CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

019898Orig1s062

Trade Name: Pravachol

Generic Name: Pravastatin Sodium

Sponsor: Bristol-Myers Squibb Co.

Approval Date: 02/28/2012

Indications:

PRAVACHOL is an HMG-CoA reductase inhibitor (statin) indicated as and adjunctive therapy to diet to: Reduce the risk of MI, revascularization, and cardiovascular mortality in hypercholesterolemic patients without clinically evident CHD; Reduce the risk of total mortality by reducing coronary death, MI, revascularization, stroke/TIA, and the progression of coronary atherosclerosis in patients with clinically evident CHD; Reduce elevated Total-C, LDL-C, ApoB, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia; Reduce elevated serum TG levels in patients with hypertriglyceridemia; Treat patients with primary dysbetalipoproteinemia who are not responding to diet; Treat children and adolescent patients ages 8 years and older with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 19898/S-062

SUPPLEMENT APPROVAL

Bristol-Myers Squibb Company
Attention: Ana Ma. Cibrian
Director, GRS Mature Products
P.O. Box 4000
Princeton, N.J. 08543

Dear Ms. Cibrian:

Please refer to your Supplemental New Drug Application (sNDA) dated September 27, 2011, received September 27, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Pravachol (pravastatin sodium) Tablets 10 mg, 20 mg, 40 mg, and 80 mg.

We acknowledge receipt of your amendments dated January 6, and February 8, 2012.

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 **DOSAGE AND ADMINISTRATION**, **WARNINGS AND PRECAUTIONS**, **ADVERSE REACTIONS**, **DRUG INTERACTIONS**, **CLINICAL PHARMACOLOGY,** and **PATIENT COUNSELING INFORMATION** sections of the Full Prescribing Information sections of the Pravachol (pravastatin) 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 Effected" (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:

019898Orig1s062

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PRAVACHOL safely and effectively. See full prescribing information for PRAVACHOL.

PRAVACHOL® (pravastatin sodium) Tablets
Initial U.S. Approval: 1991

----------INDICATIONS AND USAGE----------

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

- Reduce the risk of MI, revascularization, and cardiovascular mortality in hypercholesterolemic patients without clinically evident CHD. (1.1)
- Reduce the risk of total mortality by reducing coronary death, MI, revascularization, stroke/TIA, and the progression of coronary atherosclerosis in patients with clinically evident CHD. (1.1)
- Reduce elevated Total-C, LDL-C, ApoB, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia. (1.2)
- Reduce elevated serum TG levels in patients with hypertriglyceridemia. (1.2)
- Treat patients with primary dysbetalipoproteinemia who are not responding to diet. (1.2)
- Treat children and adolescent patients ages 8 years and older with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy. (1.2)

Limitations of use:

- PRAVACHOL has not been studied in *Fredrickson* Types I and V dyslipidemias. (1.3)

----------DOSAGE AND ADMINISTRATION----------

- Adults: the recommended starting dose is 40 mg once daily. Use 80 mg dose only for patients not reaching LDL-C goal with 40 mg. (2.2)
- Significant renal impairment: the recommended starting dose is 10 mg once daily. (2.2)
- Children (ages 8 to 13 years, inclusive): the recommended starting dose is 20 mg once daily. (2.3)
- Adolescents (ages 14 to 18 years): the recommended starting dose is 40 mg once daily. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 10 mg, 20 mg, 40 mg, 80 mg. (3)

----------CONTRAINDICATIONS----------

- Hypersensitivity to any component of this medication. (4.1, 6.2, 11)
- Active liver disease or unexplained, persistent elevations of serum transaminases. (4.2, 5.2)
- Women who are pregnant or may become pregnant. (4.3, 8.1)
- Nursing mothers. (4.4, 8.3)

----------WARNINGS AND PRECAUTIONS----------

- Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): predisposing factors include advanced age (>65), uncontrolled hypothyroidism, and renal impairment. Patients should be advised to report promptly any symptoms of myopathy. Pravastatin therapy should be discontinued if myopathy is diagnosed or suspected. (5.1, 8.5)
- 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----------

In short-term clinical trials, the most commonly reported adverse reactions (≥2% and > placebo) regardless of causality were: musculoskeletal pain, nausea/vomiting, upper respiratory infection, diarrhea, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- 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 PRAVACHOL. (7)
- Cyclosporine: combination increases exposure. Limit pravastatin to 20 mg once daily. (2.5, 7.1)
- Clarithromycin: combination increases exposure. Limit pravastatin to 40 mg once daily. (2.6, 7.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: TBD

FULL PRESCRIBING INFORMATION: CONTENTS*

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

Reference ID: 3090896

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 nonpharmacologic measures alone has been inadequate.

1.1 Prevention of Cardiovascular Disease

In hypercholesterolemic patients without clinically evident coronary heart disease (CHD), PRAVACHOL (pravastatin sodium) is indicated to:

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

In patients with clinically evident CHD, PRAVACHOL is indicated to:

- reduce the risk of total mortality by reducing coronary death.
- reduce the risk of MI.
- reduce the risk of undergoing myocardial revascularization procedures.
- reduce the risk of stroke and stroke/transient ischemic attack (TIA).
- slow the progression of coronary atherosclerosis.

1.2 Hyperlipidemia

PRAVACHOL is indicated:

- as an adjunct to diet to reduce elevated total cholesterol (Total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (ApoB), and triglyceride (TG) levels and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hypercholesterolemia and mixed dyslipidemia (*Fredrickson* Types IIa and IIb).[1]
- as an adjunct to diet for the treatment of patients with elevated serum TG levels (*Fredrickson* Type IV).
- for the treatment of patients with primary dysbetalipoproteinemia (*Fredrickson* Type III) who do not respond adequately to diet.

- as an adjunct to diet and lifestyle modification for treatment of heterozygous familial hypercholesterolemia (HeFH) in children and adolescent patients ages 8 years and older if after an adequate trial of diet the following findings are present:

  a. LDL-C remains ≥190 mg/dL or

  b. LDL-C remains ≥160 mg/dL and:

     - there is a positive family history of premature cardiovascular disease (CVD) or
     - two or more other CVD risk factors are present in the patient.

1.3 Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

The patient should be placed on a standard cholesterol-lowering diet before receiving PRAVACHOL and should continue on this diet during treatment with PRAVACHOL [see NCEP Treatment Guidelines for details on dietary therapy].

2.2 Adult Patients

The recommended starting dose is 40 mg once daily. If a daily dose of 40 mg does not achieve desired cholesterol levels, 80 mg once daily is recommended. In patients with significant renal impairment, a starting dose of 10 mg daily is recommended. PRAVACHOL can be administered orally as a single dose at any time of the day, with or without food. 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.

2.3 Pediatric Patients

Children (Ages 8 to 13 Years, Inclusive)

The recommended dose is 20 mg once daily in children 8 to 13 years of age. Doses greater than 20 mg have not been studied in this patient population.

Adolescents (Ages 14 to 18 Years)

The recommended starting dose is 40 mg once daily in adolescents 14 to 18 years of age. Doses greater than 40 mg have not been studied in this patient population.

Children and adolescents treated with pravastatin should be reevaluated in adulthood and appropriate changes made to their cholesterol-lowering regimen to achieve adult goals for LDL-C [see *Indications and Usage (1.2)*].

2.4 Concomitant Lipid-Altering Therapy

PRAVACHOL may be used with bile acid resins. When administering a bile-acid-binding resin (e.g., cholestyramine, colestipol) and pravastatin, PRAVACHOL should be given either 1 hour or more before or at least 4 hours following the resin. [See *Clinical Pharmacology (12.3)*.]

2.5 Dosage in Patients Taking Cyclosporine

In patients taking immunosuppressive drugs such as cyclosporine concomitantly with pravastatin, therapy should begin with 10 mg of pravastatin sodium once-a-day at bedtime and titration to higher doses should be done with caution. Most patients treated with this combination received a maximum pravastatin sodium dose of 20 mg/day. In patients taking cyclosporine, therapy should be limited to 20 mg of pravastatin sodium once daily [see *Warnings and Precautions (5.1)* and *Drug Interactions (7.1)*].

2.6 Dosage in Patients Taking Clarithromycin

In patients taking clarithromycin, therapy should be limited to 40 mg of pravastatin sodium once daily [see *Drug Interactions (7.2)*].

3 DOSAGE FORMS AND STRENGTHS

PRAVACHOL® Tablets are supplied as:

10 mg tablets: Pink to peach, rounded, rectangular-shaped, biconvex with a “P” embossed on one side and “PRAVACHOL 10” engraved on the opposite side.

20 mg tablets: Yellow, rounded, rectangular-shaped, biconvex with a “P” embossed on one side and “PRAVACHOL 20” engraved on the opposite side.

40 mg tablets: Green, rounded, rectangular-shaped, biconvex with a “P” embossed on one side and “PRAVACHOL 40” engraved on the opposite side.

80 mg tablets: Yellow, oval-shaped tablet with “BMS” on one side and “80” on the other side.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Hypersensitivity to any component of this medication.

4.2 Liver

Active liver disease or unexplained, persistent elevations of serum transaminases [see *Warnings and Precautions (5.2)*].

4.3 Pregnancy

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since statins decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they are contraindicated during pregnancy and in nursing mothers. PRAVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this class of drug, therapy should be discontinued immediately and the patient apprised of the potential hazard to the fetus [see *Use in Specific Populations (8.1)*].

4.4 Nursing Mothers

A small amount of pravastatin is excreted in human breast milk. Because statins have the potential for serious adverse reactions in nursing infants, women who require PRAVACHOL treatment should not breast-feed their infants [see *Use in Specific Populations (8.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with pravastatin and other drugs in this class. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

Uncomplicated myalgia has also been reported in pravastatin-treated patients [see *Adverse Reactions (6)*]. Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal (ULN), was rare (<0.1%) in pravastatin clinical trials. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Predisposing factors include advanced age (>65), uncontrolled hypothyroidism, and renal impairment. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with statins is increased with concurrent therapy with either erythromycin, cyclosporine, niacin, or fibrates. However, neither myopathy nor significant increases in CPK levels have been observed in 3 reports involving a total of 100 post-transplant patients (24 renal and 76 cardiac) treated for up to 2 years concurrently with pravastatin 10 to 40 mg and cyclosporine. Some of these patients also received other concomitant immunosuppressive therapies. Further, in clinical trials involving small numbers of patients who were treated concurrently with pravastatin and niacin, there were no reports of myopathy. Also, myopathy was not reported in a trial of combination pravastatin (40 mg/day) and gemfibrozil (1200 mg/day), although 4 of 75 patients on the combination showed marked CPK elevations versus 1 of 73 patients receiving placebo. There was a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. **The use of fibrates alone may occasionally be associated with myopathy. The**

benefit of further alterations in lipid levels by the combined use of PRAVACHOL with fibrates should be carefully weighed against the potential risks of this combination.

Cases of myopathy, including rhabdomyolysis, have been reported with pravastatin coadministered with colchicine, and caution should be exercised when prescribing pravastatin with colchicine [see *Drug Interactions (7.3)*].

