathy was not observed in a clinical trial in 74 patients involving patients who were treated with LESCOL/LESCOL XL together with niacin. Isolated cases of myopathy have been reported during post-marketing experience with concomitant administration of LESCOL/LESCOL XL and colchicine. No information is available on the pharmacokinetic interaction between LESCOL/LESCOL XL and colchicine.

Uncomplicated myalgia has also been reported in LESCOL-treated patients [see *Adverse Reactions* (6)]. In clinical trials, uncomplicated myalgia has been observed infrequently in patients treated with LESCOL at rates indistinguishable from placebo. Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in CPK values to greater than 10 times the upper limit of normal, was <0.1% in fluvastatin clinical trials. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

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

5.2 Liver Enzymes

Increases in serum transaminases (aspartate aminotransferase [AST]/serum glutamic-oxaloacetic transaminase, or alanine aminotransferase [ALT]/serum glutamic-pyruvic transaminase) have been reported with HMG-CoA reductase inhibitors, including LESCOL/LESCOL XL. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy.

Approximately 1.1% of patients treated with LESCOL capsules in worldwide trials developed dose-related, persistent elevations of serum 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 LESCOL 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 daily doses of 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 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-enzyme~~ tests be performed prior to the initiation of ~~therapy~~ LESCOL/LESCOL XL, ~~at 12 weeks~~ and ~~when clinically indicated~~ if signs or symptoms of liver injury occur.

~~Patients who develop increased transaminase levels or signs and symptoms of active liver disease while taking LESCOL should be evaluated with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormalities return to normal. Should an increase in AST or ALT of 3 times the upper limit of normal or greater persist, withdrawal of LESCOL therapy is recommended.~~

There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including fluvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with LESCOL/LESCOL XL, promptly interrupt therapy. If an alternate etiology is not found do not restart LESCOL/LESCOL XL.

In very rare cases, possibly drug-related hepatitis was observed that resolved upon discontinuation of treatment.¹ Active liver disease or unexplained serum transaminase elevations are contraindications to the use of LESCOL and LESCOL XL [see *Contraindications* (4) and *Warnings and Precautions* (5.2)]. Caution should be exercised when LESCOL is administered to patients with a history of liver disease or heavy alcohol ingestion [see *Clinical Pharmacology* (12.4)]. Such patients should be closely monitored.

5.3 Endocrine Effects

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including LESCOL/LESCOL XL.

Statins interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production.

LESCOL/LESCOL XL exhibited no effect upon non-stimulated cortisol levels and demonstrated no effect upon thyroid metabolism as assessed by measurement of thyroid stimulating hormone (TSH). Small declines in total serum 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 LESCOL/LESCOL XL 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 LESCOL 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 LESCOL or placebo.

Patients treated with LESCOL/LESCOL XL who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if a statin or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g. ketoconazole, spironolactone, cimetidine) that may decrease the levels of endogenous steroid hormones.

5.4 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 rats) 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 drug 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.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Rhabdomyolysis with myoglobinuria and acute renal failure and myopathy (including myositis) [see *Warnings and Precautions* (5.1)].
- Liver Enzyme Abnormalities [see *Warnings and Precautions* (5.2)].

6.1 Clinical Studies Experience in Adult Patients

Because clinical studies on LESCOL/LESCOL XL are conducted in varying study populations and study designs, the frequency of adverse reactions observed in the clinical studies of LESCOL/LESCOL XL cannot be directly compared with that in the clinical studies of other statins and may not reflect the frequency of adverse reactions observed in clinical practice.

In the LESCOL placebo-controlled clinical trials database of 2326 patients treated with LESCOL¹ (age range 18-75 years, 44% women, 94% Caucasians, 4% Blacks, 2% other ethnicities) with a median treatment duration of 24 weeks, 3.4% of patients on LESCOL and 2.3% patients on placebo discontinued due to adverse reactions regardless of causality. The most common adverse reactions that led to treatment discontinuation and occurred at an incidence greater than placebo were: transaminase increased (0.8%), upper abdominal pain (0.3%), dyspepsia (0.3%), fatigue (0.2%) and diarrhea (0.2%).

In the LESCOL XL database of controlled clinical trials of 912 patients treated with LESCOL XL (age range 21-87 years, 52% women, 91% Caucasians, 4% Blacks, 5% other ethnicities) with a median treatment duration of 24 weeks, 3.9% of patients on LESCOL XL discontinued due to adverse reactions regardless of causality. The most common adverse reactions that led to treatment discontinuation were abdominal pain (0.7%), diarrhea (0.5%), nausea (0.4%), dyspepsia (0.4%) and chest pain (0.3%).

Clinically relevant adverse experiences occurring in the LESCOL and LESCOL XL controlled studies with a frequency $\geq 2\%$, regardless of causality, included the following:

Table 1 Clinical adverse events reported in $>2\%$ in patients treated with LESCOL/LESCOL XL and at an incidence greater than placebo in placebo-controlled trials regardless of causality (% of ~~Patients~~patients) Pooled Dosages-

		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
	Tooth disorder	2.1	1.7	1.4
	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) compared to placebo

² Controlled trials with LESCOL XL 80 mg Tablets as compared to LESCOL Capsules

LESCOL Intervention Prevention Study

In the LESCOL Intervention Prevention Study (LIPS), the effect of LESCOL 40 mg, administered twice daily on the risk of recurrent cardiac events was assessed in 1677 patients with CHD who had undergone a percutaneous coronary intervention (PCI) procedure. This was a 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. ~~[Also see section 14.3.]~~ [\[see Clinical Studies \(14.3\)\].](#)

Table 2 Clinical adverse events reported in $\geq 2\%$ in patients treated with LESCOL/LESCOL XL and at an incidence greater than placebo in the LIPS Trial regardless of causality (% of ~~Patients~~patients)

		LESCOL 40 mg b.i.d. N=822 (%)	Placebo N=818 (%)
Cardiac disorders	Atrial fibrillation	2.4	2.0
Gastrointestinal disorders	Abdominal pain upper	6.3	4.5
	Constipation	3.3	2.1
	Dyspepsia	4.5	4.0
	Gastric disorder	2.7	2.1
	Nausea	2.7	2.3
General disorders	Fatigue	4.7	3.8
	Oedema -Edema peripheral	4.4	2.9
Infections and infestations	Bronchitis	2.3	2.0
	Nasopharyngitis	2.8	2.1
Musculoskeletal and connective tissue disorders	Arthralgia	2.1	1.8
	Myalgia	2.2	1.6
	Pain in extremity	4.1	2.7
Nervous system disorders	Dizziness	3.9	3.5
	Syncope	2.4	2.2
Respiratory disorders	Dyspnoea -Dyspnea exertional	2.8	2.4
Vascular disorders	Hypertension	5.8	4.2
	Intermittent claudication	2.3	2.1

6.2 Clinical Studies Experience in Pediatric Patients

In patients aged <18 years, efficacy and safety have not been studied for treatment periods longer than two years.

In two open-label, uncontrolled studies, 66 boys and 48 girls with heterozygous familial hypercholesterolemia (9-16 years of age, 80% Caucasian, 19% Other [mixed ethnicity], 1% Asians) were treated with fluvastatin sodium administered as LESCOL capsules 20 mg -40 mg twice daily, or LESCOL XL 80 mg extended-release tablet [see *Clinical Studies* (14.2) and *Use In Specific Populations* (8.4)].

6.3 Postmarketing Experience

Because adverse reactions from spontaneous reports are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. 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.

Musculoskeletal: muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias, muscle spasms, muscle weakness, myositis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, vertigo, paresthesia, hypoesthesia, dysesthesia, peripheral neuropathy, peripheral nerve palsy.

There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports

are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Psychiatric: anxiety, insomnia, depression, psychic disturbances

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 (erythrocyte sedimentation rate) increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity reaction, 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, cirrhosis, fulminant hepatic necrosis, hepatoma, anorexia, ~~and~~ vomiting, **[fatal and non-fatal hepatic failure](#)**.

Skin: rash, dermatitis, including bullous dermatitis, eczema, alopecia, pruritus, a variety of skin changes (e.g. nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails).

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

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

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

7 DRUG INTERACTIONS

7.1 Cyclosporine

Cyclosporine coadministration increases fluvastatin exposure. Therefore, in patients taking cyclosporine, therapy should be limited to LESCOL 20 mg twice daily [see *Warnings and Precautions* (5.1) and *Clinical Pharmacology* (12.3)].

7.2 Fluconazole

Administration of fluvastatin 40 mg single dose to healthy volunteers pre-treated with fluconazole for 4 days results in an increase of fluvastatin exposure. Therefore, in patients taking fluconazole, therapy should be limited to LESCOL 20 mg twice daily [see *Clinical Pharmacology* (12.3)].

7.3 Gemfibrozil

Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are coadministered with gemfibrozil, concomitant administration of LESCOL/LESCOL XL with gemfibrozil should be avoided.

7.43 Other Fibrates

Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors ~~may be~~ increased with concurrent administration of other fibrates, LESCOL/LESCOL XL should be administered with caution when used concomitantly with ~~gemfibrozil or~~ other fibrates [see *Warnings and Precautions* (5.1) and *Clinical Pharmacology* (12.3)].

7.54 Niacin

The risk of skeletal muscle effects may be enhanced when LESCOL is used in combination with lipid-modifying doses (≥ 1 g/day) of niacin; a reduction in LESCOL dosage should be considered in this setting [see *Warnings and Precautions* (5.1)].

7.65 Glyburide/glibenclamide

Concomitant administration of fluvastatin and glyburide/glibenclamide increased glyburide/glibenclamide exposures. Patients on concomitant therapy of glyburide/glibenclamide and fluvastatin should continue to be monitored appropriately [see *Clinical Pharmacology* (12.3)].

7.76 Phenytoin

Concomitant administration of fluvastatin and phenytoin increased phenytoin exposures. Patients should continue to be monitored appropriately when fluvastatin therapy is initiated or when fluvastatin dose is changed [see *Clinical Pharmacology* (12.3)].

7.87 Warfarin

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.

7.98 Colchicine

Cases of myopathy, including rhabdomyolysis, have been reported with fluvastatin coadministered with colchicine, and caution should be exercised when prescribing fluvastatin with colchicine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

LESCOL/LESCOL XL is contraindicated in women who are or may become pregnant [see *Contraindications (4)*].

Lipid lowering drugs are contraindicated during pregnancy, because cholesterol and cholesterol derivatives are needed for normal fetal development. Serum cholesterol and triglycerides increase during normal pregnancy. Atherosclerosis is a chronic process, and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hypercholesterolemia therapy

There are no adequate and well-controlled studies of use with LESCOL/LESCOL XL during pregnancy. Rare reports of congenital anomalies have been received following intrauterine exposure to other statins. In a review² of about 100 prospectively followed pregnancies in women exposed to other statins, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed the rate expected in the general population. The number of cases is adequate only to exclude a 3- to 4-fold increase in congenital anomalies over background incidence. In 89% of prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified.

Teratology studies with fluvastatin in rats and rabbits showed maternal toxicity at high dose levels, but there was no evidence of embryotoxic or teratogenic potential [see *Non-Clinical Toxicology (13)*].

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.

8.3 Nursing Mothers

Based on animal data, fluvastatin 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 (4)*].

8.4 Pediatric Use

The safety and efficacy of LESCOL and LESCOL XL in children and adolescent patients 9-16 years of age with heterozygous familial hypercholesterolemia have been evaluated in open-label, uncontrolled clinical trials for a duration of two years. The most common adverse events observed were influenza and infections. In these limited uncontrolled studies, there was no detectable effect on growth or sexual maturation in the adolescent boys or on menstrual cycle length in girls [see *Clinical Studies (14.2)*, *Adverse Reactions (6.3)* and *Dosage And Administration (2.2)*]. Adolescent females should be counseled on appropriate contraceptive methods while on LESCOL therapy [see *Contraindications (4)*].

8.5 Geriatric Use

Fluvastatin exposures were not significantly different between the nonelderly and elderly populations (age ≥ 65 years) [see *Clinical Pharmacology (12.3)*]. Since advanced age (≥ 65 years) is a predisposing factor for myopathy, LESCOL/LESCOL XL should be prescribed with caution in the elderly.

8.6 Hepatic Impairment

LESCOL and LESCOL XL are contraindicated in patients with active liver disease or unexplained, persistent elevations in serum transaminases [see *Clinical Pharmacology (12.3)*].

8.7 Renal Impairment

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 [see *Clinical Pharmacology(12.3)*].

10 OVERDOSAGE

To date, there has been limited experience with overdose of fluvastatin. If an overdose occurs, it should be treated symptomatically with laboratory monitoring and supportive measures should be instituted as required. The dialyzability of fluvastatin sodium and of its metabolites in humans is not known at present [see *Warnings and Precautions* (5)].

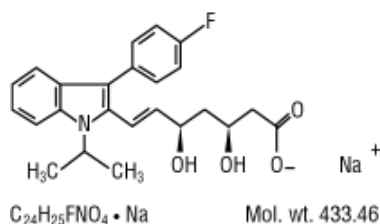
In the pediatric population, there have been reports of overdose with fluvastatin sodium in children including a 2 year-old and the other 3 years of age, either of whom may have possibly ingested fluvastatin sodium. The maximum amount of fluvastatin sodium that could have been ingested was 80 mg (4 x 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.

In the postmarketing experience there have been reports of accidental ingestion of LESCOL tablets in infants up to 3 years of age. In one case, increased serum CPK values were noted. There have been reports of intentional overdose in adolescents with the development of hepatic enzyme elevations, convulsions and gastroenteritis/vomiting/diarrhea. One case of intentional overdose as suicide attempt in a 15 year-old female reported ingestion of 2,800 mg LESCOL XL with hepatic enzyme elevation.

11 DESCRIPTION

LESCOL 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 C₂₄H₂₅FO₄•Na, its molecular weight is 433.46 and its structural formula is:



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 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: calcium carbonate, gelatin, magnesium stearate, microcrystalline cellulose, pregelatinized starch (corn), red iron oxide, sodium bicarbonate, 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, sodium lauryl sulfate, and sodium propionate.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

LESCOL is a competitive inhibitor of HMG-CoA reductase, the rate limiting enzyme that ~~converts~~ converts 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.

12.3 Pharmacokinetics

Absorption:

Following oral administration of the capsule, fluvastatin reaches peak concentrations in less than 1 hour. The absolute bioavailability is 24% (range 9%-50%) after administration of a 10 mg dose.

At steady state, administration of fluvastatin with the evening meal results in a 50% decrease in C_{max} , a 11% decrease in AUC, and a more than two-fold increase in t_{max} as compared to administration 4 hours after the evening meal. No significant differences 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 more than dose proportional plasma fluvastatin concentrations.

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%. However, the maximum concentration of LESCOL XL seen after a high-fat meal is less than the peak concentration following a single dose or twice daily dose of the 40 mg LESCOL capsule.

Distribution:

Fluvastatin is 98% bound to plasma proteins. The mean volume of distribution (VD_{ss}) is estimated at 0.35 L/kg. 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. Fluvastatin has two enantiomers. Both enantiomers of fluvastatin are metabolized in a similar manner.