5.2 Liver

Statins, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. In 3 long-term (4.8-5.9 years), placebo-controlled clinical trials (WOS, LIPID, CARE), 19,592 subjects (19,768 randomized) were exposed to pravastatin or placebo [see *Clinical Studies (14)*]. In an analysis of serum transaminase values (ALT, AST), incidences of marked abnormalities were compared between the pravastatin and placebo treatment groups; a marked abnormality was defined as a post-treatment test value greater than 3 times the upper limit of normal for subjects with pretreatment values less than or equal to the upper limit of normal, or 4 times the pretreatment value for subjects with pretreatment values greater than the upper limit of normal but less than 1.5 times the upper limit of normal. Marked abnormalities of ALT or AST occurred with similar low frequency (≤1.2%) in both treatment groups. Overall, clinical trial experience showed that liver function test abnormalities observed during pravastatin therapy were usually asymptomatic, not associated with cholestasis, and did not appear to be related to treatment duration. In a 320-patient placebo-controlled clinical trial, subjects with chronic (>6 months) stable liver disease, due primarily to hepatitis C or non-alcoholic fatty liver disease, were treated with 80 mg pravastatin or placebo for up to 9 months. The primary safety endpoint was the proportion of subjects with at least one ALT ≥2 times the upper limit of normal for those with normal ALT (≤ the upper limit of normal) at baseline or a doubling of the baseline ALT for those with elevated ALT (> the upper limit of normal) at baseline. By Week 36, 12 out of 160 (7.5%) subjects treated with pravastatin met the prespecified safety ALT endpoint compared to 20 out of 160 (12.5%) subjects receiving placebo. Conclusions regarding liver safety are limited since the study was not large enough to establish similarity between groups (with 95% confidence) in the rates of ALT elevation.

It is recommended that liver function tests be performed prior to the initiation of therapy and when clinically indicated.

Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of pravastatin [see *Contraindications (4.2)*]. Caution should be exercised when

pravastatin is administered to patients who have a recent (<6 months) history of liver disease, have signs that may suggest liver disease (e.g., unexplained aminotransferase elevations, jaundice), or are heavy users of alcohol.

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

5.3 Endocrine Function

Statins interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p<0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of statins on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if a statin or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

In a placebo-controlled study of 214 pediatric patients with HeFH, of which 106 were treated with pravastatin (20 mg in the children aged 8-13 years and 40 mg in the adolescents aged 14-18 years) for 2 years, there were no detectable differences seen in any of the endocrine parameters (ACTH, cortisol, DHEAS, FSH, LH, TSH, estradiol [girls] or testosterone [boys]) relative to placebo. There were no detectable differences seen in height and weight changes, testicular volume changes, or Tanner score relative to placebo.

6 ADVERSE REACTIONS

Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. In 4-month-long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of

placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant.

6.1 Adverse Clinical Events

Short-Term Controlled Trials

In the PRAVACHOL placebo-controlled clinical trials database of 1313 patients (age range 20-76 years, 32.4% women, 93.5% Caucasians, 5% Blacks, 0.9% Hispanics, 0.4% Asians, 0.2% Others) with a median treatment duration of 14 weeks, 3.3% of patients on PRAVACHOL and 1.2% patients on placebo discontinued due to adverse events regardless of causality. The most common adverse reactions that led to treatment discontinuation and occurred at an incidence greater than placebo were: liver function test increased, nausea, anxiety/depression, and dizziness.

All adverse clinical events (regardless of causality) reported in ≥2% of pravastatin-treated patients in placebo-controlled trials of up to 8 months duration are identified in Table 1:

Table 1: Adverse Events in ≥2% of Patients Treated with Pravastatin 5 to 40 mg and at an Incidence Greater Than Placebo in Short-Term Placebo-Controlled Trials (% of patients)

Body System/Event	5 mg N=100	10 mg N=153	20 mg N=478	40 mg N=171	Any Dose N=902	Placebo N=411
Cardiovascular						
Angina Pectoris	5.0	4.6	4.8	3.5	4.5	3.4
Dermatologic						
Rash	3.0	2.6	6.7	1.2	4.5	1.4
Gastrointestinal						
Nausea/Vomiting	4.0	5.9	10.5	2.3	7.4	7.1
Diarrhea	8.0	8.5	6.5	4.7	6.7	5.6
Flatulence	2.0	3.3	4.6	0.0	3.2	4.4
Dyspepsia/Heartburn	0.0	3.3	3.6	0.6	2.5	2.7
Abdominal Distension	2.0	3.3	2.1	0.6	2.0	2.4
General						
Fatigue	4.0	1.3	5.2	0.0	3.4	3.9
Chest Pain	4.0	1.3	3.3	1.2	2.7	1.9
Influenza	4.0	2.6	1.9	0.6	2.0	0.7
Musculoskeletal						
Musculoskeletal Pain	13.0	3.9	13.2	5.3	10.1	10.2
Myalgia	1.0	2.6	2.9	1.2	2.3	1.2

Table 1: Adverse Events in ≥2% of Patients Treated with Pravastatin 5 to 40 mg and at an Incidence Greater Than Placebo in Short-Term Placebo-Controlled Trials (% of patients)

Body System/Event	5 mg N=100	10 mg N=153	20 mg N=478	40 mg N=171	Any Dose N=902	Placebo N=411
Nervous System						
Headache	5.0	6.5	7.5	3.5	6.3	4.6
Dizziness	4.0	1.3	5.2	0.6	3.5	3.4
Respiratory						
Pharyngitis	2.0	4.6	1.5	1.2	2.0	2.7
Upper Respiratory Infection	6.0	9.8	5.2	4.1	5.9	5.8
Rhinitis	7.0	5.2	3.8	1.2	3.9	4.9
Cough	4.0	1.3	3.1	1.2	2.5	1.7
Investigation						
ALT Increased	2.0	2.0	4.0	1.2	2.9	1.2
g-GT Increased	3.0	2.6	2.1	0.6	2.0	1.2
CPK Increased	5.0	1.3	5.2	2.9	4.1	3.6

The safety and tolerability of PRAVACHOL at a dose of 80 mg in 2 controlled trials with a mean exposure of 8.6 months was similar to that of PRAVACHOL at lower doses except that 4 out of 464 patients taking 80 mg of pravastatin had a single elevation of CK >10 times ULN compared to 0 out of 115 patients taking 40 mg of pravastatin.

Long-Term Controlled Morbidity and Mortality Trials

In the PRAVACHOL placebo-controlled clinical trials database of 21,483 patients (age range 24-75 years, 10.3% women, 52.3% Caucasians, 0.8% Blacks, 0.5% Hispanics, 0.1% Asians, 0.1% Others, 46.1% Not Recorded) with a median treatment duration of 261 weeks, 8.1% of patients on PRAVACHOL and 9.3% patients on placebo discontinued due to adverse events regardless of causality.

Adverse event data were pooled from 7 double-blind, placebo-controlled trials (West of Scotland Coronary Prevention Study [WOS]; Cholesterol and Recurrent Events study [CARE]; Long-term Intervention with Pravastatin in Ischemic Disease study [LIPID]; Pravastatin Limitation of Atherosclerosis in the Coronary Arteries study [PLAC I]; Pravastatin, Lipids and Atherosclerosis in the Carotids study [PLAC II]; Regression Growth Evaluation Statin Study [REGRESS]; and Kuopio Atherosclerosis Prevention Study [KAPS]) involving a total of 10,764 patients treated with pravastatin 40 mg and 10,719 patients treated with placebo. The safety and tolerability profile in the pravastatin group was comparable to that of the placebo group. Patients were

exposed to pravastatin for a mean of 4.0 to 5.1 years in WOS, CARE, and LIPID and 1.9 to 2.9 years in PLAC I, PLAC II, KAPS, and REGRESS. In these long-term trials, the most common reasons for discontinuation were mild, non-specific gastrointestinal complaints. Collectively, these 7 trials represent 47,613 patient-years of exposure to pravastatin. All clinical adverse events (regardless of causality) occurring in ≥2% of patients treated with pravastatin in these studies are identified in Table 2.

Table 2: Adverse Events in ≥2% of Patients Treated with Pravastatin 40 mg and at an Incidence Greater Than Placebo in Long-Term Placebo-Controlled Trials

Body System/Event	**Pravastatin (N=10,764) % of patients**	**Placebo (N=10,719) % of patients**
Dermatologic		
Rash (including dermatitis)	7.2	7.1
General		
Edema	3.0	2.7
Fatigue	8.4	7.8
Chest Pain	10.0	9.8
Fever	2.1	1.9
Weight Gain	3.8	3.3
Weight Loss	3.3	2.8
Musculoskeletal		
Musculoskeletal Pain	24.9	24.4
Muscle Cramp	5.1	4.6
Musculoskeletal Traumatism	10.2	9.6
Nervous System		
Dizziness	7.3	6.6
Sleep Disturbance	3.0	2.4
Anxiety/Nervousness	4.8	4.7
Paresthesia	3.2	3.0
Renal/Genitourinary		
Urinary Tract Infection	2.7	2.6
Respiratory		
Upper Respiratory Tract Infection	21.2	20.2
Cough	8.2	7.4
Influenza	9.2	9.0
Pulmonary Infection	3.8	3.5
Sinus Abnormality	7.0	6.7
Tracheobronchitis	3.4	3.1
Special Senses		
Vision Disturbance (includes blurred vision, diplopia)	3.4	3.3
Infections		

Table 2: Adverse Events in ≥2% of Patients Treated with Pravastatin 40 mg and at an Incidence Greater Than Placebo in Long-Term Placebo-Controlled Trials

Body System/Event	Pravastatin (N=10,764) % of patients	Placebo (N=10,719) % of patients
Viral Infection	3.2	2.9

In addition to the events listed above in the long-term trials table, events of probable, possible, or uncertain relationship to study drug that occurred in <2.0% of pravastatin-treated patients in the long-term trials included the following:

Dermatologic: scalp hair abnormality (including alopecia), urticaria.

Endocrine/Metabolic: sexual dysfunction, libido change.

General: flushing.

Immunologic: allergy, edema head/neck.

Musculoskeletal: muscle weakness.

Nervous System: vertigo, insomnia, memory impairment, neuropathy (including peripheral neuropathy).

Special Senses: taste disturbance.

6.2 Postmarketing Experience

In addition to the events reported above, as with other drugs in this class, the following events have been reported rarely during postmarketing experience with PRAVACHOL, regardless of causality assessment:

Musculoskeletal: myopathy, rhabdomyolysis.

Nervous System: dysfunction of certain cranial nerves (including alteration of taste, impairment of extraocular movement, facial paresis), 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).

Hypersensitivity: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, asthenia, photosensitivity, chills, malaise, toxic epidermal necrolysis, erythema multiforme (including Stevens-Johnson syndrome).

Gastrointestinal: abdominal pain, constipation, pancreatitis, hepatitis (including chronic active hepatitis), cholestatic jaundice, fatty change in liver, cirrhosis, fulminant hepatic necrosis, hepatoma, fatal and non-fatal hepatic failure.

Dermatologic: a variety of skin changes (e.g., nodules, discoloration, dryness of mucous membranes, changes to hair/nails).

Renal: urinary abnormality (including dysuria, frequency, nocturia).

Respiratory: dyspnea.

Reproductive: gynecomastia.

Laboratory Abnormalities: liver function test abnormalities, thyroid function abnormalities.

6.3 Laboratory Test Abnormalities

Increases in ALT, AST values and CPK have been observed [see *Warnings and Precautions (5.1, 5.2)*].

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with statins.

6.4 Pediatric Patients

In a 2-year, double-blind, placebo-controlled study involving 100 boys and 114 girls with HeFH (n=214; age range 8-18.5 years, 53% female, 95% Caucasians, <1% Blacks, 3% Asians, 1% Other), the safety and tolerability profile of pravastatin was generally similar to that of placebo.