In vitro data indicate that fluvastatin metabolism involves multiple Cytochrome P450 (CYP) isozymes. CYP2C9 isoenzyme is primarily involved in the metabolism of fluvastatin (approximately 75%), while CYP2C8 and CYP3A4 isoenzymes are involved to a much less extent, i.e. approximately 5% and approximately 20%, respectively.

Excretion:

Following oral administration, fluvastatin is primarily (about 90%) excreted in the feces as metabolites, with less than 2% present as unchanged drug. Approximately 5% of a radiolabeled oral dose were recovered in urine. The elimination half-life ($t_{1/2}$) of fluvastatin is approximately 3 hours.

Specific Populations

Renal Impairment:

In patients with moderate to severe renal impairment (CL_{Cr} 10-40 mL/min), AUC and C_{max} increased approximately 1.2-fold after administration of a single dose of 40 mg fluvastatin compared to healthy volunteers. In patients with end-stage renal disease on hemodialysis, the AUC increased by approximately 1.5-fold. LESCOL XL was not evaluated in patients with renal impairment. However, systemic exposures after administration of LESCOL XL are lower than after the 40 mg immediate release capsule.

Hepatic Impairment:

In patients with hepatic impairment due to liver cirrhosis, fluvastatin AUC and C_{max} increased approximately 2.5-fold compared to healthy subjects after administration of a single 40 mg dose. The enantiomer ratios of the two isomers of fluvastatin in hepatic impairment patients were comparable to those observed in healthy subjects.

Geriatric:

Plasma levels of fluvastatin are not significantly different in patients age > 65 years compared to patients age 21 to 49 years.

Gender:

In a study evaluating the effect of age and gender on fluvastatin pharmacokinetics, there was no significant differences in fluvastatin exposures between males and females, except between younger females and younger males (both ages 21-49

years), where there was an approximate 30% increase in AUC in females. Adjusting for body weight decreases the magnitude of the differences seen. For LESCOL XL, the AUC increases 67% and 77% for women compared to men under fasted and high- fat meal fed conditions, respectively.

Pediatric:

Pharmacokinetic data in the pediatric population are not available.

Drug-Drug Interactions:

Data from drug-drug interactions studies involving coadministration of gemfibrozil, niacin, ~~itraconazole~~ itraconazole, erythromycin, ~~or~~ tolbutamide or clopidogrel indicate that the PK disposition of fluvastatin is not significantly altered when fluvastatin is coadministered with any either of these drugs.

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

Table 3 Effect of Co-administered Drugs on Fluvastatin Systemic Exposure

Co-administered drug and dosing regimen	Fluvastatin		
	Dose (mg)*	Change in AUC**	Change in Cmax**
Cyclosporine – stable dose (b.i.d.) [†]	20 mg QD for 14 weeks	↑ 90%	↑ 30%
Fluconazole 400 mg QD day 1, 200 mg b.i.d. day 2- 4 [†]	40 mg QD	↑ 84%	↑ 44%
Cholestyramine 8 g QD	20 mg QD administered 4 hrs after a meal plus cholestyramine	↓ 51%	↓ 83%
Rifampicin 600 mg QD for 6 days	20 mg QD	↓ 53%	↓ 42%
Cimetidine 400 mg b.i.d. for 5 days, QD on Day 6	20 mg QD	↑ 30%	↑ 40%
Ranitidine 150 mg b.i.d. for 5 days, QD on Day 6	20 mg QD	↑ 10%	↑ 50%
Omeprazole 40 mg QD for 6 days	20 mg QD	↑ 20%	↑ 37%
Phenytoin 300 mg QD	40 mg b.i.d. for 5 days	↑ 40 %	↑ 27%
Propranolol 40 mg b.i.d. for 3.5 days	40 mg QD	↓ 5%	No change
Digoxin 0.1 – 0.5 mg QD for 3 weeks	40 mg QD	No change	↑ 11%
Diclofenac 25 mg QD	40 mg QD for 8 days	↑50 %	↑ 80%
Glyburide <u>Glimepiride</u> 5 – 20 mg QD for 22 days	40 mg b.i.d for 14 days	↑ 51%	↑ 44%

<u>Warfarin 30 mg QD</u>	<u>40 mg QD for 8 days</u>	<u>↑ 30%</u>	<u>↑ 67%</u>
<u>Clopidogrel 300 mg loading dose on day 10, 75 mg QD for 9 days on days 11-19</u>	<u>80 mg XL QD for 19 days</u>	<u>↓ 2%</u>	<u>↑ 27%</u>

*Single dose unless otherwise noted

**Mean ratio (with/without coadministered drug and no change = 1-fold) or % change (with/without coadministered drug and no change = 0%); symbols of ↑ and ↓ indicate the exposure increase and decrease, respectively.

† Considered clinically significant [see *Dosage And Administration (2)* and *Drug Interactions (7)*]

Data from drug-drug interaction studies involving fluvastatin and coadministration of either gemfibrozil, tolbutamide or losartan indicate that the PK disposition of either gemfibrozil, tolbutamide or losartan is not significantly altered when coadministered with fluvastatin.

Table 4 Effect of Fluvastatin Co-Administration on Systemic Exposure of Other Drugs

Fluvastatin dosage regimen	Co-administered drug		
	Name and Dose (mg)*	Change in AUC**	Change in Cmax**
40 mg QD for 5 days	Phenytoin 300 mg QD†	↑ 20%	↑ 5%
40 mg b.i.d. for 21 days	Glyburide <u>Glibenclamide</u> 5 – 20 mg QD for 22 days †	↑ 70%	↑ 50%
40 mg QD for 8 days	Diclofenac 25 mg QD	↑ 25%	↑ 60%
<u>40 mg QD for 8 days</u>	<u>Warfarin 30 mg QD</u>	<u>S-warfarin: ↑7%</u> <u>R-warfarin: no change</u>	<u>S-warfarin: ↑ 10%</u> <u>R-warfarin: ↑ 6%</u>

*Single dose unless otherwise noted

**Mean ratio (with/without coadministered drug and no change = 1-fold) or % change (with/without coadministered drug and no change = 0%); symbols of ↑ and ↓ indicate the exposure increase and decrease, respectively.

† Considered clinically significant [see *Dosage And Administration (2)* and *Drug Interactions (7)*]

13 NONCLINICAL TOXICOLOGY

13.1 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 mg human daily dose based on surface area, mg/m²). 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 mg daily dose).

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/m² 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.

14 CLINICAL STUDIES

14.1 Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia

In 12 placebo-controlled studies in patients with primary hypercholesterolemia and mixed dyslipidemia, LESCOL 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 (Table 5). After 24 weeks of treatment, treatment with LESCOL resulted in significantly reduced plasma LDL-C, TC, TG, and Apo B compared to placebo and was associated with variable increases in HDL-C across the dose range.

LESCOL XL has been studied in five controlled studies of patients with primary hypercholesterolemia and mixed dyslipidemia. 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 and resulted in increases in HDL-C (Table 5).

In patients with primary mixed dyslipidemia as defined by baseline plasma TG levels ≥ 200 mg/dL and < 400 mg/dL, treatment with LESCOL/LESCOL XL produced significant decreases in Total-C, LDL-C, TG and Apo B and variable increases in HDL-C (Table 5).

**Table 5 Median Percent Change in Lipid Parameters from Baseline to Week 24 Endpoint
All Placebo-Controlled Studies (LESCOL) and Active Controlled Trials (LESCOL XL)**

Dose	Total Chol		TG		LDL		Apo B		HDL	
	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

14.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients

LESCOL was studied in two open-label, uncontrolled, dose-titration studies. The first study enrolled 29 pre-pubertal boys, 9-12 years of age, who had an LDL-C level >90th percentile for age and one parent with primary hypercholesterolemia and either a family history of premature ischemic heart disease or tendon xanthomas. The mean baseline LDL-C was 226 mg/dL (range: 137-354 mg/dL). All patients were started on LESCOL capsules 20 mg daily with dose adjustments every 6 weeks to 40 mg daily then 80 mg daily (40 mg b.i.d.) to achieve an LDL-C goal between 96.7 – 123.7 mg/dL. Endpoint analyses were performed at Year 2. LESCOL decreased plasma levels of Total-C and LDL-C by 21% and 27%, respectively. The mean achieved LDL-C was 161 mg/dL (range: 74-336 mg/dL).

The second study enrolled 85 male and female patients, 10 to 16 years of age, who had an LDL-C >190 mg/dL or LDL-C >160 mg/dL and one or more risk factors for coronary heart disease, or LDL-C >160 mg/dL and a proven LDL-receptor defect. The mean baseline LDL-C was 225 mg/dL (range: 148-343 mg/dL). All patients were started on LESCOL capsules 20 mg daily with dose adjustments every 6 weeks to 40 mg daily then 80 mg daily (LESCOL 80 mg XL tablet) to achieve an LDL-C goal of <130 mg/dL. Endpoint analyses were performed at Week 114. LESCOL decreased plasma levels of Total-C and LDL-C by 22% and 28%, respectively. The mean achieved LDL-C was 159 mg/dL (range: 90-295 mg/dL).

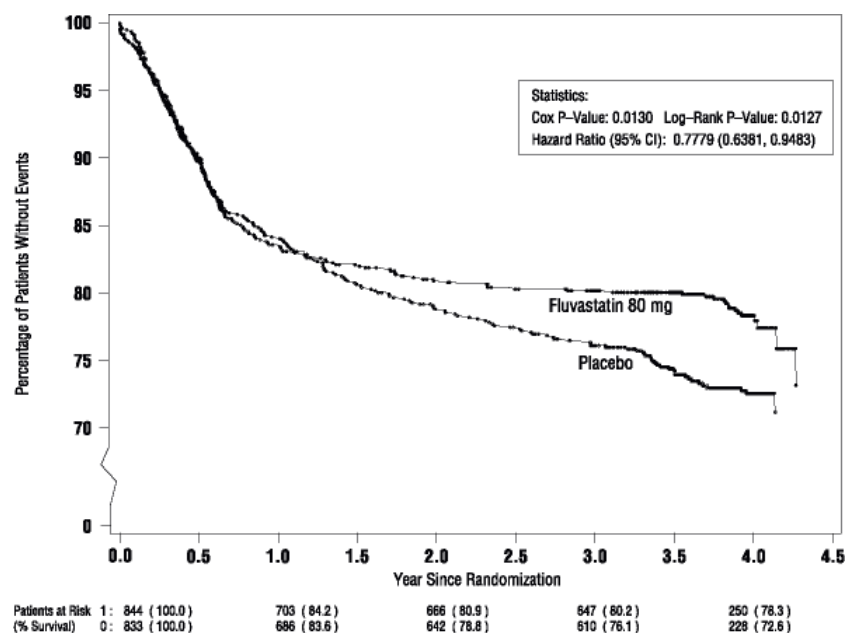
The majority of patients in both studies (83% in the first study and 89% in the second study) were titrated to the maximum daily dose of 80 mg. At study endpoint, 26% to 30% of patients in both studies achieved a targeted LDL-C goal of <130 mg/dL. The long-term efficacy of LESCOL or LESCOL XL therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

14.3 Secondary Prevention of Cardiovascular Disease

In the LESCOL Intervention Prevention Study (LIPS), 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 CHD 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. Mean baseline lipid concentrations were: total cholesterol 201 mg/dL, LDL-C 132 mg/dL, triglycerides 70 mg/dL and HDL-C 39 mg/dL.

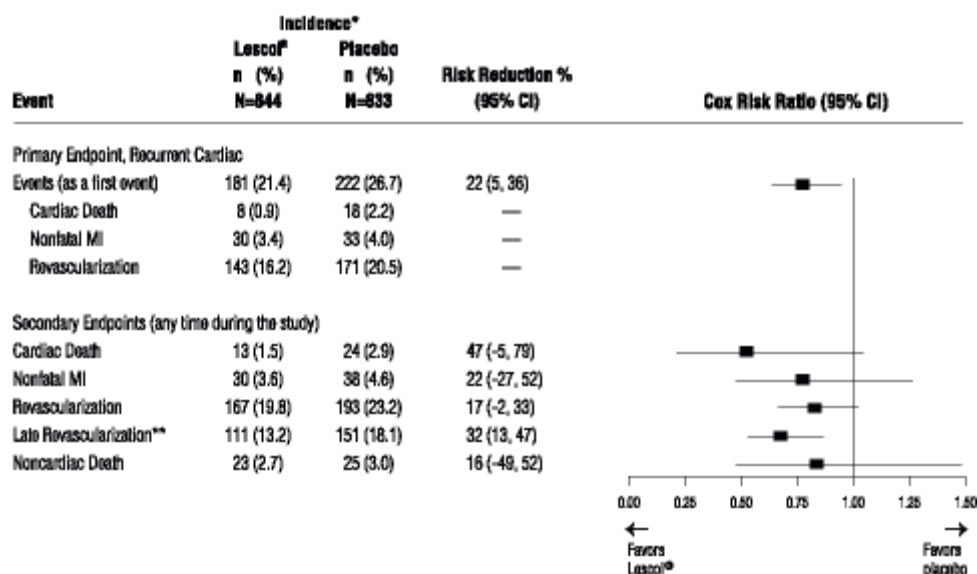
LESCOL significantly reduced the risk of recurrent cardiac events (Figure 1) by 22% (p=0.013, 181 patients in the LESCOL group vs. 222 patients in the placebo group). Revascularization procedures comprised the majority of the initial recurrent cardiac events (143 revascularization procedures in the LESCOL 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 instrumental 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

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 CAD 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 which 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.