[See *Warnings and Precautions (5.3)*, *Use in Specific Populations (8.4)*, and *Clinical Pharmacology (12.3)*.]

7 DRUG INTERACTIONS

For the concurrent therapy of either cyclosporine, fibrates, niacin (nicotinic acid), or erythromycin, the risk of myopathy increases [see *Warnings and Precautions (5.1)* and *Clinical Pharmacology (12.3)*].

7.1 Cyclosporine

The risk of myopathy/rhabdomyolysis is increased with concomitant administration of cyclosporine. Limit pravastatin to 20 mg once daily for concomitant use with cyclosporine [see *Dosage and Administration (2.5)*, *Warnings and Precautions (5.1)*, and *Clinical Pharmacology (12.3)*].

7.2 Clarithromycin

The risk of myopathy/rhabdomyolysis is increased with concomitant administration of clarithromycin. Limit pravastatin to 40 mg once daily for concomitant use with clarithromycin [see *Dosage and Administration (2.6)*, *Warnings and Precautions (5.1)*, and *Clinical Pharmacology (12.3)*].

7.3 Colchicine

The risk of myopathy/rhabdomyolysis is increased with concomitant administration of colchicine [see *Warnings and Precautions (5.1)*].

7.4 Gemfibrozil

Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are coadministered with gemfibrozil, concomitant administration of PRAVACHOL with gemfibrozil should be avoided [see *Warnings and Precautions (5.1)*].

7.5 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, PRAVACHOL should be administered with caution when used concomitantly with other fibrates [see *Warnings and Precautions (5.1)*].

7.6 Niacin

The risk of skeletal muscle effects may be enhanced when pravastatin is used in combination with niacin; a reduction in PRAVACHOL dosage should be considered in this setting [see *Warnings and Precautions (5.1)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

[See *Contraindications (4.3)*.]

Safety in pregnant women has not been established. Available data in women inadvertently taking pravastatin while pregnant do not suggest any adverse clinical events. However, there are no adequate and well-controlled studies in pregnant women. Therefore, it is not known whether pravastatin can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Pravastatin should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus and patients have been informed of the potential hazards.

Rare reports of congenital anomalies have been received following intrauterine exposure to other statins. In a review[2] of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or lovastatin, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate to exclude a ≥3- to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. As safety in pregnant women has not been established and there is no apparent benefit to therapy with PRAVACHOL during pregnancy [see

Contraindications (4.3)], treatment should be immediately discontinued as soon as pregnancy is recognized. PRAVACHOL should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.

Pravastatin was neither embryolethal nor teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 10 times (rabbit) or 120 times (rat) the human exposure at 80 mg/day maximum recommended human dose (MRHD) based on surface area (mg/m^2).

In pregnant rats given oral gavage doses of 4, 20, 100, 500, and 1000 mg/kg/day from gestation days 7 through 17 (organogenesis) increased mortality of offspring and skeletal anomalies were observed at 100 mg/kg/day systemic exposure, 10 times the human exposure at 80 mg/day MRHD based on body surface area (mg/m^2).

In pregnant rats given oral gavage doses of 10, 100, and 1000 mg/kg/day from gestation day 17 through lactation day 21 (weaning) increased mortality of offspring and developmental delays were observed at 100 mg/kg/day systemic exposure, 12 times the human exposure at 80 mg/day MRHD based on body surface area (mg/m^2).

8.3 Nursing Mothers

A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse [see *Contraindications (4.4)*].

Pravastatin crosses the placenta and is found in fetal tissue at 30% maternal plasma levels following a single 20 mg/kg dose given to pregnant rats on gestation day 18. Similar studies in lactating rats indicate secretion of pravastatin into breast milk at 0.2 to 6.5 times higher levels than maternal plasma at exposures equivalent to 2 times human exposure at the MRHD.

8.4 Pediatric Use

The safety and effectiveness of PRAVACHOL in children and adolescents from 8 to 18 years of age have been evaluated in a placebo-controlled study of 2 years duration. Patients treated with pravastatin had an adverse experience profile generally similar to that of patients treated with placebo with influenza and headache commonly reported in both treatment groups. [See *Adverse*

Reactions (6.4).] **Doses greater than 40 mg have not been studied in this population.** Children and adolescent females of childbearing potential should be counseled on appropriate contraceptive methods while on pravastatin therapy [see *Contraindications (4.3)* and *Use in Specific Populations (8.1)*]. For dosing information [see *Dosage and Administration (2.3).*]

Double-blind, placebo-controlled pravastatin studies in children less than 8 years of age have not been conducted.

8.5 Geriatric Use

Two secondary prevention trials with pravastatin (CARE and LIPID) included a total of 6593 subjects treated with pravastatin 40 mg for periods ranging up to 6 years. Across these 2 studies, 36.1% of pravastatin subjects were aged 65 and older and 0.8% were aged 75 and older. The beneficial effect of pravastatin in elderly subjects in reducing cardiovascular events and in modifying lipid profiles was similar to that seen in younger subjects. The adverse event profile in the elderly was similar to that in the overall population. Other reported clinical experience has not identified differences in responses to pravastatin between elderly and younger patients.

Mean pravastatin AUCs are slightly (25%-50%) higher in elderly subjects than in healthy young subjects, but mean maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), and half-life ($t_{½}$) values are similar in both age groups and substantial accumulation of pravastatin would not be expected in the elderly [see *Clinical Pharmacology (12.3)*].

Since advanced age (≥65 years) is a predisposing factor for myopathy, PRAVACHOL should be prescribed with caution in the elderly [see *Warnings and Precautions (5.1)* and *Clinical Pharmacology (12.3)*].

8.6 Homozygous Familial Hypercholesterolemia

Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that statins are less effective because the patients lack functional LDL receptors.

10 OVERDOSAGE

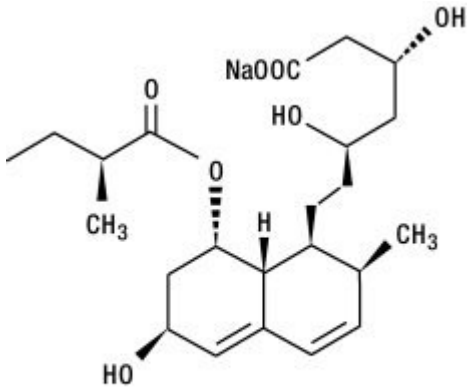
To date, there has been limited experience with overdosage of pravastatin. If an overdose occurs, it should be treated symptomatically with laboratory monitoring and supportive measures should be instituted as required.

11 DESCRIPTION

PRAVACHOL® (pravastatin sodium) is one of a class of lipid-lowering compounds, the statins, which reduce cholesterol biosynthesis. These agents are competitive inhibitors of HMG-CoA reductase, the enzyme catalyzing the early rate-limiting step in cholesterol biosynthesis, conversion of HMG-CoA to mevalonate.

Pravastatin sodium is designated chemically as 1-Naphthalene-heptanoic acid, 1,2,6,7,8,8a-hexahydro-β,δ,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-, monosodium salt, [1S-[1α(βS*,δS*),2α,6α,8β(R*),8aα]]-.

Structural formula:



$C_{23}H_{35}NaO_7$ MW 446.52

Pravastatin sodium is an odorless, white to off-white, fine or crystalline powder. It is a relatively polar hydrophilic compound with a partition coefficient (octanol/water) of 0.59 at a pH of 7.0. It is soluble in methanol and water (>300 mg/mL), slightly soluble in isopropanol, and practically insoluble in acetone, acetonitrile, chloroform, and ether.

PRAVACHOL is available for oral administration as 10 mg, 20 mg, 40 mg, and 80 mg tablets. Inactive ingredients include: croscarmellose sodium, lactose, magnesium oxide, magnesium

stearate, microcrystalline cellulose, and povidone. The 10 mg tablet also contains Red Ferric Oxide, the 20 mg and 80 mg tablets also contain Yellow Ferric Oxide, and the 40 mg tablet also contains Green Lake Blend (mixture of D&C Yellow No. 10-Aluminum Lake and FD&C Blue No. 1-Aluminum Lake).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pravastatin is a reversible inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early and rate limiting step in the biosynthetic pathway for cholesterol. In addition, pravastatin reduces VLDL and TG and increases HDL-C.

12.3 Pharmacokinetics

General

Absorption: PRAVACHOL is administered orally in the active form. In studies in man, peak plasma pravastatin concentrations occurred 1 to 1.5 hours upon oral administration. Based on urinary recovery of total radiolabeled drug, the average oral absorption of pravastatin is 34% and absolute bioavailability is 17%. While the presence of food in the gastrointestinal tract reduces systemic bioavailability, the lipid-lowering effects of the drug are similar whether taken with or 1 hour prior to meals.

Pravastatin plasma concentrations, including area under the concentration-time curve (AUC), C_{max}, and steady-state minimum (C_{min}), are directly proportional to administered dose. Systemic bioavailability of pravastatin administered following a bedtime dose was decreased 60% compared to that following an AM dose. Despite this decrease in systemic bioavailability, the efficacy of pravastatin administered once daily in the evening, although not statistically significant, was marginally more effective than that after a morning dose.

The coefficient of variation (CV), based on between-subject variability, was 50% to 60% for AUC. The geometric means of pravastatin C_{max} and AUC following a 20 mg dose in the fasted state were 26.5 ng/mL and 59.8 ng*hr/mL, respectively.

Steady-state AUCs, C_{max}, and C_{min} plasma concentrations showed no evidence of pravastatin accumulation following once or twice daily administration of PRAVACHOL tablets.

Distribution: Approximately 50% of the circulating drug is bound to plasma proteins.

Metabolism: The major biotransformation pathways for pravastatin are: (a) isomerization to 6-epi pravastatin and the 3α-hydroxyisomer of pravastatin (SQ 31,906) and (b) enzymatic ring hydroxylation to SQ 31,945. The 3α-hydroxyisomeric metabolite (SQ 31,906) has 1/10 to 1/40 the HMG-CoA reductase inhibitory activity of the parent compound. Pravastatin undergoes extensive first-pass extraction in the liver (extraction ratio 0.66).

Excretion: Approximately 20% of a radiolabeled oral dose is excreted in urine and 70% in the feces. After intravenous administration of radiolabeled pravastatin to normal volunteers, approximately 47% of total body clearance was via renal excretion and 53% by non-renal routes (i.e., biliary excretion and biotransformation).

Following single dose oral administration of ^{14}C-pravastatin, the radioactive elimination $t_{½}$ for pravastatin is 1.8 hours in humans.

Specific Populations

Renal Impairment: A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SQ 31,906). Compared to healthy subjects with normal renal function, patients with severe renal impairment had 69% and 37% higher mean AUC and C_{max} values, respectively, and a 0.61 hour shorter $t_{½}$ for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945).

Hepatic Impairment: In a study comparing the kinetics of pravastatin in patients with biopsy confirmed cirrhosis (N=7) and normal subjects (N=7), the mean AUC varied 18-fold in cirrhotic patients and 5-fold in healthy subjects. Similarly, the peak pravastatin values varied 47-fold for cirrhotic patients compared to 6-fold for healthy subjects. [See *Warnings and Precautions (5.2)*.]