Compared to placebo, LESCOL significantly slowed the progression of coronary atherosclerosis as measured by within-patient per-lesion change in minimum lumen diameter (MLD), the primary endpoint (Figure 3 below), percent diameter stenosis (Figure 4), and the formation of new lesions (13% of all fluvastatin patients versus 22% of all placebo patients). 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 Change in Minimum Lumen Diameter (mm)

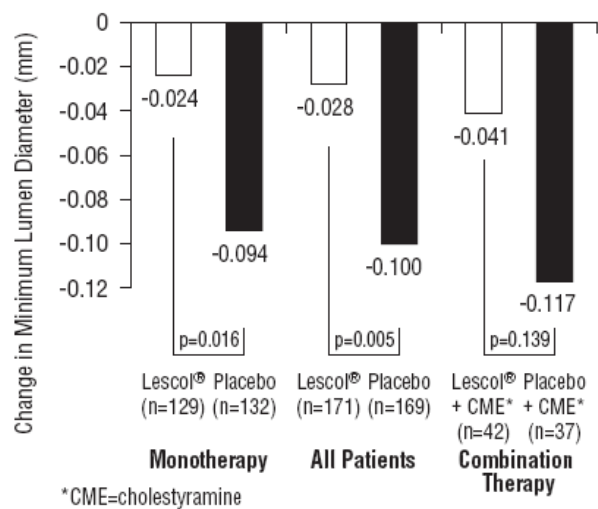
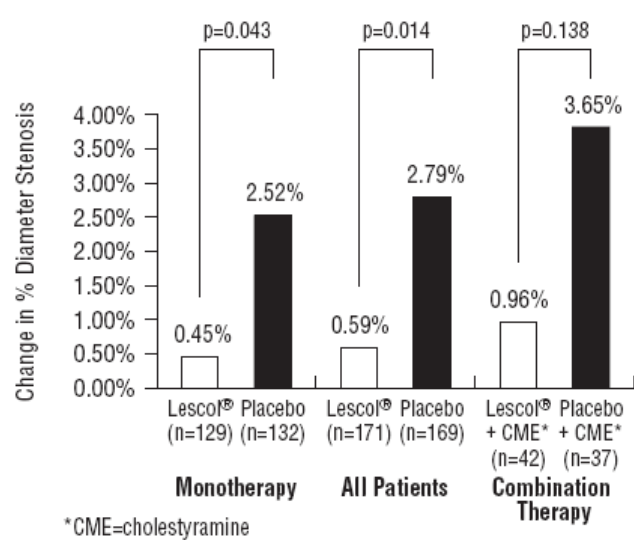


Figure 4 Change in % Diameter Stenosis



15 REFERENCES

1. National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics*. 89(3):495-501.1992.
2. Manson, J.M., Freyssinges, C., Ducrocq, M.B., Stephenson, W.P., Postmarketing Surveillance of Lovastatin and Simvastatin Exposure During Pregnancy, *Reproductive Toxicology*, 10(6): 439-446, 1996.

16 HOW SUPPLIED/STORAGE AND HANDLING

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 -30°C (59 -86°F) [see USP Controlled Room Temperature]. Dispense in a tight container. Protect from light.

17 PATIENT COUNSELING INFORMATION

Information for Patients

Patients taking LESCOL/LESCOL XL should be advised that high cholesterol is a chronic condition and they should adhere to their medication along with their National Cholesterol Education Program (NCEP)-recommended diet, a regular exercise program, and periodic testing of a fasting lipid panel to determine goal attainment.

Patients should be advised about substances they should not take concomitantly with LESCOL/LESCOL XL [see *Warnings and Precautions* (5.1)]. Patients should also be advised to inform other healthcare professionals prescribing a new medication that they are taking LESCOL/LESCOL XL.

17.1 Muscle Pain

Patients starting therapy with LESCOL/LESCOL XL should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

17.2 Liver Enzymes

It is recommended that liver ~~function-enzyme~~ tests be performed before ~~and at 12 weeks following both~~ the initiation of LESCOL/LESCOL XL therapy and ~~any elevation of dose and periodically thereafter~~ if signs or symptoms of liver injury occur. All patients treated with LESCOL/LESCOL XL should be advised to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice.

17.3 Pregnancy

Women of childbearing age should be advised to use an effective method of birth control to prevent pregnancy while using LESCOL/LESCOL XL. Discuss future pregnancy plans with your patients, and discuss when to stop taking LESCOL/LESCOL XL if they are trying to conceive. Patients should be advised that if they become pregnant they should stop taking LESCOL/LESCOL XL and call their healthcare professional.

17.4 Breastfeeding

Women who are breastfeeding should not use LESCOL/LESCOL XL. Patients who have a lipid disorder and are breastfeeding should be advised to discuss the options with their healthcare professional.

T20124-92XX

FDA-Approved Patient Labeling

LESCOL[®] (fluvastatin sodium) Capsules

20 mg, 40 mg

LESCOL[®] XL (fluvastatin sodium) Extended-Release Tablets

80 mg

Rx Only

You must read and follow all instructions before using LESCOL or LESCOL XL.

Read the Patient Information every time you or a family member gets LESCOL or LESCOL XL. There may be new information. This Patient Information does not take the place of talking with your doctor about your medical condition or treatment. If you have any questions about LESCOL or LESCOL XL, ask your doctor or pharmacist.

What are LESCOL and LESCOL XL?

LESCOL and LESCOL XL are prescription medicines called "statins" that lower cholesterol in your blood. They lower the "bad" cholesterol and triglycerides in your blood. They can raise your "good" cholesterol as well.

LESCOL and LESCOL XL are for people whose cholesterol does not come down enough with exercise and a low-fat diet alone.

LESCOL and LESCOL XL may be used in patients with heart disease (coronary artery disease) to:

- lower the chances of heart problems which would require procedures to help restore blood flow to the heart.
- slow the buildup of too much cholesterol in the arteries of the heart.

Treatment with LESCOL or LESCOL XL has not been shown to prevent heart attacks or stroke.

LESCOL and LESCOL XL have the same active ingredient, fluvastatin. However, LESCOL is a capsule that is taken one or two times a day and LESCOL XL is an extended-release tablet that is only taken one time a day.

Who should not take LESCOL or LESCOL XL?

Do not take LESCOL or LESCOL XL if you:

- are pregnant or think you may be pregnant, or are planning to become pregnant. LESCOL and LESCOL XL may harm your unborn baby. If you get pregnant, stop taking LESCOL or LESCOL XL and call your doctor right away.
- are breast-feeding. LESCOL and LESCOL XL can pass into your breast milk and may harm your baby
- have liver problems
- are allergic to LESCOL or LESCOL XL or any of its ingredients. The active ingredient in LESCOL and LESCOL XL is fluvastatin. See the end of this leaflet for a complete list of ingredients in LESCOL and LESCOL XL.

LESCOL and LESCOL XL have not been studied in children under 9 years of age.

Before taking LESCOL or LESCOL XL, tell your doctor if you:

- have muscle aches or weakness
- drink more than 2 glasses of alcohol daily
- have diabetes
- have a thyroid problem
- have kidney problems

Some medicines should not be taken with LESCOL or LESCOL XL. Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. LESCOL and LESCOL XL and certain other medicines can interact causing serious side effects. Especially tell your doctor if you take medicines for:

- your immune system
- cholesterol
- infections
- heart failure
- seizures
- diabetes
- heartburn or stomach ulcers

Know all the medicines you take. Keep a list of all the medicines you take with you to show your doctor and pharmacist.

How should I take LESCOL or LESCOL XL?

- Your doctor will prescribe the medicine that is right for you. Take LESCOL or LESCOL XL exactly as prescribed. Do not change your dose or stop LESCOL or LESCOL XL without talking to your doctor. Your doctor may do blood tests to check your cholesterol levels during treatment with LESCOL and LESCOL XL. Your dose of LESCOL or LESCOL XL may be changed based on these blood test results.
- LESCOL XL tablets may be taken at any time of the day. Take LESCOL capsules at the same time every evening. When LESCOL capsules are taken twice daily, the capsules may be taken once in the morning and once in the evening. LESCOL and LESCOL XL can be taken with or without food.
- LESCOL XL tablets must be swallowed whole with a liquid. Do not break, crush or chew LESCOL XL tablets or open LESCOL capsules. Tell your doctor if you cannot swallow tablets whole. You may need LESCOL capsules or a different medicine instead of LESCOL XL tablets.
- Your doctor should start you on a low-fat and low-cholesterol diet before giving you LESCOL or LESCOL XL. Stay on this low-fat and low-cholesterol diet while taking LESCOL or LESCOL XL.
- If you miss a dose of LESCOL or LESCOL XL, take it as soon as you remember. Do not take LESCOL or LESCOL XL if it has been more than 12 hours since your last dose. Wait and take the next dose at your regular time. Do not take 2 doses of LESCOL or LESCOL XL at the same time.
- If you take too much LESCOL or LESCOL XL or overdose, call your doctor or Poison Control Center right away. Or, go to the nearest emergency room.

What should I avoid while taking LESCOL or LESCOL XL?

- Talk to your doctor before you start any new medicines. This includes prescription and nonprescription medicines, vitamins and herbal supplements. LESCOL and LESCOL XL and certain other medicines can interact causing serious side effects.
- Do not get pregnant. If you get pregnant, stop taking LESCOL or LESCOL XL right away and call your doctor.

What are the possible side effects of LESCOL and LESCOL XL?

When taking LESCOL and LESCOL XL, some patients may develop serious side effects, including:

muscle problems. These serious muscle problems can sometimes lead to kidney problems, including kidney failure. You have a higher chance for muscle problems if you are taking certain other medicines with LESCOL or LESCOL XL. Call your doctor right away if you have:

- muscle problems like weakness, tenderness, or pain that happen without a good reason, especially if you also have a fever or feel more tired than usual

liver problems. Your doctor ~~may~~ should do blood tests to check your liver before you start taking LESCOL or LESCOL XL, and ~~while you are taking one of them~~ if you have symptoms of liver problems while you take LESCOL or LESCOL XL. Call your doctor right away if you have the following symptoms of liver problems:

- feel tired or weak
- loss of appetite
- upper belly pain

- dark amber colored urine
- yellowing of your skin or the whites of your eyes

Call your doctor right away if you have:

- ~~muscle problems like weakness, tenderness, or pain that happen without a good reason, especially if you also have a fever or feel more tired than usual~~
- ~~nausea and vomiting~~
- ~~passing brown or dark colored urine~~
- ~~you feel more tired than usual~~
- ~~your skin and whites of your eyes get yellow~~
- ~~stomach pain~~

The most common side effects of LESCOL or LESCOL XL are headache, upset stomach and stomach pain, diarrhea, flu-like symptoms, muscle pain, sinus infection, tiredness, or trouble sleeping. These side effects are usually mild and may go away. The following additional side effects have been reported with LESCOL/LESCOL XL: memory loss, and confusion.

Talk to your doctor or pharmacist if you have side effects that bother you or that will not go away.

These are not all the side effects of LESCOL and LESCOL XL. Ask your doctor or pharmacist for a complete list.

How should I store LESCOL and LESCOL XL?

- Store LESCOL and LESCOL XL at room temperature, 59° to 86° F (15° to 30° C). Protect from light.
- Do not keep medicine that is out of date or that you no longer need.
- Keep LESCOL and LESCOL XL out of the reach of children. Be sure that if you throw medicines away, it is out of the reach of children.

General information about LESCOL and LESCOL XL

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use LESCOL or LESCOL XL for a condition for which it was not prescribed. Do not give LESCOL or LESCOL XL to other people, even if they have the same problem you have; it may harm them.

For more information, you can also visit the Novartis Internet site at www.LESCOLXL.com or call the Novartis help line at 1-888-669-6682.

What are the ingredients in LESCOL and LESCOL XL?

Active Ingredient: fluvastatin sodium

Inactive Ingredients:

LESCOL Capsules: calcium carbonate, gelatin, magnesium stearate, microcrystalline cellulose, pregelatinized starch (corn), red iron oxide, sodium bicarbonate, talc, titanium dioxide, yellow iron oxide, and other ingredients. The capsules may also contain benzyl alcohol, black iron oxide, butylparaben, carboxymethylcellulose sodium, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide, sodium lauryl sulfate, and sodium propionate.

LESCOL XL Tablets: microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, potassium bicarbonate, povidone, magnesium stearate, yellow iron oxide, titanium dioxide and polyethylene glycol 8000.

Distributed by:

Novartis Pharmaceuticals Corporation

East Hanover, New Jersey 07936

© Novartis

T201~~24-92XX~~/T201~~24-93XX~~

February~~July 2011/July 2011~~Month 2012~~Year/ February 2012~~Month~~Year~~

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
021192Orig1s019

MEDICAL REVIEW(S)

Clinical Review for Statin Class Labeling Changes

February 15, 2012

Amy G. Egan, M.D., M.P.H.

On August 11, 2011 the Division of Metabolism and Endocrinology Products (DMEP) issued supplement request letters to the sponsors of all HMG-CoA reductase inhibitor (statin) drugs requesting changes to the labeling so as to furnish adequate information for the safe and effective use of their statin. These labeling changes were based on FDA's comprehensive review of the statin class of drugs, including clinical trial data, Adverse Event Reporting System (AERS) reports, the published literature, and the labels of other approved drugs containing information on statin co-administration. This review will serve to summarize the safety issues and the sources and reviews of the data.

1. Liver enzyme abnormalities – TSI #57

On March 19, 2007 DMEP opened Tracked Safety Issue (TSI) #57 to evaluate hepatotoxicity associated with the statin class of drugs. This was based on articles in the published literature which suggested that FDA should re-evaluate current recommendations in statin labeling for routine periodic monitoring of liver enzyme tests.

In March 2008, DMEP issued Information Request letters to the statin sponsors requesting the following:

- a. Does <<APPLICANT>> have an opinion or recommendation regarding the utility of baseline and/or periodic monitoring of serum aminotransferase activity prior to and/or during treatment with <<STATIN>>? Please address this question for subjects with normal liver function and for those with asymptomatic liver disease (e.g., NAFLD, hepatitis C).
- b. Upon what clinical evidence or other consideration are these opinions or recommendations based?
- c. Please provide the number of phase 2 and 3 trials conducted with <<STATIN>> for which you have access to the raw data.

The table below summarizes the sponsors' responses to the first question:

Table 10. Overview of Industry responses to FDA questions on hepatotoxicity of statins			
Sponsor	Product	Text suggests interest in withdrawal of monitoring	caveats
Andrx	Lovastatin ER	No	none
AstraZeneca	rosuvastatin	Yes	none
Bristol-Myers Squibb	pravastatin	N/A	No text to delete
Merck	lovastatin	No	None
Merck	simvastatin	No	None
Novartis	fluvastatin	No	None
Pfizer	atorvastatin	Yes	10 mg dose only

In general, most sponsors agreed that liver enzyme testing prior to initiation of statin therapy was appropriate, but acknowledged that there appeared to be limited utility to routine liver biochemistry monitoring during treatment. One sponsor commented on the recommendations of the Liver Expert Panel convened by the National Lipid Association which stated that “because there is no evidence that a relation exists between elevated serum aminotransferase levels and significant liver injury, or that routine monitoring of liver biochemistries will identify individuals likely to develop rare cases of idiosyncratic liver failure, the requirement for routine liver biochemistry monitoring in patients receiving any of the currently marketed statin therapies should be re-examined.” Another sponsor noted that “nearly 50% of hyperlipidemic patients have coexisting non-alcoholic fatty liver disease (NAFLD) and it is well known that LFT levels fluctuate in NAFLD.”

In conjunction with the request to statin sponsors, DMEP requested that the Office of Surveillance and Epidemiology (OSE) conduct a review to characterize the risk of clinically serious hepatotoxicity in association with statins and assist in a determination if the statin class labeling for liver enzyme monitoring should be retained, revised, or removed. OSE had conducted 5 postmarket reviews of statins and hepatotoxicity between 2000 and 2009. Those reviews had consistently noted that reporting of statin-associated serious liver injury to AERS was extremely low (reporting rate of ≤ 2 per one million patient-years).

The OSE review of AERS was completed May 13, 2011. The review focused on cases of severe liver injury, defined as a 4 (severe liver injury) or a 5 (death or liver transplant) using the Drug Induced Liver Injury Network (DILIN) liver injury severity scale. Cases meeting those criteria were further assessed for causality. Seventy-five cases (27 with a severity score of 4 and 48 with a severity score of 5 [37 deaths and 11 liver transplants]) were assessed for causality, 30 of which (14 deaths, 7 liver transplantations, and 9 severe liver injury) were assessed as possibly (25-49% likelihood) or probably (50-74% likelihood) associated with

statin therapy. No cases were assessed as highly likely (75-95% likelihood) or definitely (>95% likelihood) associated with statin therapy. OSE noted that “despite rising use of statins as a class since the late 1990s, there has not been a detectable uptick in the annual rates of fatal (deaths or liver transplant) or severe liver injury possibly or probably causally associated cases.” The cases are summarized in the table below:

Table 6. Characteristics of U.S. AERS Cases With A Liver Injury Severity Score of 4 (Severe) or 5 (Death or Transplant) and Causally Associated* With Statin Therapy. Source: AERS, marketing through January 1, 2009)			
Liver Injury Severity Score	5 (Death)	5 (Transplant)	4 (Severe)
# of Cases	14	7	9
Median Age in Years (range)	66 (51-89)	48 (40-71)	58 (47-71)
Percent Female	79% (11/14)	71% (5/7)	67% (6/9)
Statin at the Time of Event Median Daily Dose in mg (range [n])			
Atorvastatin	4 -- (10, 10 [n=2])	3 10 (10-20 [n=3])	4 10 (10-20 [n=3])
Cerivastatin	--	--	--
Fluvastatin	--	--	1 -- (20 [n=1])
Lovastatin	1 -- (20 [n=1])	1 -- (-- [n=0])	--
Pravastatin	3 -- (20, 40 [n=2])	--	1 -- (10 [n=1])
Rosuvastatin	--	--	--
Simvastatin	6 20 (10-40 [n=5])	3 20 (20-40 [n=3])	3 -- (40 [n=1])
Time to Onset in Months**, Median (range)	2.5 (3 wk – 12 mo)	1.5 (2.4 wk - 6 mo)	2 (5 wk – 8 mo)
Peak Serum Total Bilirubin Level in mg/dL, Median (range [n])	23 (2.9-51 [n=12])	27 (22-32 [n=4])	10 (1.2-25 [n=9])
Peak Serum ALT Level in units/L, Median (range[n]) reference range: 6-41 units/L	1,127 (148-4,300 [n=10])	2,912 (2,037-13,531[n=4])	1,319 (538-3,000 [n=9])
Peak Serum AST Level in units/L, Median (range[n]) reference range: 9-34 units/L	1,497 (81-7,200 [n=11])	2,294 (1,755-6,815 [n=4])	1,260 (853-3,000 [n=9])
Peak Serum ALP Level in units/L, Median (range[n]) reference range: 37-116 units/L	206 (155-623 [n=9])	-- (290, 602 [n=2])	307 (131-800 [n=4])

*Defined as probably associated (supported by the evidence as implicating the drug but not definite or highly likely) or possibly associated (causality is not supported by the preponderance of evidence, but one cannot definitively exclude the possibility)

**Time to onset defined as the interval between exposure time or time after dose increased to reported liver injury event

OSE also looked at cases from the DILIN and Acute Liver Failure Study Group (ALFSG), organizations which have been systematically submitting reports to FDA of drug associated liver injury referred to their respective liver injury outcome studies. For statin associated liver injury, DILIN has submitted 25 reports to FDA as of January 1, 2011, twelve of which resulted in an outcome of hospitalization. In the ALFSG database, there were 9 reports of drug-induced liver injury (DILI) associated with statin therapy. OSE cited a 2010 article from

ALFSG that included 133 prospectively identified cases of idiopathic DILI resulting in acute liver failure. Fifteen patients were taking statins and in 6 of these 15 individuals a statin was identified as the only potential DILI agent. The authors noted that statin hepatotoxicity is “generally benign” and the identification of these 6 cases represents a “provocative observation”.

Using the AERS and drug utilization databases, reporting rates were calculated for U.S. statin cases associated with liver injury and an outcome of death or liver transplant, from the time of initial marketing approval through January 1, 2009. It should be noted that reporting rates are subject to secular reporting trends which normally preclude generation of reporting rates between products with initial marketing dates greater than 2-4 years apart. Despite the limitations of the analysis, it appears that reporting levels for serious liver injury in association with currently marketed statins are generally similar.

Table 9. Number of U.S. Statin Cases Associated with Liver Injury and an Outcome of Death or Liver Transplant (Severity Score 5). Initial Marketing Approval Through January 1, 2009			
Generic Name (Brand)	Number of cases	Total Number of Prescriptions (TRxs) Dispensed by U.S. Retail Pharmacies, 1991-2008† (in millions)	Observed reporting rate as cases per (b) (4)
Lovastatin (Mevacor, Advicor, Altocor)	23		(b) (4)
Pravastatin (Pravachol)	11		
Simvastatin (Zocor, Vytorin, Simcor)	51		
Fluvastatin (Lescol)	4		
Atorvastatin (Lipitor)	64		
Rosuvastatin (Crestor)	3		
Total	156		

OSE also reviewed current monitoring guidelines including the National Lipid Association’s Liver Expert Panel, which state:

The Liver Expert Panel does not believe that the available scientific evidence supports the routine monitoring of liver biochemistries in asymptomatic patients receiving statins. The Panel makes this recommendation because (1) irreversible liver damage resulting from statins is exceptionally rare and is likely idiosyncratic in nature, and (2) no data exist to show that routine monitoring of liver biochemistries is effective in identifying the very rare individual who may develop significant liver injury from ongoing statin therapy. In the view of the Panel, routine monitoring will instead identify patients with isolated

increased aminotransferase levels, which could motivate physicians to alter or discontinue statin therapy, thereby placing patients at increased risk for cardiovascular events.

OSE further noted that the NLA's Statin Safety Task Force had a slightly divergent opinion and made the following recommendation:

Until there is a change in the FDA-approved prescribing information for statins, it is appropriate to continue to measure transaminase levels before starting therapy, 12 weeks after initiating therapy, after a dose increase, and periodically thereafter. However, routine monitoring of liver function tests is not supported by the available evidence and the current recommendation for monitoring needs to be reconsidered by the FDA.

The OSE review concluded:

Serious, hepatocellular DILI can be caused by statins. Although the routine monitoring of serum ALT and other markers for liver injury is vital for drug development, it does not appear to be useful in a post marketing, non study, ambulatory setting to routinely detect and prevent serious liver injury in association with statins. In place of current recommendations for serum enzyme monitoring, labeling for statins should focus on an alert to identify serious liver injury and clinical symptoms of liver injury, interruption of therapy, physician interactions, and emphasize the importance of appropriate diagnostic work up.

OSE further recommended:

It is justified that the recommendation to perform routine periodic serum ALT monitoring in all treated patients at prespecified intervals currently in place for some marketed statins be removed.

Based on these recommendations, DMEP requested the following changes to statin labeling:

Under HIGHLIGHTS OF PRESCRIBING INFORMATION, under **WARNINGS AND PRECAUTIONS**:

Liver enzyme abnormalities: Persistent elevations in hepatic transaminases can occur. Check liver enzyme tests before initiating therapy and as clinically indicated thereafter.

Under **5 WARNINGS AND PRECAUTIONS**, (b) (4)

It is recommended that liver enzyme tests be performed before the initiation of <<STATIN>> (b) (4)

There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including <<STATIN>>. If serious liver injury with clinical symptoms and/or

hyperbilirubinemia or jaundice occurs during treatment with <<STATIN>>, promptly interrupt therapy. If an alternate etiology is not found do not restart <<STATIN>>.

Under 6 ADVERSE REACTIONS, Post-Marketing Experience:

(b) (4)

Under 17 PATIENT COUNSELING INFORMATION, Liver Enzymes:

It is recommended that liver enzyme tests be (b) (4) before the initiation of <<STATIN>> and if signs or symptoms of liver injury occur. All patients treated with <<STATIN>> should be advised to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice.

(b) (4)

2. Cognitive effects – TSI #772

On September 2, 2009 DMEP opened TSI #772 to evaluate the effect of statins on cognition. This was based on a complaint received from Joe Graedon of the People's Pharmacy, and an unpublished study by Duane Graveline, M.D., M.P.H. and Jay S. Cohen, M.D. entitled "Lipitor-associated memory loss: analysis of 662 cases of cognitive damage", as well as other articles from the published literature.

In attempting to assess this risk, DMEP looked initially at pre-clinical data. Several of the statin drug sponsors had performed pre-clinical cognition studies; however, those studies only address the issue of dementia syndromes, and are less helpful in addressing the issue of acute confusional states or memory impairment. Therefore, it was determined that there was no value added to re-assessing the pre-clinical data.

DMEP sent information request letters to those statin sponsors who had conducted clinical trials in which some form of neurocognitive assessment had been conducted as part of the study protocol. Those trials included: Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), Heart Protection Study (HPS), and Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH).

The findings were as follows:

- **PROSPER:** Subjects were screened with a Mini Mental Status Exam (MMSE) and excluded if their score was <24. Cognitive function was assessed in all 5,804 participants at six different time points during the study.

Four neuropsychological tests were performed, two of which tested executive function (attention and speed) and two of which tested memory (immediate and delayed). All tests showed a significant decline over time (3-year follow-up); however, there was no difference between treatment groups, pravastatin 40 mg versus placebo.

- **HPS:** A modified Telephone Interview for Cognitive Status (TICS-m) questionnaire was administered to participants during their final follow-up, either face-to-face in the clinic or over the telephone. Data were available on 8086/10269 (79%) of simvastatin-allocated subjects and 7834/10267 (76%) of placebo-allocated subjects. No significant differences were observed between the treatment groups in the percentages of participants classified as cognitively impaired (defined as a TICS-m score below 22 out of 39), either overall (23.7% simvastatin 40 mg-allocated vs. 24.2% placebo-allocated) or in subgroups defined with respect to their age at study entry (<65 years: 17.1% vs. 17.8%; 65-69 years: 25.8% vs. 25.4%; 70-80 years: 34.6% vs. 36.2%) or their previous history of cerebrovascular disease (no prior stroke: 22.8% vs. 23.3%; prior stroke: 31.9% vs. 33.3%). Nor was there any significant difference between the groups in mean TICS-m score (24.08 vs. 24.06). Similar numbers of participants in each treatment group were reported to have developed dementia during follow-up (31 [0.3%] vs. 31 [0.3%]).

There was a slightly higher frequency of cases of Alzheimer's disease or Alzheimer's type dementia in patients on simvastatin (n=6) compared to placebo (n=3). When looking at all patients with potential diagnoses of dementia including Alzheimer's disease, confusion, disorientation, dementia or cognitive impairment, there was no difference in the frequency of patients in the simvastatin group (n=35; 0.34%) compared to placebo (n=33; 0.32%).

- **SEARCH:** Assessment of cognitive function, using the TICS-m score, was a tertiary endpoint for the folate arm of the trial. It was performed in 8891 subjects – 4473 on simvastatin 80 mg and 4418 on simvastatin 20 mg – at the final visit. There was no difference in mean TICS-m score between treatment groups (24.3 ± 4.1 for simvastatin 80 mg vs. 24.3 ± 4.3 for simvastatin 20 mg), and no difference in percentages of patients with scores <20, ≥ 20 , <22, ≥ 22 , <25, ≥ 25 , <30, ≥ 30 between treatment groups. The TICS-m score reflects memorizing ability in large part. Verbal fluency scores also did not differ among patients allocated to simvastatin 80 mg and simvastatin 20 mg. Hearing thresholds were assessed at final follow-up and did not differ between the simvastatin groups.

The incidence of memory loss attributed to study treatment was 17 (0.3%) in patients allocated to simvastatin 80 mg, and 8 (0.1%) in patients allocated to simvastatin 20 mg.

It should also be noted that while no formal neurocognitive assessment was performed in the Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), there was noted a

statistically significant increase in the reported adverse event of confusional state in subjects allocated to rosuvastatin 20 mg (n=8 [0.2%]) versus subjects allocated to placebo (n=4 [0.04%]).

DMEP was aware of a Phase III efficacy study of atorvastatin that had been conducted in patients with mild to moderate Alzheimer's Disease. The clinical study report for this study (Study A2581078) was requested from the sponsor and consulted to the Division of Neurology Products (DNP) for review. DNP's findings were as follows:

The results of Study A2581078, an adequately-designed Phase III efficacy and safety study of atorvastatin (Lipitor) in patients with mild to moderate Probable Alzheimer's Disease, provide no evidence that the administration of Lipitor results in cognitive worsening in this population; neither was there any evidence of a worsening of global function in those treated with atorvastatin in this study.

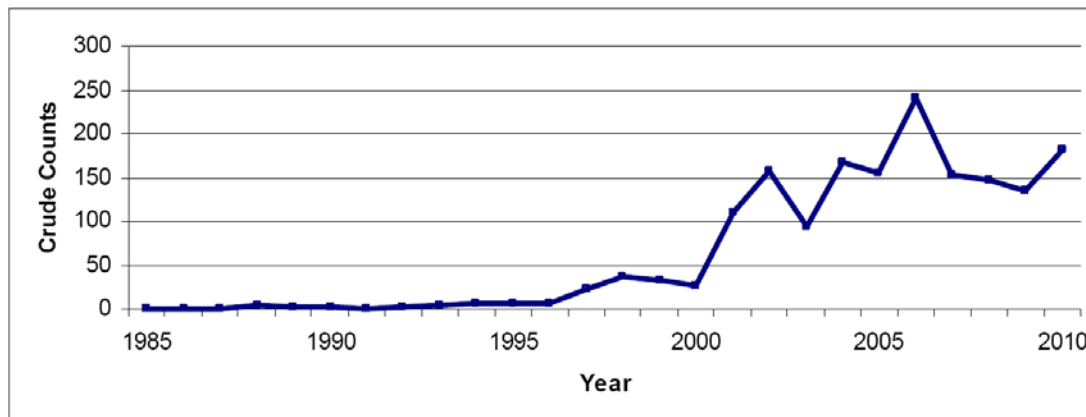
DMEP consulted OSE and requested that a review of AERS and the published literature be conducted to further assess the effect of statins on cognition. In 2002, OSE had performed a review of 279 statin reports associated with transient memory loss. This review had been requested by DMEP in response to a consumer report of transient global amnesia (TGA) with atorvastatin. At that time, OSE determined that the calculated reporting rate for statin-associated TGA (0.12-0.55 per 100,000 patient years) was well below the background incidence rate (3.4-32/100,000 population per year). As memory loss was already included in the statin labels, no labeling change was recommended at that time.

OSE's updated review of AERS focused on reports of serious cases of memory impairment, using the following High Level Terms (HLT):

- Mental Impairment (excluding dementia and memory loss)
- Memory Loss (excluding dementia)
- Amnestic Symptoms
- Confusion and Disorientation

Through January 1, 2011 there were 1,698 U.S. serious reports (crude counts) in AERS.

Figure 1. Number of U.S. Serious Statin* Reports (Crude Counts) Associated with Cognitive Change†, by Year Received. Source: AERS, Initial Marketing Approval Through January 1, 2011 (n=1,698)



*Includes single ingredient and combination statin products approved by FDA.