Geriatric: In a single oral dose study using pravastatin 20 mg, the mean AUC for pravastatin was approximately 27% greater and the mean cumulative urinary excretion (CUE) approximately 19% lower in elderly men (65-75 years old) compared with younger men (19-31 years old). In a similar study conducted in women, the mean AUC for pravastatin was approximately 46% higher and the mean CUE approximately 18% lower in elderly women

(65-78 years old) compared with younger women (18-38 years old). In both studies, C_{max}, T_{max}, and $t_{½}$ values were similar in older and younger subjects. [See *Use in Specific Populations (8.5).*]

Pediatric: After 2 weeks of once-daily 20 mg oral pravastatin administration, the geometric means of AUC were 80.7 (CV 44%) and 44.8 (CV 89%) ng*hr/mL for children (8-11 years, N=14) and adolescents (12-16 years, N=10), respectively. The corresponding values for C_{max} were 42.4 (CV 54%) and 18.6 ng/mL (CV 100%) for children and adolescents, respectively. No conclusion can be made based on these findings due to the small number of samples and large variability. [See *Use in Specific Populations (8.4).*]

Drug-Drug Interactions

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}**
Cyclosporine 5 mg/kg single dose	40 mg single dose	↑282%	↑327%
Clarithromycin 500 mg BID for 9 days	40 mg OD for 8 days	↑110%	↑128%
Darunavir 600 mg BID/Ritonavir 100 mg BID for 7 days	40 mg single dose	↑81%	↑63%
Colestipol 10 g single dose	20 mg single dose	↓47%	↓53%
Cholestyramine 4 g single dose Administered simultaneously Administered 1 hour prior to cholestyramine Administered 4 hours after cholestyramine	20 mg single dose	 ↓40% ↑12% ↓12%	 ↓39% ↑30% ↓6.8%
Cholestyramine 24 g OD for 4 weeks	20 mg BID for 8 weeks 5 mg BID for 8 weeks 10 mg BID for 8 weeks	↓51% ↓38% ↓18%	↑4.9% ↑23% ↓33%
Fluconazole 200 mg IV for 6 days 200 mg PO for 6 days	 20 mg PO+10 mg IV 20 mg PO+10 mg IV	 ↓34% ↓16%	 ↓33% ↓16%
Kaletra 400 mg/100 mg BID for 14 days	20 mg OD for 4 days	↑33%	↑26%
Verapamil IR 120 mg for 1 day and Verapamil ER 480 mg for 3 days	40 mg single dose	↑31%	↑42%
Cimetidine 300 mg QID for 3 days	20 mg single dose	↑30%	↑9.8%
Antacids 15 mL QID for 3 days	20 mg single dose	↓28%	↓24%

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}
Digoxin 0.2 mg OD for 9 days	20 mg OD for 9 days	↑23%	↑26%
Probucol 500 mg single dose	20 mg single dose	↑14%	↑24%
Warfarin 5 mg OD for 6 days	20 mg BID for 6 days	↓13%	↑6.7%
Itraconazole 200 mg OD for 30 days	40 mg OD for 30 days	↑11% (compared to Day 1)	↑17% (compared to Day 1)
Gemfibrozil 600 mg single dose	20 mg single dose	↓7.0%	↓20%
Aspirin 324 mg single dose	20 mg single dose	↑4.7%	↑8.9%
Niacin 1 g single dose	20 mg single dose	↓3.6%	↓8.2%
Diltiazem	20 mg single dose	↑2.7%	↑30%
Grapefruit juice	40 mg single dose	↓1.8%	↑3.7%

BID = twice daily; OD = once daily; QID = four times daily

Table 4: Effect of Pravastatin on the Pharmacokinetics of Coadministered Drugs

Pravastatin Dosing Regimen	Name and Dose	Change in AUC	Change in C_{max}
20 mg BID for 6 days	Warfarin 5 mg OD for 6 days Change in mean prothrombin time	↑17% ↑0.4 sec	↑15%
20 mg OD for 9 days	Digoxin 0.2 mg OD for 9 days	↑4.6%	↑5.3%
20 mg BID for 4 weeks 10 mg BID for 4 weeks 5 mg BID for 4 weeks	Antipyrine 1.2 g single dose	↑3.0% ↑1.6% ↑ Less than 1%	Not Reported
20 mg OD for 4 days	Kaletra 400 mg/100 mg BID for 14 days	No change	No change

BID = twice daily; OD = once daily

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p<0.01$). These

effects in rats were observed at approximately 12 times the human dose (HD) of 80 mg based on body surface area (mg/m^2) and at approximately 4 times the HD, based on AUC.

In a 2-year study in mice fed pravastatin at doses of 250 and 500 mg/kg/day, there was an increased incidence of hepatocellular carcinomas in males and females at both 250 and 500 mg/kg/day ($p<0.0001$). At these doses, lung adenomas in females were increased ($p=0.013$). These effects in mice were observed at approximately 15 times (250 mg/kg/day) and 23 times (500 mg/kg/day) the HD of 80 mg, based on AUC. In another 2-year study in mice with doses up to 100 mg/kg/day (producing drug exposures approximately 2 times the HD of 80 mg, based on AUC), there were no drug-induced tumors.

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*; a forward mutation assay in L5178Y TK +/− mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a fertility study in adult rats with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance.

13.2 Animal Toxicology and/or Pharmacology

CNS Toxicity

CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day. These effects in dogs were observed at approximately 59 times the HD of 80 mg/day, based on AUC. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at

Reference ID: 3090896

180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

When administered to juvenile rats (postnatal days [PND] 4 through 80 at 5-45 mg/kg/day), no drug related changes were observed at 5 mg/kg/day. At 15 and 45 mg/kg/day, altered body-weight gain was observed during the dosing and 52-day recovery periods as well as slight thinning of the corpus callosum at the end of the recovery period. This finding was not evident in rats examined at the completion of the dosing period and was not associated with any inflammatory or degenerative changes in the brain. The biological relevance of the corpus callosum finding is uncertain due to the absence of any other microscopic changes in the brain or peripheral nervous tissue and because it occurred at the end of the recovery period. Neurobehavioral changes (enhanced acoustic startle responses and increased errors in water-maze learning) combined with evidence of generalized toxicity were noted at 45 mg/kg/day during the later part of the recovery period. Serum pravastatin levels at 15 mg/kg/day are approximately ≥1 times (AUC) the maximum pediatric dose of 40 mg. No thinning of the corpus callosum was observed in rats dosed with pravastatin (≥250 mg/kg/day) beginning PND 35 for 3 months suggesting increased sensitivity in younger rats. PND 35 in a rat is approximately equivalent to an 8- to 12-year-old human child. Juvenile male rats given 90 times (AUC) the 40 mg dose had decreased fertility (20%) with sperm abnormalities compared to controls.

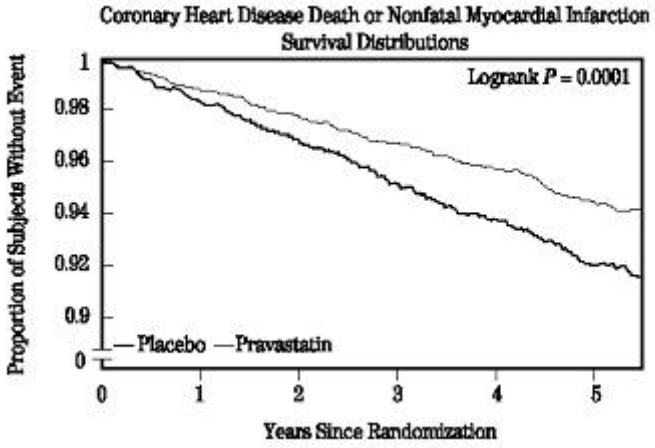
14 CLINICAL STUDIES

14.1 Prevention of Coronary Heart Disease

In the Pravastatin Primary Prevention Study (WOS),[3] the effect of PRAVACHOL on fatal and nonfatal CHD was assessed in 6595 men 45 to 64 years of age, without a previous MI, and with LDL-C levels between 156 to 254 mg/dL (4-6.7 mmol/L). In this randomized, double-blind, placebo-controlled study, patients were treated with standard care, including dietary advice, and either PRAVACHOL 40 mg daily (N=3302) or placebo (N=3293) and followed for a median duration of 4.8 years. Median (25^{th}, 75^{th} percentile) percent changes from baseline after 6 months of pravastatin treatment in Total-C, LDL-C, TG, and HDL-C were −20.3 (−26.9, −11.7), −27.7 (−36.0, −16.9), −9.1 (−27.6, 12.5), and 6.7 (−2.1, 15.6), respectively.

PRAVACHOL significantly reduced the rate of first coronary events (either CHD death or nonfatal MI) by 31% (248 events in the placebo group [CHD death=44, nonfatal MI=204] versus 174 events in the PRAVACHOL group [CHD death=31, nonfatal MI=143], p=0.0001 [see figure

below]). The risk reduction with PRAVACHOL was similar and significant throughout the entire range of baseline LDL cholesterol levels. This reduction was also similar and significant across the age range studied with a 40% risk reduction for patients younger than 55 years and a 27% risk reduction for patients 55 years and older. The Pravastatin Primary Prevention Study included only men, and therefore it is not clear to what extent these data can be extrapolated to a similar population of female patients.



PRAVACHOL also significantly decreased the risk for undergoing myocardial revascularization procedures (coronary artery bypass graft [CABG] surgery or percutaneous transluminal coronary angioplasty [PTCA]) by 37% (80 vs 51 patients, p=0.009) and coronary angiography by 31% (128 vs 90, p=0.007). Cardiovascular deaths were decreased by 32% (73 vs 50, p=0.03) and there was no increase in death from non-cardiovascular causes.

14.2 Secondary Prevention of Cardiovascular Events

In the LIPID[4] study, the effect of PRAVACHOL, 40 mg daily, was assessed in 9014 patients (7498 men; 1516 women; 3514 elderly patients [age ≥65 years]; 782 diabetic patients) who had experienced either an MI (5754 patients) or had been hospitalized for unstable angina pectoris (3260 patients) in the preceding 3 to 36 months. Patients in this multicenter, double-blind, placebo-controlled study participated for an average of 5.6 years (median of 5.9 years) and at randomization had Total-C between 114 and 563 mg/dL (mean 219 mg/dL), LDL-C between 46 and 274 mg/dL (mean 150 mg/dL), TG between 35 and 2710 mg/dL (mean 160 mg/dL), and HDL-C between 1 and 103 mg/dL (mean 37 mg/dL). At baseline, 82% of patients were receiving aspirin and 76% were receiving antihypertensive medication. Treatment with PRAVACHOL

significantly reduced the risk for total mortality by reducing coronary death (see Table 5). The risk reduction due to treatment with PRAVACHOL on CHD mortality was consistent regardless of age. PRAVACHOL significantly reduced the risk for total mortality (by reducing CHD death) and CHD events (CHD mortality or nonfatal MI) in patients who qualified with a history of either MI or hospitalization for unstable angina pectoris.