†Reports identified in AERS using four HLTs: Mental Impairment (excluding dementia & memory loss), Memory Loss (excluding dementia), Amnesic Symptoms, and Confusion and Disorientation

Further case review was limited to 182 reports received by FDA in 2010. Of those reports, 57 unique cases described transient cognitive change as the primary adverse event. Sixty nine percent (n=125) of the cases were excluded because they reported multiple events such as rhabdomyolysis, renal failure, and confusion (n=81), were duplicates (n=18), hearsay (n=3), reported by attorneys (n=5), or solicited reports (n=16).

Characteristics of the 57 cases included:

- Age: median of 62 years (30-85)
- Sex: 62% male
- Exposure time: median of 3 years (1 month-12 years)

The literature review included case series of transient cognitive impairment associated with statin use, as well as observational studies on the association between statin use and the incidence of dementia. The observational evidence was summarized based on a meta-analysis by Zhou and colleagues:

After conducting a systematic review, the authors identified four cohort studies and three case control studies which examined the association between statin use and dementia. The average observation period ranged from three to nine years. Three case control studies suggested statin use may lower the incidence of dementia; while the remaining four cohort studies failed to demonstrate an association between statin use and incident dementia. A pooled analysis also failed to demonstrate an association between statin use and incident dementia.

OSE further noted:

Results from three prospective cohort studies published within the last year provide similar conflicting results. Analyses of Baltimore Longitudinal Study of Aging and the Ginkgo Evaluation of Memory Study suggested that statin use is associated with a lower risk of dementia. A nested case control study in the Neurological Disorders in Central Spain cohort failed to detect an association between statin use and cross sectional performance on a neuropsychological test battery.

Table 5. Observational Studies Summary: Statin Use and Cognition				
Author (Publication Date)	Study Design	Total Sample Size (% Exposed to Statins)	Outcome	Key Result
Zhou (2007)	Meta-Analysis – Observational Studies	10523 (12%)	Incident Dementia	Adjusted OR=0.77 (95%: 0.45-1.30)
Beydoun (2010)	Cohort Study	1604 (7%)	Incident Dementia	Adjusted HR=0.21 (95%: 0.09-0.48)
Betterman (2011)	Cohort Study	3069 (25%)	Incident Dementia	Adjusted HR=0.79 (95%: 0.65-0.96)
Benito-Leon (2010)	Nested Case-Control	548 (25%)	Neuropsychological Test Performance	No treatment effect observed in any test neuropsychological test administered (global cognition, verbal fluency, psychomotor speed, confrontational naming, verbal memory, logical memory)

OSE concluded:

The postmarket statin reports associated with transient cognitive change generally describe individuals over the age of 50 years who experience notable (sometimes described as “dramatic”), but ill defined memory loss or impairment (e.g., “lost my mind”) that is reversible upon discontinuation of statin therapy. The statin exposure time to onset of the event is highly variable (1 day to years). These cases do not appear to be associated with fixed or progressive dementia, such as Alzheimer’s disease.

Like the previous (2002) OSE review, the analyzed data in this review did not reveal any discernible dose event or age (the reported age at the time of event is similar to the age of the population using statins) trends or effects between statins and other drugs; few reports described neurologic follow-up or standardized testing results. Findings from this review (and the 2002 OSE review) are also similar to patient survey results recently published by the University of California San Diego (UCSD) Statin Effects Study investigators. Cognitive issues were reported for all statins, with atorvastatin and simvastatin most frequently reported. The time to onset was variable (1 day to 10 years). Ninety percent reported symptom improvement after the statin was discontinued. Complete recovery time varied from 1 day to several years (median time to first noted improvement was 2.5 weeks). Of 29 participants who underwent rechallenge, 19 reported recurrence of events.

An analysis of the epidemiologic evidence and clinical trials did not provide evidence that chronic statin use is associated with cognitive decline at the population level. Two studies demonstrated that exposure to statins for up to six months may prevent the acquisition of a practice effect on select neuropsychological measures. However, the clinical significance of an absent practice effect in the context of normal cognitive performance is questionable. Furthermore, no study systematically assessed patients who experienced statin associated cognitive impairment during both dechallenge and rechallenge. Such systematic studies would provide additional evidence to support a causal association and better characterize the clinical phenotype.

OSE recommended that DMEP consider statin class labeling that would characterize the nature of the cognitive changes. In response, DMEP requested that the following be added to the **Adverse Reactions, Postmarketing Experience** sub-section of all statin labels:

There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

(b) (4)

3. Drug-drug interaction with protease inhibitors – TSI #756

On July 23, 2009 TSI #756 was opened to examine the drug-drug interaction between statins and protease inhibitors.

In July 2009, the sponsor for rosuvastatin (CRESTOR) submitted a prior approval supplement (PAS) proposing to include information on increased rosuvastatin exposure when CRESTOR was co-administered with the combinations of protease inhibitors tipranavir/ritonavir, atazanavir/ritonavir or fosamprenavir/ritonavir, based on studies in the published literature. Previous CRESTOR labeling had noted a DDI with lopinavir/ritonavir (KALETRA) resulting in a dose cap of 10 mg of CRESTOR when co-administered with KALETRA.

In a January 2010 review of the PAS, it was noted that there were inconsistencies between the statin labels and the protease inhibitor labels regarding recommendations for co-administration of these products. It was therefore determined that the Office of Clinical Pharmacology (OCP) would review the relevant data on DDIs between statins and HIV and HCV protease inhibitors.

On August 3, 2011 OCP completed its review of the cross labeling initiative for drug interaction updates between protease inhibitors and statins. DMEP was requested to make changes to the atorvastatin and pravastatin labels to provide the results of DDI studies conducted with certain protease inhibitors, and in the case of atorvastatin, to provide dose caps where appropriate, based on the results of the following DDI studies:

- Tipranavir/ritonavir increases atorvastatin AUC and C_{max} 9.4-fold and 8.6-fold, respectively. Because clinical data demonstrating an increased risk of myopathy or rhabdomyolysis with co-administration are lacking, a contraindication was not supported and “Avoid atorvastatin” was recommended for labeling.
- Telaprevir increases atorvastatin AUC and C_{max} 7.88-fold and 10.6-fold, respectively. Because clinical data demonstrating an increased risk of myopathy or rhabdomyolysis with co-administration are lacking, a contraindication was not supported and “Avoid atorvastatin” was recommended for labeling.
- Darunavir/ritonavir increases atorvastatin AUC and C_{max} 3.4-fold and 2.25-fold, respectively. A dose cap of atorvastatin 20 mg was recommended for labeling.
- Fosamprenavir increases atorvastatin AUC and C_{max} 2.3-fold and 4.04-fold, respectively. A dose cap of atorvastatin 20 mg was recommended for labeling.

(b) (4)

Based on OCP's recommendation, DMEP requested the following changes to the atorvastatin and pravastatin labels:

Atorvastatin:

Under HIGHLIGHTS OF PRESCRIBING INFORMATION, **DRUG INTERACTIONS**, Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis (2.6, 5.1, 7, 12.3)	
Interacting Agents	Prescribing Recommendations
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Do not exceed 10 mg atorvastatin daily Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (ritonavir plus saquinavir plus ritonavir, lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	Caution when exceeding doses >20mg atorvastatin daily. The lowest dose necessary should be used. Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir)	Do not exceed 40 mg atorvastatin daily

Under **DOSAGE AND ADMINISTRATION**:

2.6 Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors ~~a Combination of Ritonavir plus Saquinavir or Lopinavir plus Ritonavir~~

In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the Hepatitis C protease inhibitor (telaprevir), therapy ~~should be limited to with~~ LIPITOR ~~40 mg once daily~~ should be avoided. In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing LIPITOR and the lowest dose necessary employed. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of ~~ritonavir plus saquinavir plus ritonavir, or lopinavir plus ritonavir~~ darunavir plus ritonavir, fosamprenavir, ~~or fosamprenavir plus ritonavir for~~ doses of therapy with LIPITOR ~~should be limited to exceeding 20 mg~~, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of LIPITOR is employed. In patients with HIV taking nelfinavir, therapy with LIPITOR should be limited to 40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of LIPITOR is employed.

Under **5 WARNINGS AND PRECAUTIONS, 5.1 Skeletal Muscle**:

The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, clarithromycin, the hepatitis C protease inhibitor telaprevir, combinations of HIV protease inhibitors, including ~~ritonavir plus~~ saquinavir plus ritonavir, ~~or~~ lopinavir plus ritonavir, ~~tipranavir plus~~ ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with LIPITOR and fibric acid derivatives, erythromycin, clarithromycin, a combination of ~~ritonavir plus~~ saquinavir plus ritonavir, ~~or~~ lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, ~~immunosuppressive drugs~~, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug.

Under **Table 1. Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis:**

Table 1. Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Cyclosporine, <u>HIV protease inhibitors (tipranavir plus ritonavir)</u> , hepatitis C protease inhibitor (<u>telaprevir</u>)	<u>Do not exceed 10 mg atorvastatin daily</u> <u>Avoid atorvastatin</u>
<u>HIV protease inhibitor (lopinavir plus ritonavir)</u>	<u>Use with caution and lowest dose necessary</u>
Clarithromycin, itraconazole, HIV protease inhibitors (<u>ritonavir plus saquinavir plus ritonavir*</u> , or <u>lopinavir plus ritonavir</u> , <u>darunavir plus ritonavir</u> , <u>fosamprenavir</u> , <u>fosamprenavir plus ritonavir</u>)	<u>Caution when exceeding doses >20mg atorvastatin daily. The lowest dose necessary should be used.</u> <u>Do not exceed 20 mg atorvastatin daily</u>
<u>HIV protease inhibitor (nelfinavir)</u>	<u>Do not exceed 40 mg atorvastatin daily</u>

*Use with caution and with the lowest dose necessary

Under **DRUG INTERACTIONS, Combination of Protease Inhibitors, 7.1 Strong Inhibitors of CYP 3A4:**

Combination of Protease Inhibitors: Atorvastatin AUC was significantly increased with concomitant administration of LIPITOR ~~40 mg~~ with several combinations of HIV protease inhibitors, as well as with the Hepatitis C protease inhibitor telaprevir, ritonavir plus saquinavir (400 mg twice daily) or LIPITOR 20 mg with lopinavir plus ritonavir (400 mg + 100 mg twice daily) compared to that of LIPITOR alone [see *Clinical Pharmacology* (12.3)]. Therefore, in patients taking the HIV protease inhibitors tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of LIPITOR should be avoided. In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing LIPITOR and the lowest dose necessary should be used. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the

dose of LIPITOR should not exceed 20 mg and should be used with caution. ~~caution should be used when the LIPITOR dose exceeds 20 mg.~~

Under 12 CLINICAL PHARMACOLOGY, 12.3 Pharmacokinetics, TABLE 3. Effect of Coadministered Drugs on the Pharmacokinetics of Atorvastatin:

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC	Change in Cmax
Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	10 mg, SD	↑9.4 fold	↑8.6 fold
Nelfinavir 1250 mg BID, 14 days	10 mg QD for 28 days	↑74%	↑2.2-fold
Fosamprenavir 1400 mg BID, 14 days	10 mg QD for 4 days	↑2.3-fold	↑4.04-fold
Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	10 mg QD for 4 days	↑2.53-fold	↑2.84-fold
Darunavir 300 mg BID/ritonavir 100 mg BID, 9 days	10 mg QD for 4 days	↑3.4-fold	↑2.25-fold
Telaprevir 750 mg q8h, 10 days	20 mg, SD	↑7.88-fold	↑10.6-fold

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC	Change in Cmax
^{#, ‡} Ritonavir Saquinavir 400 mg BID/saquinavir ritonavir 400 mg BID, 15 days	40 mg QD for 4 days	↑3.9-fold	↑4.3-fold

[‡]The dose of saquinavir plus ritonavir in this study is not the clinically used dose. The increase in atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore caution should be applied and the lowest dose necessary should be used.

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC ^{&}	Change in Cmax ^{&}
[#] Lopinavir 400 mg BID/ ritonavir 100 mg BID, 14 days	20 mg QD for 4 days	⊖5.9 fold	⊖4.7 fold

Under 12 CLINICAL PHARMACOLOGY, 12.3 Pharmacokinetics, TABLE 4. Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs:

Atorvastatin	Co-administered drug and dosing regimen		
	Drug/Dose (mg)	Change in AUC	Change in C _{max}
<u>10 mg, SD</u>	<u>Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days</u>	<u>No change</u>	<u>No change</u>
<u>10 mg QD for 4 days</u>	<u>Fosamprenavir 1400 mg BID, 14 days</u>	<u>↓27%</u>	<u>↓18%</u>
<u>10 mg QD for 4 days</u>	<u>Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days</u>	<u>No change</u>	<u>No change</u>

Pravastatin:

Under 12 CLINICAL PHARMACOLOGY, 12.2 Pharmacokinetics, Table 3: Effect of Coadministered Drugs on the Pharmacokinetics of Pravastatin:

Coadministered Drug and Dosing Regimen	Pravastatin		
	Dose (mg)	Change in AUC	Change in C _{max}
<u>Darunavir 600 mg BID/Ritonavir 100 mg BID for 7 days</u>	<u>40 mg single dose</u>	<u>↑81%</u>	<u>↑63%</u>
<u>Kaletra 400 mg/100 mg BID for 14 days</u>	<u>20 mg OD for 4 days</u>	<u>↑33%</u>	<u>↑26%</u>

Under 12 CLINICAL PHARMACOLOGY, 12.2 Pharmacokinetics, Table 4: Effect of Pravastatin on the Pharmacokinetics of Coadministered Drugs

Pravastatin Dosing Regimen	Name and Dose	Change in AUC	Change in C _{max}
<u>20 mg OD for 4 days</u>	<u>Kaletra 400 mg/100 mg BID for 14 days</u>	<u>No change</u>	<u>No change</u>

A December 6, 2011 OCP review of DDI's with lovastatin noted that available data support a contraindication with strong CYP3A4 inhibitors, such as the HIV protease inhibitors. The data were summarized as follows:

- *According to the Guidance for Industry Drug Interaction Studies, lovastatin is listed as one of the sensitive in vivo CYP3A4 substrates. Therefore, strong CYP3A4 inhibitors are predicted to significantly increase lovastatin exposure because lovastatin is extensively metabolized by CYP3A4 isozyme.*
- *Literature survey indicates that itraconazole increases lovastatin exposure up to 15- to 20-fold and the drug interaction seems to result in rhabdomyolysis. Itraconazole is the representative strong CYP3A4 inhibitor and therefore, the effect of itraconazole on lovastatin exposure can be extrapolated to other strong CYP3A4 inhibitors listed in the Guidance as well as the FDA website.*

- *Strong CYP3A4 inhibitors are contraindicated for simvastatin because of the significant drug interaction and its potential for the increased risk on the rhabdomyolysis. Physicochemical and pharmacokinetic properties of lovastatin are comparable with those of simvastatin. Meanwhile, itraconazole increased the exposure of lovastatin (up to 20-fold) more than that of simvastatin (up to 13-fold), and it indicates that strong CYP3A4 inhibitor can cause greater lovastatin exposure increase compared to that of simvastatin. Therefore, it seems reasonable to extrapolate the effect of strong CYP3A4 inhibitors on simvastatin to that on lovastatin.*

Therefore, concomitant use of lovastatin with HIV protease inhibitors, as well as the HCV protease inhibitors boceprevir and telaprevir, will be contraindicated.

Lovastatin:

Under CONTRAINDICATIONS:

Concomitant administration with strong CYP3A4 inhibitors, e.g., itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone)

Under WARNINGS, Myopathy/Rhabdomyolysis, Strong inhibitors of CYP3A4:

Lovastatin, like several other inhibitors of HMG-CoA reductase, is a substrate of cytochrome P450 3A4 (CYP3A4). When lovastatin is used with a strong inhibitor of CYP3A4, elevated plasma levels of HMG-CoA reductase inhibitory activity can increase the risk of myopathy and rhabdomyolysis, particularly with higher doses of lovastatin. Certain drugs which inhibit this metabolic pathway can raise the plasma levels of lovastatin and may increase the risk of myopathy. These include itraconazole, ketoconazole, and posaconazole, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors, boceprevir, telaprevir, or the antidepressant nefazodone. Combination of these drugs with lovastatin is contraindicated.

Under **WARNINGS, Myopathy/Rhabdomyolysis**, Table VII: Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis:

Interacting Agents	Prescribing Recommendations
Itraconazole Ketoconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors <u>Boceprevir</u> <u>Telaprevir</u> Nefazodone	<u>Avoid- Contraindicated</u> with lovastatin

Under **PRECAUTIONS, Drug Interactions, CYP3A4 Interactions:**

Lovastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. Strong inhibitors of CYP3A4 (e.g., below itraconazole, ketoconazole, posaconazole, clarithromycin, telithromycin, HIV protease inhibitors, bocprevir, telaprevir, nefazodone, and erythromycin, and large quantities of grapefruit juice increase the risk of myopathy by reducing the elimination of lovastatin.

Itraconazole

Ketoconazole

Erythromycin

Clarithromycin

Telithromycin

HIV protease inhibitors

Nefazodone

Large quantities of grapefruit juice (>1 quart daily)

4. Increases in HbA1c and fasting plasma glucose – TSI #891

On April 8, 2010 TSI #891 was opened to evaluate the effect of statins on increases in HbA1c and fasting plasma glucose. This was based on findings from the JUPITER trial, which reported a 27% increase in investigator-reported diabetes mellitus in rosuvastatin-exposed subjects compared to placebo-exposed subjects. High-dose atorvastatin had previously been associated with worsening glycemic control in the PROVE-IT TIMI 22 substudy.

Several articles from the published literature were also considered, including:

- Sattar N et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomized statin trials. *Lancet*.2010;375:735-742
- Sukhija R et al. Effect of Statins on Fasting Plasma Glucose in Diabetic and Nondiabetic Patients. *Journal of Investigative Medicine*.2009;57(3): 495-499
- Rajpathak SN et al. Statin Therapy and Risk of Developing Type 2 Diabetes: A Meta-Analysis. *Diabetes Care*.2009;32:1924-1929
- Koh KK et al. Atorvastatin Causes Insulin Resistance and Increases Ambient Glycemia in Hypercholesterolemic Patients. *JACC*.2010;55(12):1209-1216
- Thongtang N et al. Effects of Maximal Atorvastatin and Rosuvastatin Treatment on Markers of Glucose Homeostasis and Inflammation. *Am J Cardiol*.2011;107:387-392
- Kostapanos MS et al. Do Statins Beneficially or Adversely Affect Glucose Homeostasis? *Current Vascular Pharmacology*.2010;8:612-631
- Mills EJ et al. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170255 patients from 76 randomized trials. *Q J Med*.2011;104:109-124

- Culver AL et al. Statin Use and Risk of Diabetes Mellitus in Postmenopausal Women in the Women's Health Initiative. *Arch Intern Med*. Published online January 9, 2012.

The Sattar meta-analysis, which looked at 13 statin trials with 91,140 participants, reported that “statin therapy was associated with a 9% increased risk for incident diabetes (odds ratio [OR] 1.09; 95% CI 1.02-1.17), with little heterogeneity ($I^2=11\%$) between trials.”

The Rajpathak meta-analysis, which looked at 6 statin trials with 57,593 participants, reported a “small increase in diabetes risk” (relative risk [RR] 1.13; 95% CI 1.03-1.23), with “no evidence of heterogeneity across trials”.

The Mills meta-analysis, which looked at 76 randomized clinical trials (RCTs) with 170,255 participants, reported that 17 RCTs reported on increased risk of development of incident diabetes (Odds ratio [OR] 1.09; 95% CI 1.02-1.17, $p=0.001$, $I^2=11\%$).

Culver et al looked at postmenopausal women participating in the Women's Health Initiative (WHI) to investigate whether the incidence of new-onset diabetes mellitus is associated with statin use. The study involved 153,840 women. Statin use at baseline was associated with an increased risk of DM (hazard ratio [HR], 1.71; 95% CI, 1.61-1.83); the multivariate-adjusted HR was 1.48; 95% CI, 1.38-1.59. The association was observed for all types of statin medications.

At the time of approval of the JUPITER supplement, the following labeling was required for CRESTOR:

5.5 Endocrine Effects

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including CRESTOR.

The data for an effect of statins on incident diabetes, and increases in HbA1c and/or fasting plasma glucose seem to indicate a class effect; however, given the limitations of epidemiological data, and the findings from the West of Scotland Coronary Prevention Study (WOSCOPS) clinical trial, which suggested that pravastatin may decrease the incidence of diabetes by 30%, the division did not seek a labeling change for pravastatin.

Therefore, based on clinical trial data, epidemiological data, and the published literature, the following labeling change was requested for all statins except pravastatin:

5.X Endocrine Function:

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including <<STATIN>>.

5. Drug-drug interaction with ranolazine – TSI #988

TSI #988 was opened by the Division of Cardiovascular and Renal Products (DCRP) in July 2010 when during routine data monitoring of the AERS database for cases of ranolazine and torsades de pointes, a signal was identified for rhabdomyolysis in patients receiving ranolazine and statins.

Nine cases of drug interaction were related to concomitant use of ranolazine and a statin. Of those nine cases, seven (all male) involved the statin associated adverse events of rhabdomyolysis (6) and myalgia (1). Four of those six patients were stable on long-term statin therapy prior to the initiation of ranolazine. Most cases involved the use of simvastatin.

According to the OCP review:

Ranolazine and SV are both cleared via CYP3A metabolism. Hence, concomitant administration of the two may lead to pharmacokinetic DDI. Administration of ranolazine (1000 mg twice daily) with SV (80 mg once daily) resulted in a ~2-fold increase in C_{max} and ~1.5-fold increase in AUC of SV and SVA, at steady state. Increased systemic exposure to SV and SVA has been associated with increased risk of myopathy and rhabdomyolysis. The 80 mg dose of SV has been shown to be associated with increased incidence of myopathy and rhabdomyolysis. In addition, there is little gain in effectiveness of the 80 mg over 40 mg dose. The DMEP regulatory briefing held on 6/4/2010 suggested progressive removal of 80 mg dose of simvastatin from the market, leaving 40 mg as the highest available dose. Therefore, given the 2-fold increase in systemic exposure expected on concomitant administration of ranolazine and SV, limiting the dose of SV to 20 mg will avoid exposures similar or greater to that observed with 80 mg.

In addition, for other statins which are primarily metabolized by CYP3A (e.g., lovastatin and atorvastatin), concomitant medications which are CYP3A inhibitors are expected to elevate statin exposure, and risk of myopathy. However, at present, definitive data (such as available with simvastatin) is not available for other statins, in order to recommend dose-adjustments.

On June 8, 2011, in conjunction with the approval of new dosing restrictions with the 80 mg dose of simvastatin, DMEP approved a dose cap of simvastatin 20 mg when simvastatin is coadministered with ranolazine.

In addition, the current ranolazine label recommends a dose adjustment of sensitive CYP3A4 substrates such as lovastatin based on the 2-fold simvastatin exposure increase by ranolazine.

Based on the information above, the following recommendations for labeling changes were made:

Mevacor:

Under **WARNINGS**, *Myopathy/Rhabdomyolysis*:

Ranolazine: The risk of myopathy, including rhabdomyolysis, may be increased by concomitant administration of ranolazine. Dose adjustment of lovastatin may be considered during co-administration.

Under **PRECAUTIONS**, *Other Drug Interactions*:

Ranolazine: The risk of myopathy, including rhabdomyolysis, may be increased by concomitant administration of ranolazine.

Altoprev:



Advicor:



6. Myopathy with concomitant administration with colchicine

In June 2010, a Regulatory Briefing was conducted to discuss the increased risk of myopathy, including rhabdomyolysis, associated with the use of simvastatin 80

mg, based on DMEP's review of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) clinical trial. In preparation for the briefing, OSE noted an interaction between statins and colchicine resulting in an increased risk of myopathy. Colchicine, a substrate of P-glycoprotein and CYP3A4, carried the following information in its label:

5.4 Neuromuscular Toxicity

Colchicine-induced neuromuscular toxicity and rhabdomyolysis have been reported with chronic treatment in therapeutic doses. Patients with renal dysfunction and elderly patients, even those with normal renal and hepatic function, are at increased risk. Concomitant use of atorvastatin, simvastatin, pravastatin, fluvastatin, gemfibrozil, fenofibrate, fenofibric acid, or benzafibrate (themselves associated with myotoxicity) or cyclosporine may potentiate the development of myopathy. Once colchicine is stopped, the symptoms generally resolve within 1 week to several months.

This was based on reports from the literature as summarized in the table below, and adapted from a 2008 OCP review of NDA 22-352 (Colstat [colchicine tablets]).

Lipid Lowering Agents			
HMG-CoA Reductase Inhibitors	Simvastatin: Baker et al. (2004) ; Hsu et al. (2002)	Both are CYP3A4 and P-gp substrates; P-gp inhibition by simvastatin	Acute myopathy or rhabdomyolysis (could be attributed to either drug)
	Fluvastatin: Atasoyu et al. (2005)	Synergistic myotoxicity via PK & PD mechanism; fluvastatin is not a P-gp inhibitor	
	Pravastatin: Alayli et al. (2005)	Synergistic myotoxicity via PK & PD mechanism; pravastatin is not a P-gp inhibitor	
	Atorvastatin: Tufan et al. (2006)	Both are CYP3A4 substrates; P-gp inhibition by atorvastatin	
Fibrates	Gemfibrozil: Atmaca et al., 2002	Synergistic toxic effect of both drugs	
	Fenofibrate & Diltiazem: Sinsawaiwong et al., 1997	Mechanism-based inhibition of CYP3A4 by diltiazem.	

On June 8, 2011, the following changes were approved for the simvastatin-containing drugs:

5 WARNINGS AND PRECAUTIONS

5.1 Myopathy/Rhabdomyolysis

Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing simvastatin with colchicine.

7 DRUG INTERACTIONS

7.7 Colchicine

Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing simvastatin with colchicine.

In order to harmonize and update the appropriate statin labels, similar labeling changes were requested for atorvastatin, pravastatin, and fluvastatin. Furthermore, because of physicochemical and pharmacokinetic similarities between lovastatin and simvastatin, similar labeling changes were requested for lovastatin.

7. Myopathy with concomitant administration with fibrates

A National Institutes of Health (NIH) funded trial, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Trial, was reviewed by DMEP and discussed at an Advisory Committee meeting on May 19, 2011. ACCORD-Lipid evaluated the occurrence of major adverse cardiovascular events (MACE), a composite of nonfatal heart attack, nonfatal stroke, and cardiovascular death in patients receiving simvastatin plus fenofibrate, compared to simvastatin alone. The trial found that there was no difference in cardiovascular outcomes between the two groups (Hazard Ratio = 0.92; 95% Confidence Interval: 0.79-1.08; p=0.32).

This was the second failed cardiovascular outcome trial for fenofibrate. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, fenofibrate demonstrated a non-significant 11% relative reduction in the primary outcome of coronary heart disease events (Hazard Ratio = 0.89; 95% Confidence Interval: 0.75-1.05; p=0.04) versus placebo.

The absence to date of proven cardiovascular benefit with fenofibrates must be viewed in the context of observational data showing an increase in the risk of myopathy with fenofibrates, especially when co-administered with a statin. In 2011, OSE conducted a review of observational data on rhabdomyolysis with fenofibrates and gemfibrozil in combination with statins. Their review looked at 3 studies:

- Graham DJ, Staffa JA, Shatin D et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-2590.
- Amend KL, Landon J, Thyagarajan V, Niemcryk S, McAfee A. Incidence of hospitalized rhabdomyolysis with statin and fibrate use in an insured US population. *Ann Pharmacother* 2011;45:1230-1239.
- Enger C, Gately R, Ming EE, Niemcryk SJ, Williams L, McAfee AT. Pharmacoepidemiology safety study of fibrate and statin concomitant therapy. *Am J Cardiol* 2010;106:1594-1601.

According to the OSE review, the best available evidence suggests that fenofibrate-statin combination is associated with an increased hazard rate for rhabdomyolysis (HR, 3.26, 95% CI, 1.21-8.80) relative to statin monotherapy. There also appears to be a differential risk associated with the gemfibrozil-statin combination therapy versus the fenofibrate-statin combination therapy, with a

numerically higher rate of rhabdomyolysis observed with gemfibrozil-statin combination therapy (HR, 11.93, 95% CI, 3.96-35.93) compared to statin monotherapy.

Most statin labels contain language in the FPI (Warnings and Precautions and Drug Interactions sections) regarding the increased risk of myopathy, including rhabdomyolysis, when statins and fibrates are co-administered. In order to highlight this increased risk, as well as to note the differential risk between gemfibrozil-statin combination therapy and fenofibrate-statin combination therapy, all sponsors of statin drugs with labels in the PLR format (i.e., all except the lovastatin products) were requested to add the following information to the Highlights page. The following language was also provided in the Drug Interactions section of the PI's, depending on the level of risk determined for each statin product:

-----**DRUG INTERACTIONS**-----

Other Lipid-lowering Medications: Use with other fibrate products or lipid-modifying doses (≥ 1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with <<STATIN>>.

7.X Lipid-Lowering Drugs That Can Cause Myopathy When Given Alone

Gemfibrozil: <<Contraindicated or Avoid>> with <<STATIN>>

Other fibrates: Caution should be used when prescribing with <<STATIN>>

7.X Gemfibrozil

Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are coadministered with gemfibrozil, concomitant administration of <<STATIN>> with gemfibrozil should be avoided.

7.X Other Fibrates

Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of other fibrates, <<STATIN>> should be administered with caution when used concomitantly with other fibrates.