Table 5: LIPID - Primary and Secondary Endpoints

	Number (%) of Subjects			
Event	**Pravastatin 40 mg (N=4512)**	**Placebo (N=4502)**	**Risk Reduction**	***p*-value**
Primary Endpoint				
CHD mortality	287 (6.4)	373 (8.3)	24%	0.0004
Secondary Endpoints				
Total mortality	498 (11.0)	633 (14.1)	23%	<0.0001
CHD mortality or nonfatal MI	557 (12.3)	715 (15.9)	24%	<0.0001
Myocardial revascularization procedures (CABG or PTCA)	584 (12.9)	706 (15.7)	20%	<0.0001
Stroke				
All-cause	169 (3.7)	204 (4.5)	19%	0.0477
Non-hemorrhagic	154 (3.4)	196 (4.4)	23%	0.0154
Cardiovascular mortality	331 (7.3)	433 (9.6)	25%	<0.0001

In the CARE[5] study, the effect of PRAVACHOL, 40 mg daily, on CHD death and nonfatal MI was assessed in 4159 patients (3583 men and 576 women) who had experienced a MI in the preceding 3 to 20 months and who had normal (below the 75th percentile of the general population) plasma total cholesterol levels. Patients in this double-blind, placebo-controlled study participated for an average of 4.9 years and had a mean baseline Total-C of 209 mg/dL. LDL-C levels in this patient population ranged from 101 to 180 mg/dL (mean 139 mg/dL). At baseline, 84% of patients were receiving aspirin and 82% were taking antihypertensive medications. Median (25th, 75th percentile) percent changes from baseline after 6 months of pravastatin treatment in Total-C, LDL-C, TG, and HDL-C were −22.0 (−28.4, −14.9), −32.4 (−39.9, −23.7), −11.0 (−26.5, 8.6), and 5.1 (−2.9, 12.7), respectively. Treatment with PRAVACHOL significantly reduced the rate of first recurrent coronary events (either CHD death or nonfatal MI), the risk of undergoing revascularization procedures (PTCA, CABG), and the risk for stroke or TIA (see Table 6).

Reference ID: 3090896

Table 6: CARE - Primary and Secondary Endpoints

	Number (%) of Subjects			
Event	**Pravastatin 40 mg (N=2081)**	**Placebo (N=2078)**	**Risk Reduction**	***p*-value**
Primary Endpoint				
CHD mortality or nonfatal MI[a]	212 (10.2)	274 (13.2)	24%	0.003
Secondary Endpoints				
Myocardial revascularization procedures (CABG or PTCA)	294 (14.1)	391 (18.8)	27%	<0.001
Stroke or TIA	93 (4.5)	124 (6.0)	26%	0.029

[a] The risk reduction due to treatment with PRAVACHOL was consistent in both sexes.

In the PLAC I[6] study, the effect of pravastatin therapy on coronary atherosclerosis was assessed by coronary angiography in patients with coronary disease and moderate hypercholesterolemia (baseline LDL-C range: 130-190 mg/dL). In this double-blind, multicenter, controlled clinical trial, angiograms were evaluated at baseline and at 3 years in 264 patients. Although the difference between pravastatin and placebo for the primary endpoint (per-patient change in mean coronary artery diameter) and 1 of 2 secondary endpoints (change in percent lumen diameter stenosis) did not reach statistical significance, for the secondary endpoint of change in minimum lumen diameter, statistically significant slowing of disease was seen in the pravastatin treatment group (p=0.02).

In the REGRESS[7] study, the effect of pravastatin on coronary atherosclerosis was assessed by coronary angiography in 885 patients with angina pectoris, angiographically documented coronary artery disease, and hypercholesterolemia (baseline total cholesterol range: 160-310 mg/dL). In this double-blind, multicenter, controlled clinical trial, angiograms were evaluated at baseline and at 2 years in 653 patients (323 treated with pravastatin). Progression of coronary atherosclerosis was significantly slowed in the pravastatin group as assessed by changes in mean segment diameter (p=0.037) and minimum obstruction diameter (p=0.001).

Analysis of pooled events from PLAC I, PLAC II,[8] REGRESS, and KAPS[9] studies (combined N=1891) showed that treatment with pravastatin was associated with a statistically significant reduction in the composite event rate of fatal and nonfatal MI (46 events or 6.4% for placebo versus 21 events or 2.4% for pravastatin, p=0.001). The predominant effect of pravastatin was to reduce the rate of nonfatal MI.

14.3 Primary Hypercholesterolemia (*Fredrickson* Types IIa and IIb)

PRAVACHOL is highly effective in reducing Total-C, LDL-C, and TG in patients with heterozygous familial, presumed familial combined, and non-familial (non-FH) forms of primary hypercholesterolemia, and mixed dyslipidemia. A therapeutic response is seen within 1 week, and the maximum response usually is achieved within 4 weeks. This response is maintained during extended periods of therapy. In addition, PRAVACHOL is effective in reducing the risk of acute coronary events in hypercholesterolemic patients with and without previous MI.

A single daily dose is as effective as the same total daily dose given twice a day. In multicenter, double-blind, placebo-controlled studies of patients with primary hypercholesterolemia, treatment with pravastatin in daily doses ranging from 10 to 40 mg consistently and significantly decreased Total-C, LDL-C, TG, and Total-C/HDL-C and LDL-C/HDL-C ratios (see Table 7).

In a pooled analysis of 2 multicenter, double-blind, placebo-controlled studies of patients with primary hypercholesterolemia, treatment with pravastatin at a daily dose of 80 mg (N=277) significantly decreased Total-C, LDL-C, and TG. The 25th and 75th percentile changes from baseline in LDL-C for pravastatin 80 mg were −43% and −30%. The efficacy results of the individual studies were consistent with the pooled data (see Table 7).

Treatment with PRAVACHOL modestly decreased VLDL-C and PRAVACHOL across all doses produced variable increases in HDL-C (see Table 7).

Table 7: Primary Hypercholesterolemia Studies: Dose Response of PRAVACHOL Once Daily Administration

Dose	Total-C	LDL-C	HDL-C	TG
Mean Percent Changes From Baseline After 8 Weeks[a]				
Placebo (N=36)	−3%	−4%	+1%	−4%
10 mg (N=18)	−16%	−22%	+7%	−15%
20 mg (N=19)	−24%	−32%	+2%	−11%
40 mg (N=18)	−25%	−34%	+12%	−24%
Mean Percent Changes From Baseline After 6 Weeks[b]				
Placebo (N=162)	0%	−1%	−1%	+1%
80 mg (N=277)	−27%	−37%	+3%	−19%

[a] A multicenter, double-blind, placebo-controlled study.

[b] Pooled analysis of 2 multicenter, double-blind, placebo-controlled studies.

In another clinical trial, patients treated with pravastatin in combination with cholestyramine (70% of patients were taking cholestyramine 20 or 24 g per day) had reductions equal to or greater than 50% in LDL-C. Furthermore, pravastatin attenuated cholestyramine-induced increases in TG levels (which are themselves of uncertain clinical significance).

14.4 Hypertriglyceridemia (*Fredrickson* Type IV)

The response to pravastatin in patients with Type IV hyperlipidemia (baseline TG >200 mg/dL and LDL-C <160 mg/dL) was evaluated in a subset of 429 patients from the CARE study. For pravastatin-treated subjects, the median (min, max) baseline TG level was 246.0 (200.5, 349.5) mg/dL (see Table 8.)

Table 8: Patients with *Fredrickson* Type IV Hyperlipidemia Median (25^{th}, 75^{th} percentile) % Change from Baseline

	Pravastatin 40 mg (N=429)	**Placebo (N=430)**
TG	−21.1 (−34.8, 1.3)	−6.3 (−23.1, 18.3)
Total-C	−22.1 (−27.1, −14.8)	0.2 (−6.9, 6.8)
LDL-C	−31.7 (−39.6, −21.5)	0.7 (−9.0, 10.0)
HDL-C	7.4 (−1.2, 17.7)	2.8 (−5.7, 11.7)
Non-HDL-C	−27.2 (−34.0, −18.5)	−0.8 (−8.2, 7.0)

14.5 Dysbetalipoproteinemia (*Fredrickson* Type III)

The response to pravastatin in two double-blind crossover studies of 46 patients with genotype E2/E2 and *Fredrickson* Type III dysbetalipoproteinemia is shown in Table 9.

Table 9: Patients with *Fredrickson* Type III Dysbetalipoproteinemia Median (min, max) % Change from Baseline

	Median (min, max) at Baseline (mg/dL)	Median % Change (min, max) Pravastatin 40 mg (N=20)
Study 1		
Total-C	386.5 (245.0, 672.0)	−32.7 (−58.5, 4.6)
TG	443.0 (275.0, 1299.0)	−23.7 (−68.5, 44.7)
VLDL-C[a]	206.5 (110.0, 379.0)	−43.8 (−73.1, −14.3)
LDL-C[a]	117.5 (80.0, 170.0)	−40.8 (−63.7, 4.6)

Table 9: Patients with *Fredrickson* Type III Dysbetalipoproteinemia Median (min, max) % Change from Baseline

	Median (min, max) at Baseline (mg/dL)	Median % Change (min, max) Pravastatin 40 mg (N=20)
HDL-C	30.0 (18.0, 88.0)	6.4 (−45.0, 105.6)
Non-HDL-C	344.5 (215.0, 646.0)	−36.7 (−66.3, 5.8)
[a] N=14		
	Median (min, max) at Baseline (mg/dL)	Median % Change (min, max) Pravastatin 40 mg (N=26)
Study 2		
Total-C	340.3 (230.1, 448.6)	−31.4 (−54.5, −13.0)
TG	343.2 (212.6, 845.9)	−11.9 (−56.5, 44.8)
VLDL-C	145.0 (71.5, 309.4)	−35.7 (−74.7, 19.1)
LDL-C	128.6 (63.8, 177.9)	−30.3 (−52.2, 13.5)
HDL-C	38.7 (27.1, 58.0)	5.0 (−17.7, 66.7)
Non-HDL-C	295.8 (195.3, 421.5)	−35.5 (−81.0, −13.5)

14.6 Pediatric Clinical Study

A double-blind, placebo-controlled study in 214 patients (100 boys and 114 girls) with heterozygous familial hypercholesterolemia (HeFH), aged 8 to 18 years was conducted for 2 years. The children (aged 8-13 years) were randomized to placebo (N=63) or 20 mg of pravastatin daily (N=65) and the adolescents (aged 14-18 years) were randomized to placebo (N=45) or 40 mg of pravastatin daily (N=41). Inclusion in the study required an LDL-C level >95th percentile for age and sex and one parent with either a clinical or molecular diagnosis of familial hypercholesterolemia. The mean baseline LDL-C value was 239 mg/dL and 237 mg/dL in the pravastatin (range: 151-405 mg/dL) and placebo (range: 154-375 mg/dL) groups, respectively.

Pravastatin significantly decreased plasma levels of LDL-C, Total-C, and ApoB in both children and adolescents (see Table 10). The effect of pravastatin treatment in the 2 age groups was similar.

Table 10: Lipid-Lowering Effects of Pravastatin in Pediatric Patients with Heterozygous Familial Hypercholesterolemia: Least-Squares Mean % Change from Baseline at Month 24 (Last Observation Carried Forward: Intent-to-Treat)[a]

	Pravastatin 20 mg (Aged 8-13 years) N=65	Pravastatin 40 mg (Aged 14-18 years) N=41	Combined Pravastatin (Aged 8-18 years) N=106	Combined Placebo (Aged 8-18 years) N=108	95% CI of the Difference Between Combined Pravastatin and Placebo
LDL-C	−26.04[b]	−21.07[b]	−24.07[b]	−1.52	(−26.74, −18.86)
TC	−20.75[b]	−13.08[b]	−17.72[b]	−0.65	(−20.40, −13.83)
HDL-C	1.04	13.71	5.97	3.13	(−1.71, 7.43)
TG	−9.58	−0.30	−5.88	−3.27	(−13.95, 10.01)
ApoB (N)	−23.16[b] (61)	−18.08[b] (39)	−21.11[b] (100)	−0.97 (106)	(−24.29, −16.18)

[a] The above least-squares mean values were calculated based on log-transformed lipid values.

[b] Significant at $p \leq 0.0001$ when compared with placebo.

The mean achieved LDL-C was 186 mg/dL (range: 67-363 mg/dL) in the pravastatin group compared to 236 mg/dL (range: 105-438 mg/dL) in the placebo group.

The safety and efficacy of pravastatin doses above 40 mg daily have not been studied in children. The long-term efficacy of pravastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

15 REFERENCES

1. Fredrickson DS, Levy RI, Lees RS. Fat transport in lipoproteins - An integrated approach to mechanisms and disorders. *N Engl J Med*. 1967;276: 34-44, 94-103, 148-156, 215-225, 273-281.

2. Manson JM, Freyssinges C, Ducrocq MB, Stephenson WP. Postmarketing surveillance of lovastatin and simvastatin exposure during pregnancy. *Reprod Toxicol*. 1996;10(6):439-446.

3. Shepherd J, Cobbe SM, Ford I, et al, for the West of Scotland Coronary Prevention Study Group (WOS). Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med*. 1995;333:1301-1307.

Reference ID: 3090896

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

5. Sacks FM, Pfeffer MA, Moye LA, et al, for the Cholesterol and Recurrent Events Trial Investigators (CARE). The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med*. 1996;335:1001-1009.

6. Pitt B, Mancini GBJ, Ellis SG, et al, for the PLAC I Investigators. Pravastatin limitation of atherosclerosis in the coronary arteries (PLAC I): Reduction in atherosclerosis progression and clinical events. *J Am Coll Cardiol*. 1995;26:1133-1139.

7. Jukema JW, Bruschke AVG, van Boven AJ, et al, for the Regression Growth Evaluation Statin Study Group (REGRESS). Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic man with normal to moderately elevated serum cholesterol levels. *Circ*. 1995;91:2528-2540.

8. Crouse JR, Byington RP, Bond MG, et al. Pravastatin, lipids, and atherosclerosis in the carotid arteries: Design features of a clinical trial with carotid atherosclerosis outcome (PLAC II). *Control Clin Trials*. 1992;13:495-506.

9. Salonen R, Nyyssonen K, Porkkala E, et al. Kuopio Atherosclerosis Prevention Study (KAPS). A population-based primary preventive trial of the effect of LDL lowering on atherosclerotic progression in carotid and femoral arteries. *Circ*. 1995;92:1758-1764.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

PRAVACHOL® (pravastatin sodium) Tablets are supplied as:

10 mg tablets: Pink to peach, rounded, rectangular-shaped, biconvex with a “P” embossed on one side and “PRAVACHOL 10” engraved on the opposite side. They are supplied in bottles of 90 (NDC 0003-5154-05). Bottles contain a desiccant canister.

20 mg tablets: Yellow, rounded, rectangular-shaped, biconvex with a “P” embossed on one side and “PRAVACHOL 20” engraved on the opposite side. They are supplied in bottles of 90 (NDC 0003-5178-05). Bottles contain a desiccant canister.

40 mg tablets: Green, rounded, rectangular-shaped, biconvex with a “P” embossed on one side and “PRAVACHOL 40” engraved on the opposite side. They are supplied in bottles of 90 (NDC 0003-5194-10). Bottles contain a desiccant canister.

80 mg tablets: Yellow, oval-shaped tablet with “BMS” on one side and “80” on the other side. They are supplied in bottles of 90 (NDC 0003-5195-10). Bottles contain a desiccant canister.

16.2 Storage

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Keep tightly closed (protect from moisture). Protect from light.

17 PATIENT COUNSELING INFORMATION

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever [see *Warnings and Precautions (5.1)*].

It is recommended that liver enzyme tests be performed before the initiation of PRAVACHOL, and thereafter when clinically indicated. All patients treated with PRAVACHOL should be advised to promptly report any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice [see *Warnings and Precautions (5.2)*].

Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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Tracked Changes Label

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PRAVACHOL safely and effectively. See full prescribing information for PRAVACHOL.

PRAVACHOL® (pravastatin sodium) Tablets
Initial U.S. Approval: 1991

----------INDICATIONS AND USAGE----------

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

- Reduce the risk of MI, revascularization, and cardiovascular mortality in hypercholesterolemic patients without clinically evident CHD. (1.1)
- Reduce the risk of total mortality by reducing coronary death, MI, revascularization, stroke/TIA, and the progression of coronary atherosclerosis in patients with clinically evident CHD. (1.1)
- Reduce elevated Total-C, LDL-C, ApoB, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia. (1.2)
- Reduce elevated serum TG levels in patients with hypertriglyceridemia. (1.2)
- Treat patients with primary dysbetalipoproteinemia who are not responding to diet. (1.2)
- Treat children and adolescent patients ages 8 years and older with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy. (1.2)

Limitations of use:

- PRAVACHOL has not been studied in *Fredrickson* Types I and V dyslipidemias. (1.3)

----------DOSAGE AND ADMINISTRATION----------

- Adults: the recommended starting dose is 40 mg once daily. Use 80 mg dose only for patients not reaching LDL-C goal with 40 mg. (2.2)
- Significant renal impairment: the recommended starting dose is 10 mg once daily. (2.2)
- Children (ages 8 to 13 years, inclusive): the recommended starting dose is 20 mg once daily. (2.3)
- Adolescents (ages 14 to 18 years): the recommended starting dose is 40 mg once daily. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 10 mg, 20 mg, 40 mg, 80 mg. (3)

----------CONTRAINDICATIONS----------

- Hypersensitivity to any component of this medication. (4.1, 6.2, 11)
- Active liver disease or unexplained, persistent elevations of serum transaminases. (4.2, 5.2)
- Women who are pregnant or may become pregnant. (4.3, 8.1)
- Nursing mothers. (4.4, 8.3)

----------WARNINGS AND PRECAUTIONS----------

- Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): predisposing factors include advanced age (>65), uncontrolled hypothyroidism, and renal impairment. Patients should be advised to report promptly any symptoms of myopathy. Pravastatin therapy should be discontinued if myopathy is diagnosed or suspected. (5.1, 8.5)
- Liver enzyme abnormalities ~~and monitoring~~: persistent elevations in hepatic transaminases can occur. Check ~~Monitor~~ liver enzyme~~s~~ tests before initiating therapy and ~~during treatment~~ as clinically indicated thereafter. (5.2)

----------ADVERSE REACTIONS----------

In short-term clinical trials, the most commonly reported adverse reactions (≥2% and > placebo) regardless of causality were: musculoskeletal pain, nausea/vomiting, upper respiratory infection, diarrhea, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- ~~Fibrates~~Concomitant lipid-lowering therapies: use with fibrates ~~products may~~or lipid-modifying doses (>1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with PRAVACHOL. (~~2.4, 5.1~~7)
- Cyclosporine: combination increases exposure. Limit pravastatin to 20 mg once daily. (2.5, 7.1)
- Clarithromycin: combination increases exposure. Limit pravastatin to 40 mg once daily. (2.6, 7.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: ~~05/2011~~TBD

FULL PRESCRIBING INFORMATION: CONTENTS*

* 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 nonpharmacologic measures alone has been inadequate.

1.1 Prevention of Cardiovascular Disease

In hypercholesterolemic patients without clinically evident coronary heart disease (CHD), PRAVACHOL (pravastatin sodium) is indicated to:

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

In patients with clinically evident CHD, PRAVACHOL is indicated to:

- reduce the risk of total mortality by reducing coronary death.
- reduce the risk of MI.
- reduce the risk of undergoing myocardial revascularization procedures.
- reduce the risk of stroke and stroke/transient ischemic attack (TIA).
- slow the progression of coronary atherosclerosis.

1.2 Hyperlipidemia

PRAVACHOL is indicated:

- as an adjunct to diet to reduce elevated total cholesterol (Total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (ApoB), and triglyceride (TG) levels and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hypercholesterolemia and mixed dyslipidemia (*Fredrickson* Types IIa and IIb).[1]
- as an adjunct to diet for the treatment of patients with elevated serum TG levels (*Fredrickson* Type IV).
- for the treatment of patients with primary dysbetalipoproteinemia (*Fredrickson* Type III) who do not respond adequately to diet.

- as an adjunct to diet and lifestyle modification for treatment of heterozygous familial hypercholesterolemia (HeFH) in children and adolescent patients ages 8 years and older if after an adequate trial of diet the following findings are present:

  a. LDL-C remains ≥190 mg/dL or

  b. LDL-C remains ≥160 mg/dL and:

     - there is a positive family history of premature cardiovascular disease (CVD) or
     - two or more other CVD risk factors are present in the patient.

1.3 Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

The patient should be placed on a standard cholesterol-lowering diet before receiving PRAVACHOL and should continue on this diet during treatment with PRAVACHOL [see NCEP Treatment Guidelines for details on dietary therapy].

2.2 Adult Patients

The recommended starting dose is 40 mg once daily. If a daily dose of 40 mg does not achieve desired cholesterol levels, 80 mg once daily is recommended. In patients with significant renal impairment, a starting dose of 10 mg daily is recommended. PRAVACHOL can be administered orally as a single dose at any time of the day, with or without food. 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.

2.3 Pediatric Patients

Children (Ages 8 to 13 Years, Inclusive)

The recommended dose is 20 mg once daily in children 8 to 13 years of age. Doses greater than 20 mg have not been studied in this patient population.

Adolescents (Ages 14 to 18 Years)

The recommended starting dose is 40 mg once daily in adolescents 14 to 18 years of age. Doses greater than 40 mg have not been studied in this patient population.

Children and adolescents treated with pravastatin should be reevaluated in adulthood and appropriate changes made to their cholesterol-lowering regimen to achieve adult goals for LDL-C [see *Indications and Usage (1.2)*].

2.4 Concomitant Lipid-Altering Therapy

PRAVACHOL may be used with bile acid resins. When administering a bile-acid-binding resin (e.g., cholestyramine, colestipol) and pravastatin, PRAVACHOL should be given either 1 hour or more before or at least 4 hours following the resin. [See *Clinical Pharmacology (12.3)*.]

~~The combination of statins and fibrates should generally be used with caution. [See *Warnings and Precautions (5.1)*.]~~

2.5 Dosage in Patients Taking Cyclosporine

In patients taking immunosuppressive drugs such as cyclosporine concomitantly with pravastatin, therapy should begin with 10 mg of pravastatin sodium once-a-day at bedtime and titration to higher doses should be done with caution. Most patients treated with this combination received a maximum pravastatin sodium dose of 20 mg/day. In patients taking cyclosporine, therapy should be limited to 20 mg of pravastatin sodium once daily [see *Warnings and Precautions (5.1)* and *Drug Interactions (7.1)*].

2.6 Dosage in Patients Taking Clarithromycin

In patients taking clarithromycin, therapy should be limited to 40 mg of pravastatin sodium once daily [see *Drug Interactions (7.2)*].

3 DOSAGE FORMS AND STRENGTHS

PRAVACHOL® Tablets are supplied as:

10 mg tablets: Pink to peach, rounded, rectangular-shaped, biconvex with a “P” embossed on one side and “PRAVACHOL 10” engraved on the opposite side.