8. Myopathy with concomitant administration with lipid-modifying doses of niacin

In March 2010, DMEP approved a labeling revision for simvastatin based on interim results from an ongoing clinical trial - the Heart Protection Study 2 (HPS2) – Treatment of HDL to Reduce the Incidence of Vascular Events (THRIVE), a cardiovascular outcome trial being conducted in 20,000 patients with vascular disease from the UK, China and Scandinavia to investigate whether combining niacin with a new drug (laropiprant) that minimizes niacin's flushing effect can reduce the risk of serious heart attacks and strokes among people already taking treatment to lower their LDL-cholesterol. The interim HPS2 – THRIVE results showed that the incidence of myopathy was higher in patients of

Chinese descent (0.43%) compared with patients not of Chinese descent (0.03%) taking 40 mg simvastatin plus cholesterol-modifying doses (≥ 1 g/day) of a niacin-containing product. The exact mechanism of this drug interaction is not fully understood.

Drug-drug interaction studies report an increase in simvastatin exposure of 41-64% with co-administration of simvastatin and ER niacin. According to OCP, the cause of the observed changes in exposure of simvastatin due to ER niacin is not well established as this is not due to changes in the known pathways (e.g., via CYP3A4 or OATP1B1). Furthermore, a PK study of simvastatin in Chinese subjects showed no significant differences in Chinese and non-Asian subjects in simvastatin C_{max} and AUC_{0-last} , and simvastatin acid AUC_{0-last} or C_{max} .

The OCP Genomics Group further noted that the SLCO1B1 genotype that has been associated with statin-induced myopathy, is less prevalent in Asian populations than European populations and, therefore, does not seem to explain the higher myopathy risk rates among Chinese subjects in HPS2-THRIVE.

So, it remains unclear if this increased risk of myopathy with statin and niacin co-administration is unique to Chinese subjects, or applies to other Asians and non-Asians as well.

Furthermore, in the AIM-HIGH study, which compared ER-niacin with simvastatin to simvastatin alone in reducing the residual cardiovascular risk in patients with established cardiovascular disease, “there was no incremental clinical benefit from the addition of niacin to statin therapy during a 36-month follow-up period, despite significant improvements in HDL cholesterol and triglyceride levels”.

The lack of clear benefit in conjunction with uncertainty as to the nature of the increased risk of myopathy in patients treated with niacin plus a statin led FDA to believe that this risk needed to be highlighted in statin labeling.

The labeling approved for simvastatin in March 2010 noted that patients of Chinese descent should not receive simvastatin 80 mg with cholesterol-modifying doses of niacin-containing products.

In June 2011, in conjunction with labeling revisions required based on the Agency’s review of the SEARCH trial, this language was modified to note that “caution should be used when treating Chinese patients with simvastatin doses exceeding 20 mg/day coadministered with lipid-modifying doses of niacin-containing products.”

Most statin labels contain information in the FPI (Warnings and Precautions and Drug Interactions sections) noting that “The risk of skeletal muscle effects may be enhanced when <<STATIN>> is used in combination with niacin; a reduction in

<<STATIN>> dosage should be considered in this setting.” All sponsors of statin drugs with labels in the PLR format were requested to modify the HIGHLIGHTS page, with corresponding changes to the FPI if indicated, as follows:

-----**DRUG INTERACTIONS**-----

Other Lipid-lowering Medications: Use with other fibrate products or lipid-modifying doses (≥ 1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with <<STATIN>>.

7.X Niacin

The risk of skeletal muscle effects may be enhanced when <<STATIN>> is used in combination with lipid-modifying doses (≥ 1 g/day) of niacin; a reduction in <<STATIN>> dosage should be considered in this setting.

9. Update to lovastatin drug-drug interactions and dose caps

Subsequent to the June 2011 labeling revisions to the simvastatin-containing products which were largely based on the SEARCH clinical trial data and the increased risk of myopathy associated with the 80 mg dose of simvastatin, a review of drug-drug interactions with lovastatin was conducted. The physicochemical and pharmacokinetic properties of lovastatin are comparable with those of simvastatin. Lovastatin is a sensitive *in vivo* CYP3A4 substrate; therefore, strong CYP3A4 inhibitors are predicted to significantly increase lovastatin exposure. According to OCP:

Itraconazole increased the exposure of lovastatin (up to 20-fold) more than that of simvastatin (up to 13-fold), and it indicates that strong CYP3A4 inhibitor can cause greater lovastatin exposure increase compared to that of simvastatin. Therefore, it seems reasonable to extrapolate the effect of strong CYP3A4 inhibitors on simvastatin to that on lovastatin.

Based on available studies from the literature, as well as extrapolation from simvastatin data, the following changes to the lovastatin label were recommended:

Under **CONTRAINDICATIONS**:

Concomitant administration with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone).

Under **WARNINGS, Myopathy/Rhabdomyolysis, Strong Potent inhibitors of CYP3A4**:

Lovastatin, like several other inhibitors of HMG-CoA reductase, is a substrate of cytochrome P450 3A4 (CYP3A4). ~~When lovastatin is used with a potent inhibitor of~~

CYP3A4, elevated plasma levels of HMG-CoA reductase inhibitory activity can increase the risk of myopathy and rhabdomyolysis, particularly with higher doses of lovastatin. Certain drugs which inhibit this metabolic pathway can raise the plasma levels of lovastatin and may increase the risk of myopathy. These include itraconazole, ketoconazole, and posaconazole, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors, bocepravir, telaprevir, or the antidepressant nefazodone. Combination of these drugs with lovastatin is contraindicated.

~~The use of lovastatin concomitantly with the potent CYP3A4 inhibitors itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily) should be avoided.~~ Concomitant use of other medicines labeled as having a potent strong inhibitory effect on CYP3A4 should be avoided unless the benefits of combined therapy outweigh the increased risk. If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with lovastatin should be suspended during the course of treatment.

Although not studied clinically, voriconazole has been shown to inhibit lovastatin metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentration of lovastatin. It is recommended that dose adjustment of lovastatin be considered during coadministration. Increased lovastatin concentration in plasma has been associated with an increased risk of myopathy/rhabdomyolysis.

Under **WARNINGS, Myopathy/Rhabdomyolysis:**

~~Gemfibrozil, particularly with higher doses of lovastatin: The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with gemfibrozil. The combined use of lovastatin with gemfibrozil should be avoided, unless the benefits are likely to outweigh the increased risks of this drug combination.~~

~~Other lipid-lowering drugs (other fibrates or ≥ 1 g/day of niacin): The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with other fibrates or ≥ 1 g/day of niacin.~~ Caution should be used when prescribing other fibrates or lipid-lowering doses (≥ 1 g/day) of niacin with lovastatin, as these agents can cause myopathy when given alone. **The benefit of further alterations in lipid levels by the combined use of lovastatin with other fibrates or niacin should be carefully weighed against the potential risks of these combinations.**

Cyclosporine: The use of lovastatin with cyclosporine should be avoided.

~~Cyclosporine or d~~Danazol, diltiazem or verapamil with higher doses of lovastatin: The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with ~~cyclosporine or danazol, diltiazem, or verapamil.~~ The benefits of the use of lovastatin in patients receiving cyclosporine or danazol, diltiazem, or verapamil should be carefully weighed against the risks of these combinations.

~~Amiodarone or verapamil: The dose of lovastatin should not exceed 40 mg daily in patients receiving concomitant medication with amiodarone or verapamil.~~ The combined use of lovastatin at doses higher than 40 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy. The risk of myopathy/rhabdomyolysis is

increased when either amiodarone or verapamil is used concomitantly with higher doses of a closely related member of the HMG-CoA reductase inhibitor class.

Under **WARNINGS, Myopathy/Rhabdomyolysis:**

Cyclosporine: The use of lovastatin with cyclosporine should be avoided.

Amiodarone or verapamil: The dose of lovastatin should not exceed 40 mg daily in patients receiving concomitant medication with amiodarone or verapamil. The combined use of lovastatin at doses higher than 40 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy. The risk of myopathy/rhabdomyolysis is increased when either amiodarone or verapamil is used concomitantly with higher doses of a closely related member of the HMG-CoA reductase inhibitor class.

Cyclosporine, or danazol, diltiazem or verapamil with higher doses of lovastatin: The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with cyclosporine, or danazol, diltiazem, or verapamil. The benefits of the use of lovastatin in patient receiving cyclosporine, or danazol, diltiazem, or verapamil should be carefully weighed against the risks of these combinations.

Under **WARNINGS, Myopathy/Rhabdomyolysis**, Table VII: Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis:

Interacting Agents	Prescribing Recommendations
Ketoconazole Itraconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Boceprevir Telaprevir Nefazodone	<u>Avoid</u> <u>Contraindicated</u> with lovastatin
<u>Gemfibrozil</u> <u>Cyclosporine</u>	<u>Avoid with lovastatin</u>
<u>Gemfibrozil</u> <u>Other fibrates</u> <u>Lipid lowering doses (≥1 g/day) of niacin</u> <u>Cyclosporine</u> <u>Danazol</u> <u>Diltiazem</u> <u>Verapamil</u>	Do not exceed 20 mg lovastatin daily
Amiodarone <u>Verapamil</u>	Do not exceed 40 mg lovastatin daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

Under **PRECAUTIONS, Drug Interactions, CYP3A4 Interactions:**

Lovastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. ~~Potent~~ Strong inhibitors of CYP3A4 (e.g., below itraconazole, ketoconazole, posaconazole, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone and erythromycin), and large quantities of grapefruit juice increase the risk of myopathy by reducing the elimination of lovastatin

Itraconazole
Ketoconazole
Erythromycin
Clarithromycin
Telithromycin
HIV protease inhibitors
Nefazodone
Large quantities of grapefruit juice (>1 quart daily)

In vitro studies have demonstrated that voriconazole inhibits the metabolism of lovastatin. Adjustment of the lovastatin dose may be needed to reduce the risk of myopathy, including rhabdomyolysis, if voriconazole must be used concomitantly with lovastatin.

Under **PRECAUTIONS, Other Drug Interactions:**

~~Cyclosporine or Danazol:~~ The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine ~~or danazol~~ particularly with higher doses of lovastatin.

Danazol, Diltiazem, or Verapamil: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of danazol, diltiazem, or verapamil particularly with higher doses of lovastatin.

~~Amiodarone or Verapamil:~~ The risk of myopathy/rhabdomyolysis is increased when either amiodarone ~~or verapamil~~ is used concomitantly with a closely related member of the HMG-CoA reductase inhibitor class.

Under **PRECAUTIONS, Endocrine Function:**

Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ~~ketoconazole~~, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

Under **DOSAGE AND ADMINISTRATION:**

Dosage in Patients taking ~~Cyclosporine, or Danazol, Diltiazem, or Verapamil~~

In patients taking ~~cyclosporine, or danazol, diltiazem, or verapamil~~ concomitantly with lovastatin, therapy should begin with 10 mg of lovastatin and should not exceed 20 mg/day.

Dosage in Patients taking Amiodarone ~~or Verapamil~~

In patients taking amiodarone ~~or verapamil~~ concomitantly with MEVACOR, the dose should not exceed 40 mg/day.

Concomitant Lipid-Lowering Therapy

MEVACOR is effective alone or when used concomitantly with bile-acid sequestrants. If MEVACOR is used in combination with gemfibrozil, other fibrates or lipid lowering doses (≥ 1 g/day) of niacin, the dose of MEVACOR should not exceed 20 mg/day.

Under CLINICAL PHARMACOLOGY:

	Number of Subjects	Dosing of Coadministered Drug or Grapefruit Juice	Dosing of Lovastatin	AUC Ratio* (with / without coadministered drug) No Effect = 1.00	
				Lovastatin	Lovastatin acid [†]
Gemfibrozil	11	600 mg BID for 3 days	40 mg	0.96	2.80
Itraconazole [‡]	12	200 mg QD for 4 days	40 mg on Day 4	> 36 [§]	22
	10	100 mg QD for 4 days	40 mg on Day 4	> 14.8 [§]	15.4
Grapefruit Juice [¶] (high dose)	10	200 mL of double-strength TID [#]	80 mg single dose	15.3	5.0
Grapefruit Juice [¶] (low dose)	16	8 oz (about 250 mL) of single-strength [‡] for 4 days	40 mg single dose	1.94	1.57
Cyclosporine	16	Not described [‡]	10 mg QD for 10 days	5- to 8-fold	ND [‡]
	Number of Subjects	Dosing of Coadministered Drug or Grapefruit Juice	Dosing of Lovastatin	AUC Ratio* (with / without coadministered drug) No Effect = 1.00	
				Total Lovastatin acid [‡]	
Diltiazem	10	120 mg BID for 14 days	20 mg	3.57 [‡]	

* Results based on a chemical assay

[†] Lovastatin acid refers to the β -hydroxyacid of lovastatin

[‡] The mean total AUC of lovastatin without itraconazole phase could not be determined accurately. Results could be representative of strong CYP3A4 inhibitors such as ketoconazole, posaconazole, clarithromycin, telithromycin, HIV protease inhibitors, and nefazodone

[§] Estimated minimum change

[¶] The effect of amounts of grapefruit juice between those used in these two studies on lovastatin pharmacokinetics has not been studied

[#] Double-strength: one can of frozen concentrate diluted with one can of water. Grapefruit juice was administered TID for 2 days, and 200 mL together with single dose lovastatin and 30 and 90 minutes following single dose lovastatin on Day 3

[‡] Single-strength: one can of frozen concentrate diluted with 3 cans of water. Grapefruit juice was administered with breakfast for 3 days, and lovastatin was administered in the evening on Day 3

[‡] Cyclosporine-treated patients with psoriasis or post kidney or heart transplant patients with stable graft function, transplanted at least 9 months prior to study

10. Update to simvastatin and lovastatin drug-drug interaction:

In May 2011, the hepatitis C protease inhibitors boceprevir and telaprevir were approved. These protease inhibitors have been characterized as being strong CYP3A4 inhibitors. Because simvastatin is contraindicated with strong CYP3A4 inhibitors, and because the simvastatin label individually lists strong CYP3A4 inhibitors with which simvastatin is contraindicated, these two recently approved protease inhibitors will be added to the list in all simvastatin-containing products (Zocor, Vytorin, and Simcor).

Because of the physicochemical and pharmacokinetic similarities between simvastatin and lovastatin, and consistent with changes being made to the lovastatin labeling which include a new contraindication with strong CYP3A4 inhibitors, the labeling for lovastatin will be modified to add boceprevir and telaprevir to the list of strong CYP3A4 inhibitors with which lovastatin is contraindicated.

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

/s/

AMY G EGAN
02/27/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
021192Orig1s019

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

Clinical Pharmacology Memorandum

Memo Date:	October 27, 2011
Subject:	Prior Approval Supplement – addition of new DDI information
NDA:	NDA 20-261/S046 Lescol® (fluvastatin sodium) capsules and 21-192/S-019 Lescol® XL (fluvastatin sodium) extended release tablet
Sponsor	Novartis
Indication	Lipid altering therapy: • in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIa and IIb) • in pediatric patients with heterozygous familial hypercholesterolemia
Reviewer	Immo Zdrojewski, Ph.D.
Team Leader (acting)	Jaya Vaidyanathan, Ph.D.