20 mg tablets: Yellow, rounded, rectangular-shaped, biconvex with a “P” embossed on one side and “PRAVACHOL 20” engraved on the opposite side.

40 mg tablets: Green, rounded, rectangular-shaped, biconvex with a “P” embossed on one side and “PRAVACHOL 40” engraved on the opposite side.

80 mg tablets: Yellow, oval-shaped tablet with “BMS” on one side and “80” on the other side.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Hypersensitivity to any component of this medication.

4.2 Liver

Active liver disease or unexplained, persistent elevations of serum transaminases [see *Warnings and Precautions (5.2)*].

4.3 Pregnancy

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since statins decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they are contraindicated during pregnancy and in nursing mothers. PRAVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this class of drug, therapy should be discontinued immediately and the patient apprised of the potential hazard to the fetus [see *Use in Specific Populations (8.1)*].

4.4 Nursing Mothers

A small amount of pravastatin is excreted in human breast milk. Because statins have the potential for serious adverse reactions in nursing infants, women who require PRAVACHOL treatment should not breast-feed their infants [see *Use in Specific Populations (8.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with pravastatin and other drugs in this class. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

Uncomplicated myalgia has also been reported in pravastatin-treated patients [see *Adverse Reactions (6)*]. Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal (ULN), was rare (<0.1%) in pravastatin clinical trials. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Predisposing factors include advanced age (>65), uncontrolled hypothyroidism, and renal impairment. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with statins is increased with concurrent therapy with either erythromycin, cyclosporine, niacin, or fibrates. However, neither myopathy nor significant increases in CPK levels have been observed in 3 reports involving a total of 100 post-transplant patients (24 renal and 76 cardiac) treated for up to 2 years concurrently with pravastatin 10 to 40 mg and cyclosporine. Some of these patients also received other concomitant immunosuppressive therapies. Further, in clinical trials involving small numbers of patients who were treated concurrently with pravastatin and niacin, there were no reports of myopathy. Also, myopathy was not reported in a trial of combination pravastatin (40 mg/day) and gemfibrozil

(1200 mg/day), although 4 of 75 patients on the combination showed marked CPK elevations versus 1 of 73 patients receiving placebo. There was a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. **The use of fibrates alone may occasionally be associated with myopathy. The benefit of further alterations in lipid levels by the combined use of PRAVACHOL with fibrates should be carefully weighed against the potential risks of this combination.**

Cases of myopathy, including rhabdomyolysis, have been reported with pravastatin coadministered with colchicine, and caution should be exercised when prescribing pravastatin with colchicine [see *Drug Interactions (7.3)*].

5.2 Liver

Statins, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. In 3 long-term (4.8-5.9 years), placebo-controlled clinical trials (WOS, LIPID, CARE), 19,592 subjects (19,768 randomized) were exposed to pravastatin or placebo [see *Clinical Studies (14)*]. In an analysis of serum transaminase values (ALT, AST), incidences of marked abnormalities were compared between the pravastatin and placebo treatment groups; a marked abnormality was defined as a post-treatment test value greater than 3 times the upper limit of normal for subjects with pretreatment values less than or equal to the upper limit of normal, or 4 times the pretreatment value for subjects with pretreatment values greater than the upper limit of normal but less than 1.5 times the upper limit of normal. Marked abnormalities of ALT or AST occurred with similar low frequency (≤1.2%) in both treatment groups. Overall, clinical trial experience showed that liver function test abnormalities observed during pravastatin therapy were usually asymptomatic, not associated with cholestasis, and did not appear to be related to treatment duration. In a 320-patient placebo-controlled clinical trial, subjects with chronic (>6 months) stable liver disease, due primarily to hepatitis C or non-alcoholic fatty liver disease, were treated with 80 mg pravastatin or placebo for up to 9 months. The primary safety endpoint was the proportion of subjects with at least one ALT ≥2 times the upper limit of normal for those with normal ALT (≤ the upper limit of normal) at baseline or a doubling of the baseline ALT for those with elevated ALT (> the upper limit of normal) at baseline. By Week 36, 12 out of 160 (7.5%) subjects treated with pravastatin met the prespecified safety ALT endpoint compared to 20 out of 160 (12.5%) subjects receiving placebo. Conclusions regarding liver safety are limited since the study was not large enough to establish similarity between groups (with 95% confidence) in the rates of ALT elevation.

It is recommended that liver function tests be performed prior to the initiation of therapy and when clinically indicated.

Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of pravastatin [see *Contraindications (4.2)*]. Caution should be exercised when pravastatin is administered to patients who have a recent (<6 months) history of liver disease, have signs that may suggest liver disease (e.g., unexplained aminotransferase elevations, jaundice), or are heavy users of alcohol.

~~Patients who develop increased transaminase levels or signs and symptoms of active liver disease while taking pravastatin should be evaluated with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) returns to normal. Should an increase in AST or ALT of 3 times the upper limit of normal or greater persist, withdrawal of pravastatin therapy is recommended.~~There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including pravastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with PRAVACHOL, promptly interrupt therapy. If an alternate etiology is not found do not restart PRAVACHOL.

5.3 Endocrine Function

Statins interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p<0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of statins on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if a statin or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

In a placebo-controlled study of 214 pediatric patients with HeFH, of which 106 were treated with pravastatin (20 mg in the children aged 8-13 years and 40 mg in the adolescents aged 14-18 years) for 2 years, there were no detectable differences seen in any of the endocrine parameters (ACTH, cortisol, DHEAS, FSH, LH, TSH, estradiol [girls] or testosterone [boys]) relative to placebo. There were no detectable differences seen in height and weight changes, testicular volume changes, or Tanner score relative to placebo.

6 ADVERSE REACTIONS

Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. In 4-month-long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant.

6.1 Adverse Clinical Events

Short-Term Controlled Trials

In the PRAVACHOL placebo-controlled clinical trials database of 1313 patients (age range 20-76 years, 32.4% women, 93.5% Caucasians, 5% Blacks, 0.9% Hispanics, 0.4% Asians, 0.2% Others) with a median treatment duration of 14 weeks, 3.3% of patients on PRAVACHOL and 1.2% patients on placebo discontinued due to adverse events regardless of causality. The most common adverse reactions that led to treatment discontinuation and occurred at an incidence greater than placebo were: liver function test increased, nausea, anxiety/depression, and dizziness.

All adverse clinical events (regardless of causality) reported in ≥2% of pravastatin-treated patients in placebo-controlled trials of up to 8 months duration are identified in Table 1:

Table 1: Adverse Events in ≥2% of Patients Treated with Pravastatin 5 to 40 mg and at an Incidence Greater Than Placebo in Short-Term Placebo-Controlled Trials (% of patients)

Body System/Event	5 mg N=100	10 mg N=153	20 mg N=478	40 mg N=171	Any Dose N=902	Placebo N=411
Cardiovascular Angina Pectoris	5.0	4.6	4.8	3.5	4.5	3.4
Dermatologic	3.0	2.6	6.7	1.2	4.5	1.4

Table 1: Adverse Events in ≥2% of Patients Treated with Pravastatin 5 to 40 mg and at an Incidence Greater Than Placebo in Short-Term Placebo-Controlled Trials (% of patients)

Body System/Event	5 mg N=100	10 mg N=153	20 mg N=478	40 mg N=171	Any Dose N=902	Placebo N=411
Rash						
Gastrointestinal						
Nausea/Vomiting	4.0	5.9	10.5	2.3	7.4	7.1
Diarrhea	8.0	8.5	6.5	4.7	6.7	5.6
Flatulence	2.0	3.3	4.6	0.0	3.2	4.4
Dyspepsia/Heartburn	0.0	3.3	3.6	0.6	2.5	2.7
Abdominal Distension	2.0	3.3	2.1	0.6	2.0	2.4
General						
Fatigue	4.0	1.3	5.2	0.0	3.4	3.9
Chest Pain	4.0	1.3	3.3	1.2	2.7	1.9
Influenza	4.0	2.6	1.9	0.6	2.0	0.7
Musculoskeletal						
Musculoskeletal Pain	13.0	3.9	13.2	5.3	10.1	10.2
Myalgia	1.0	2.6	2.9	1.2	2.3	1.2
Nervous System						
Headache	5.0	6.5	7.5	3.5	6.3	4.6
Dizziness	4.0	1.3	5.2	0.6	3.5	3.4
Respiratory						
Pharyngitis	2.0	4.6	1.5	1.2	2.0	2.7
Upper Respiratory Infection	6.0	9.8	5.2	4.1	5.9	5.8
Rhinitis	7.0	5.2	3.8	1.2	3.9	4.9
Cough	4.0	1.3	3.1	1.2	2.5	1.7
Investigation						
ALT Increased	2.0	2.0	4.0	1.2	2.9	1.2
g-GT Increased	3.0	2.6	2.1	0.6	2.0	1.2
CPK Increased	5.0	1.3	5.2	2.9	4.1	3.6

The safety and tolerability of PRAVACHOL at a dose of 80 mg in 2 controlled trials with a mean exposure of 8.6 months was similar to that of PRAVACHOL at lower doses except that 4 out of 464 patients taking 80 mg of pravastatin had a single elevation of CK >10 times ULN compared to 0 out of 115 patients taking 40 mg of pravastatin.

Long-Term Controlled Morbidity and Mortality Trials

In the PRAVACHOL placebo-controlled clinical trials database of 21,483 patients (age range 24-75 years, 10.3% women, 52.3% Caucasians, 0.8% Blacks, 0.5% Hispanics, 0.1% Asians,

0.1% Others, 46.1% Not Recorded) with a median treatment duration of 261 weeks, 8.1% of patients on PRAVACHOL and 9.3% patients on placebo discontinued due to adverse events regardless of causality.

Adverse event data were pooled from 7 double-blind, placebo-controlled trials (West of Scotland Coronary Prevention Study [WOS]; Cholesterol and Recurrent Events study [CARE]; Long-term Intervention with Pravastatin in Ischemic Disease study [LIPID]; Pravastatin Limitation of Atherosclerosis in the Coronary Arteries study [PLAC I]; Pravastatin, Lipids and Atherosclerosis in the Carotids study [PLAC II]; Regression Growth Evaluation Statin Study [REGRESS]; and Kuopio Atherosclerosis Prevention Study [KAPS]) involving a total of 10,764 patients treated with pravastatin 40 mg and 10,719 patients treated with placebo. The safety and tolerability profile in the pravastatin group was comparable to that of the placebo group. Patients were exposed to pravastatin for a mean of 4.0 to 5.1 years in WOS, CARE, and LIPID and 1.9 to 2.9 years in PLAC I, PLAC II, KAPS, and REGRESS. In these long-term trials, the most common reasons for discontinuation were mild, non-specific gastrointestinal complaints. Collectively, these 7 trials represent 47,613 patient-years of exposure to pravastatin. All clinical adverse events (regardless of causality) occurring in ≥2% of patients treated with pravastatin in these studies are identified in Table 2.