The purpose of this memorandum is to evaluate the drug-drug interaction (DDI) information submitted for coadministration of clopidogrel and Lescol® XL and inclusion of the information into the approved labeling.

Background:

On September, 20, 2011, the Agency requested additional information requesting references included in the supplements (NDA 20-261/S046 & NDA 21-192/S019) for the clopidogrel DDI study. In this submission, the sponsor enclosed the literature reference to support this DDI information: Ayalasomayajula et al. “Effect of Clopidogrel on the Steady-State Pharmacokinetics of Fluvastatin”, J Clin Pharmacol. 2007 May;47(5):613-9.

Study design:

On study day 1 through day 19, healthy subjects received (Lescol XL) 80 mg daily. On day 10, a loading dose of 300 mg Plavix® (clopidogrel bisulfate), was co-administered with Lescol XL. From Day 11 through 19, Lescol XL and 75mg Plavix® were co-administered daily. All study medications were administered by the study center personnel with 240 mL of water after at least a 10-hour fast. Serial PK samples for the analysis of fluvastatin were collected on Day 9 and Day 19. The effect of clopidogrel on fluvastatin PK was evaluated by comparing Day 19 and Day 9 PK. The clopidogrel effect on platelet function in the presence of fluvastatin was also evaluated using adenosine diphosphate (ADP)-induced platelet aggregation method and prolongation of bleeding time.

Pharmacokinetic sampling: For the determination of serum concentrations of fluvastatin, 3-mL predose blood samples were collected into serum separator tubes on

days 7, 8, 17, and 18. Serial blood samples were collected on days 9 and 19 at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 hours postdose.

The literature report stated that there was no sensitive bioanalytical method available to measure plasma clopidogrel concentrations at a steady state therapeutic dose (75 mg).

Concentrations for clopidogrel or metabolites have not been determined in this study.

Therefore, to assess the fluvastatin effect on clopidogrel, ADP-induced platelet aggregation and bleeding time were measured.

Pharmacokinetic results:

Coadministration of fluvastatin and clopidogrel increased fluvastatin C_{max} from 61.5 ng/mL to 71.2 ng/mL. This corresponds to an increase of 27% in C_{max} after coadministration with a 90% confidence interval of the geometric mean ration of 1.08 to 1.50. The area under the curve of the dosing interval (AUC_t) of fluvastatin after coadministration was 2% lower than when fluvastatin was given alone. The 90% confidence interval of the geometric mean ranged from 0.85 to 1.13. (Table 1). The literature reports that the assay was validated within a concentration range of 2 to 2000 ng/mL. The accuracy and precision (percentage coefficient of variation [%CV]) for calibration, intra-day, and inter-day samples ranged from 96.0% to 112.0% and 1.1% to 17.2%, respectively.

Table 1 Effects of Clopidogrel on Steady-State Pharmacokinetic Parameters of Fluvastatin

	Fluvastatin Alone	Fluvastatin + Clopidogrel	Geometric Mean Ratios	90% Confidence Interval (P Value)
C_{max} , ng/mL	61.5 (47.5)	71.2 (31.6)	1.27	1.08-1.50 (.018)
AUC_t , ng·h/mL	233.2 (52.0)	222.6 (46.3)	0.98	0.85-1.13 (.824)
C_{trough} , ng/mL	1.9 (180.3)	1.1 (170)		
t_{max} , h ^a	2.00 (0.50-8.00)	2.50 (1.00-4.00)		
$t_{1/2}$, h	5.9 (96.3)	4.6 (91.1)		

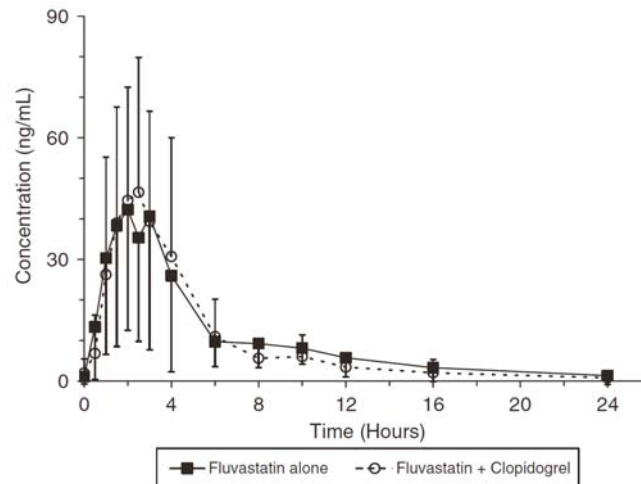
Data are expressed as mean (percentage coefficient of variation [%CV]), n = 24.

a. Data are median (minimum, maximum).

Best Available Copy

The steady state plasma concentration-time profiles of fluvastatin when administered alone or in combination with clopidogrel are shown in Figure 1.

Figure 1 *Steady-state concentration-time profile following multiple-dose administrations of 80 mg fluvastatin (extended-release formulation) with and without clopidogrel. Fluvastatin alone (solid square) and fluvastatin + clopidogrel (open circle). Data are mean (SD), n = 24.*



Reviewer comment: The pharmacokinetic results seem acceptable.

Pharmacodynamic results:

The pharmacodynamic activity of clopidogrel in the presence of fluvastatin was measured as the change from baseline (fluvastatin dosing only, day 9 measurement) in ADP-induced platelet aggregation (Table 2) and as prolongation of bleeding time (Table 3). Results from the literature are that administration of the loading dose of clopidogrel (day 10) decreased platelet aggregation by 33.1% (range, 28%-38%) compared to baseline ($P < .001$). Maintenance doses of clopidogrel resulted in inhibition of platelet aggregation by 46.3% to 49.2% (days 12, 14, 16, and 19) compared to baseline ($P < .001$).

Table 2 Effect of Clopidogrel on ADP-Induced Platelet Aggregation in the Presence of Fluvastatin

Day of Treatment	Day 9 (Fluvastatin Alone)	Clopidogrel + Fluvastatin Treatment					End of Study, Day 24
		Day 10	Day 12	Day 14	Day 16	Day 19	
Mean, %	76.9	43.6	30.0	29.5	27.5	30.3	62.9
(SD)	(11.5)	(19.4)	(14.9)	(15.8)	(13.9)	(15.1)	(14.8)
P value ^a		<.001	<.001	<.001	<.001	<.001	<.001

Platelet aggregation (%) was measured in response to 5 μ M adenosine diphosphate (ADP). Mean values are compared to fluvastatin alone (day 9), n = 24.
a. Based on a linear mixed model for repeated measurements with day/visit as fixed factor and compound symmetry covariance structure.

Table 3 Effect of Clopidogrel on Prolongation of Bleeding Time in the Presence of Fluvastatin

Day of Treatment	Day 9 (Fluvastatin Alone)	Clopidogrel + Fluvastatin Treatment					End of Study, Day 24
		Day 10	Day 12	Day 14	Day 16	Day 19	
Geometric mean, min	5.9	6.2	6.7	6.7	7.4	8.0	5.5
Geometric mean ratios (90% CI) ^a		1.05 (0.88-1.25)	1.13 (0.94-1.35)	1.14 (0.95-1.36)	1.24 (1.04-1.49)	1.35 (1.13-1.61)	0.93 (0.78-1.11)
P value ^a		.663	.266	.234	.043	.006	.498

Data are geometric means and geometric mean ratios (90% confidence interval [CI]) compared to fluvastatin alone (day 9), n = 24.
a. Based on a linear mixed model for repeated measurements with day/visit as fixed factor and compound symmetry covariance structure.

Label information clopidogrel (Plavix):

Dose-dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of Plavix. Repeated doses of 75 mg Plavix per day inhibit ADP-induced platelet aggregation on the first day, and inhibition reaches steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg Plavix per day was between 40% and 60%. Platelet aggregation and bleeding time gradually return to baseline values after treatment is discontinued, generally in about 5 days

Reviewer comment: This study did not include a clopidogrel only arm. Thus comparison of pharmacodynamic effect with and without coadministration of fluvastatin is not possible. Although the decrease in platelet aggregation time seems to be similar to platelet aggregation times reported in the label, no definitive conclusion of the influence of fluvastatin can be made without a clopidogrel only arm.

2. Preliminary Labeling Recommendations

Labeling statements to be removed are shown in ~~red strikethrough~~ and suggested labeling to be included is shown in underline blue font.

Drug-Drug Interactions:

Data from drug-drug interactions studies involving coadministration of gemfibrozil, niacin, itraconazole, erythromycin, tolbutamide or clopidogrel indicate that the PK disposition of fluvastatin is not significantly altered when fluvastatin is coadministered with either of these drugs. (b) (4)

The below listed drug interaction information is derived from studies using LESCOL. Similar studies have not been conducted using the LESCOL XL tablet (except clopidogrel).

Table 3 Effect of Co-administered Drugs on Fluvastatin Systemic Exposure

Co-administered drug and dosing regimen	Fluvastatin		
	Dose (mg)*	Change in AUC ^{**}	Change in C _{max} ^{**}
Cyclosporine – stable dose	20 mg QD for 14	↑ 90%	↑ 30%

(b.i.d.) [†]	weeks		
Fluconazole 400 mg QD day 1, 200 mg b.i.d. day 2- 4 [†]	40 mg QD	↑ 84%	↑ 44%
Cholestyramine 8 g QD	20 mg QD administered 4 hrs after a meal plus cholestyramine	↓ 51%	↓ 83%
Rifampicin 600 mg QD for 6 days	20 mg QD	↓ 53%	↓ 42%
Cimetidine 400 mg b.i.d. for 5 days, QD on Day 6	20 mg QD	↑ 30%	↑ 40%
Rantidine 150 mg b.i.d. for 5 days, QD on Day 6	20 mg QD	↑ 10%	↑ 50%
Omeprazole 40 mg QD for 6 days	20 mg QD	↑ 20%	↑ 37%
Phenytoin 300 mg QD	40 mg b.i.d. for 5 days	↑ 40 %	↑ 27%
Propranolol 40 mg b.i.d. for 3.5 days	40 mg QD	↓ 5%	No change
Digoxin 0.1 – 0.5 mg QD for 3 weeks	40 mg QD	No change	↑ 11%
Diclofenac 25 mg QD	40 mg QD for 8 days	↑ 50 %	↑ 80%
Warfarin 30 mg QD	40 mg QD for 8 days	↑ 30%	↑ 67%
Clopidogrel 300 mg loading dose QD for 9 days on day 10. 75 mg QD on days 11-19	80 mg XL QD for 19 days	↓ 2%	↑ 27%

*Single dose unless otherwise noted

**Mean ratio (with/without coadministered drug and no change = 1-fold) or % change (with/without coadministered drug and no change = 0%); symbols of ↑ and ↓ indicate the exposure increase and decrease, respectively.

† Considered clinically significant [see *Dosage And Administration (2)* and *Drug Interactions (7)*]

Data from drug-drug interaction studies involving fluvastatin and coadministration of either gemfibrozil, tolbutamide or losartan indicate that the PK disposition of either gemfibrozil, tolbutamide or losartan is not significantly altered when coadministered with fluvastatin.

Table 4 Effect of Fluvastatin Co-Administration on Systemic Exposure of Other Drugs

Fluvastatin dosage regimen	Co-administered drug		
	Name and Dose (mg)*	Change in AUC**	Change in Cmax**
40 mg QD for 5 days	Phenytoin 300 mg QD [†]	↑ 20%	↑ 5%
40 mg b.i.d. for 21 days	Glibenclamide 5 – 20 mg QD for 22 days [†]	↑ 70%	↑ 50%
40 mg QD for 8 days	Diclofenac 25 mg QD	↑ 25%	↑ 60%

40 mg QD for 8 days	Warfarin 30 mg QD	S-warfarin: ↑7% R-warfarin: no change	S-warfarin: ↑ 10% R-warfarin: ↑ 6%
---------------------	-------------------	---	--

*Single dose unless otherwise noted

**Mean ratio (with/without coadministered drug and no change = 1-fold) or % change (with/without coadministered drug and no change = 0%); symbols of ↑ and ↓ indicate the exposure increase and decrease, respectively.

† Considered clinically significant [see *Dosage And Administration* (2) and *Drug Interactions* (7)]

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

/s/

IMMO ZADEZENSKY

10/28/2011

JAYABHARATHI VAIDYANATHAN

10/28/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
021192Orig1s019

OTHER REVIEW(S)

Division of Metabolic & Endocrine Drug Products

Labeling Review

Application Number: NDA 20-261/S-046

NDA 21-192/S-019

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: September 1, 2011; Final PI/PPI February 27, 2012 (email)

Background and Summary:

Lescol is indicated in:

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

The last approved labeling for Lescol/Lescol XL was supplement NDA 20-261/S-042 (Lescol Capsules) and NDA 21-192/S-016 (Lescol XL Extended-Release Tablets). This supplement was approved on June 17, 2011, and provided for changes in the format of the Lescol/Lescol XL package insert in response to the Physician's Labeling Rule (PLR).

This prior approval labeling supplement, NDA 20-261/S-046/ NDA 21-192/S-019, provides for revisions to the **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS** sections of the Highlights of Prescribing Information section and changes to the **WARNINGS AND PRECAUTIONS**, **ADVERSE REACTIONS**, **DRUG INTERACTIONS**, **CLINICAL PHARMACOLOGY**, and **PATIENT COUNSELING INFORMATION** sections of the Full Prescribing Information sections of the Lescol/Lescol XL package insert, and corresponding revisions to the Lescol/Lescol XL patient package insert.

Review:

A track change version including all labeling changes since the last approved label and a final, clean version of the PI and PPI have been attached to the approval letter.

Conclusion:

The Agency will issue an approval action.

Reviewed by: M.A. Simoneau, R.Ph., Regulatory Project Manager

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

/s/

MARGARET A SIMONEAU
02/28/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021192Orig1s019

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



NDA 20261/S-046
NDA 21192/S-019

**ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT**

Novartis Pharmaceuticals Corporation
Attention: Raffy H. Chilingirian, DMH
Global Drug Regulatory Affairs
One Health Plaza
East Hanover, New Jersey
07636-1080

Dear Dr. Chilingirian:

We have received your September 1, 2011, Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER:	NDA's 20261 and 21192
SUPPLEMENT NUMBER:	S-046 for NDA 20261 and S-019 for NDA 21192
PRODUCT NAME:	Lescol (fluvastatin sodium) Capsules (NDA 20-261) and Lescol XL (fluvastatin sodium) Extended-Release Tablets (NDA 21-192)
DATE OF SUBMISSION:	September 1, 2011
DATE OF RECEIPT:	September 2, 2011

This supplemental application proposes changes to the Lescol and Lescol XL package insert in response to our August 11, 2011, prior approval supplement request letter.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 1, 2011, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be March 2, 2012.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, please call me at (301) 796-1295.

Sincerely,

{See appended electronic signature page}

Margaret Simoneau, M.S., RPh.
Regulatory Project Manager
Division of Metabolism and Endocrinology 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 A SIMONEAU
09/20/2011