Table 2: Adverse Events in ≥2% of Patients Treated with Pravastatin 40 mg and at an Incidence Greater Than Placebo in Long-Term Placebo-Controlled Trials

Body System/Event	**Pravastatin (N=10,764) % of patients**	**Placebo (N=10,719) % of patients**
Dermatologic		
Rash (including dermatitis)	7.2	7.1
General		
Edema	3.0	2.7
Fatigue	8.4	7.8
Chest Pain	10.0	9.8
Fever	2.1	1.9
Weight Gain	3.8	3.3
Weight Loss	3.3	2.8

Table 2: Adverse Events in ≥2% of Patients Treated with Pravastatin 40 mg and at an Incidence Greater Than Placebo in Long-Term Placebo-Controlled Trials

Body System/Event	Pravastatin (N=10,764) % of patients	Placebo (N=10,719) % of patients
Musculoskeletal		
Musculoskeletal Pain	24.9	24.4
Muscle Cramp	5.1	4.6
Musculoskeletal Traumatism	10.2	9.6
Nervous System		
Dizziness	7.3	6.6
Sleep Disturbance	3.0	2.4
Anxiety/Nervousness	4.8	4.7
Paresthesia	3.2	3.0
Renal/Genitourinary		
Urinary Tract Infection	2.7	2.6
Respiratory		
Upper Respiratory Tract Infection	21.2	20.2
Cough	8.2	7.4
Influenza	9.2	9.0
Pulmonary Infection	3.8	3.5
Sinus Abnormality	7.0	6.7
Tracheobronchitis	3.4	3.1
Special Senses		
Vision Disturbance (includes blurred vision, diplopia)	3.4	3.3
Infections		
Viral Infection	3.2	2.9

In addition to the events listed above in the long-term trials table, events of probable, possible, or uncertain relationship to study drug that occurred in <2.0% of pravastatin-treated patients in the long-term trials included the following:

Dermatologic: scalp hair abnormality (including alopecia), urticaria.

Endocrine/Metabolic: sexual dysfunction, libido change.

General: flushing.

Immunologic: allergy, edema head/neck.

Musculoskeletal: muscle weakness.

Nervous System: vertigo, insomnia, memory impairment, neuropathy (including peripheral neuropathy).

Special Senses: taste disturbance.

6.2 Postmarketing Experience

In addition to the events reported above, as with other drugs in this class, the following events have been reported rarely during postmarketing experience with PRAVACHOL, regardless of causality assessment:

Musculoskeletal: myopathy, rhabdomyolysis.

Nervous System: dysfunction of certain cranial nerves (including alteration of taste, impairment of extraocular movement, facial paresis), 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).

Hypersensitivity: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, asthenia, photosensitivity, chills, malaise, toxic epidermal necrolysis, erythema multiforme (including Stevens-Johnson syndrome).

Gastrointestinal: abdominal pain, constipation, pancreatitis, hepatitis (including chronic active hepatitis), cholestatic jaundice, fatty change in liver, cirrhosis, fulminant hepatic necrosis, hepatoma, fatal and non-fatal hepatic failure.

Dermatologic: a variety of skin changes (e.g., nodules, discoloration, dryness of mucous membranes, changes to hair/nails).

Renal: urinary abnormality (including dysuria, frequency, nocturia).

Respiratory: dyspnea.

Reproductive: gynecomastia.

Laboratory Abnormalities: liver function test abnormalities, thyroid function abnormalities.

6.3 Laboratory Test Abnormalities

Increases in ALT, AST values and CPK have been observed [see *Warnings and Precautions (5.1, 5.2)*].

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with statins.

6.4 Pediatric Patients

In a 2-year, double-blind, placebo-controlled study involving 100 boys and 114 girls with HeFH (n=214; age range 8-18.5 years, 53% female, 95% Caucasians, <1% Blacks, 3% Asians, 1% Other), the safety and tolerability profile of pravastatin was generally similar to that of placebo. [See *Warnings and Precautions (5.3)*, *Use in Specific Populations (8.4)*, and *Clinical Pharmacology (12.3)*.]

7 DRUG INTERACTIONS

For the concurrent therapy of either cyclosporine, fibrates, niacin (nicotinic acid), or erythromycin, the risk of myopathy increases [see *Warnings and Precautions (5.1)* and *Clinical Pharmacology (12.3)*].

7.1 Cyclosporine

The risk of myopathy/rhabdomyolysis is increased with concomitant administration of cyclosporine. Limit pravastatin to 20 mg once daily for concomitant use with cyclosporine [see *Dosage and Administration (2.5)*, *Warnings and Precautions (5.1)*, and *Clinical Pharmacology (12.3)*].

7.2 Clarithromycin

The risk of myopathy/rhabdomyolysis is increased with concomitant administration of clarithromycin. Limit pravastatin to 40 mg once daily for concomitant use with clarithromycin

[see *Dosage and Administration (2.6)*, *Warnings and Precautions (5.1)*, and *Clinical Pharmacology (12.3)*].

7.3 Colchicine

The risk of myopathy/rhabdomyolysis is increased with concomitant administration of colchicine [see *Warnings and Precautions (5.1)*].

7.4 Gemfibrozil

Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are coadministered with gemfibrozil, concomitant administration of PRAVACHOL with gemfibrozil should be avoided [see *Warnings and Precautions (5.1)*].

7.5 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, PRAVACHOL should be administered with caution when used concomitantly with other fibrates [see *Warnings and Precautions (5.1)*].

7.6 Niacin

The risk of skeletal muscle effects may be enhanced when pravastatin is used in combination with niacin; a reduction in PRAVACHOL dosage should be considered in this setting [see *Warnings and Precautions (5.1)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

[See *Contraindications (4.3)*.]

Safety in pregnant women has not been established. Available data in women inadvertently taking pravastatin while pregnant do not suggest any adverse clinical events. However, there are

no adequate and well-controlled studies in pregnant women. Therefore, it is not known whether pravastatin can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Pravastatin should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus and patients have been informed of the potential hazards.

Rare reports of congenital anomalies have been received following intrauterine exposure to other statins. In a review[2] of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or lovastatin, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate to exclude a ≥3- to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. As safety in pregnant women has not been established and there is no apparent benefit to therapy with PRAVACHOL during pregnancy [see *Contraindications (4.3)*], treatment should be immediately discontinued as soon as pregnancy is recognized. PRAVACHOL should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.

Pravastatin was neither embryolethal nor teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 10 times (rabbit) or 120 times (rat) the human exposure at 80 mg/day maximum recommended human dose (MRHD) based on surface area (mg/m^2).

In pregnant rats given oral gavage doses of 4, 20, 100, 500, and 1000 mg/kg/day from gestation days 7 through 17 (organogenesis) increased mortality of offspring and skeletal anomalies were observed at 100 mg/kg/day systemic exposure, 10 times the human exposure at 80 mg/day MRHD based on body surface area (mg/m^2).

In pregnant rats given oral gavage doses of 10, 100, and 1000 mg/kg/day from gestation day 17 through lactation day 21 (weaning) increased mortality of offspring and developmental delays were observed at 100 mg/kg/day systemic exposure, 12 times the human exposure at 80 mg/day MRHD based on body surface area (mg/m^2).

8.3 Nursing Mothers

A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse [see *Contraindications (4.4)*].

Pravastatin crosses the placenta and is found in fetal tissue at 30% maternal plasma levels following a single 20 mg/kg dose given to pregnant rats on gestation day 18. Similar studies in lactating rats indicate secretion of pravastatin into breast milk at 0.2 to 6.5 times higher levels than maternal plasma at exposures equivalent to 2 times human exposure at the MRHD.

8.4 Pediatric Use

The safety and effectiveness of PRAVACHOL in children and adolescents from 8 to 18 years of age have been evaluated in a placebo-controlled study of 2 years duration. Patients treated with pravastatin had an adverse experience profile generally similar to that of patients treated with placebo with influenza and headache commonly reported in both treatment groups. [See *Adverse Reactions (6.4).*] **Doses greater than 40 mg have not been studied in this population.** Children and adolescent females of childbearing potential should be counseled on appropriate contraceptive methods while on pravastatin therapy [see *Contraindications (4.3)* and *Use in Specific Populations (8.1)*]. For dosing information [see *Dosage and Administration (2.3).*]

Double-blind, placebo-controlled pravastatin studies in children less than 8 years of age have not been conducted.

8.5 Geriatric Use

Two secondary prevention trials with pravastatin (CARE and LIPID) included a total of 6593 subjects treated with pravastatin 40 mg for periods ranging up to 6 years. Across these 2 studies, 36.1% of pravastatin subjects were aged 65 and older and 0.8% were aged 75 and older. The beneficial effect of pravastatin in elderly subjects in reducing cardiovascular events and in modifying lipid profiles was similar to that seen in younger subjects. The adverse event profile in the elderly was similar to that in the overall population. Other reported clinical experience has not identified differences in responses to pravastatin between elderly and younger patients.

Mean pravastatin AUCs are slightly (25%-50%) higher in elderly subjects than in healthy young subjects, but mean maximum plasma concentration (C_{max}), time to maximum plasma

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concentration (T_{max}), and half-life ($t_{½}$) values are similar in both age groups and substantial accumulation of pravastatin would not be expected in the elderly [see *Clinical Pharmacology (12.3)*].

Since advanced age (≥65 years) is a predisposing factor for myopathy, PRAVACHOL should be prescribed with caution in the elderly [see *Warnings and Precautions (5.1)* and *Clinical Pharmacology (12.3)*].

8.6 Homozygous Familial Hypercholesterolemia

Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that statins are less effective because the patients lack functional LDL receptors.

10 OVERDOSAGE

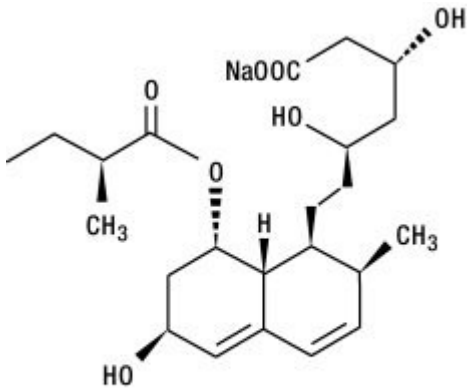
To date, there has been limited experience with overdosage of pravastatin. If an overdose occurs, it should be treated symptomatically with laboratory monitoring and supportive measures should be instituted as required.

11 DESCRIPTION

PRAVACHOL® (pravastatin sodium) is one of a class of lipid-lowering compounds, the statins, which reduce cholesterol biosynthesis. These agents are competitive inhibitors of HMG-CoA reductase, the enzyme catalyzing the early rate-limiting step in cholesterol biosynthesis, conversion of HMG-CoA to mevalonate.

Pravastatin sodium is designated chemically as 1-Naphthalene-heptanoic acid, 1,2,6,7,8,8a-hexahydro-β,δ,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-, monosodium salt, [1S-[1α(βS*,δS*),2α,6α,8β(R*),8aα]]-.

Structural formula:



$C_{23}H_{35}NaO_7$ MW 446.52

Pravastatin sodium is an odorless, white to off-white, fine or crystalline powder. It is a relatively polar hydrophilic compound with a partition coefficient (octanol/water) of 0.59 at a pH of 7.0. It is soluble in methanol and water (>300 mg/mL), slightly soluble in isopropanol, and practically insoluble in acetone, acetonitrile, chloroform, and ether.

PRAVACHOL is available for oral administration as 10 mg, 20 mg, 40 mg, and 80 mg tablets. Inactive ingredients include: croscarmellose sodium, lactose, magnesium oxide, magnesium stearate, microcrystalline cellulose, and povidone. The 10 mg tablet also contains Red Ferric Oxide, the 20 mg and 80 mg tablets also contain Yellow Ferric Oxide, and the 40 mg tablet also contains Green Lake Blend (mixture of D&C Yellow No. 10-Aluminum Lake and FD&C Blue No. 1-Aluminum Lake).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pravastatin is a reversible inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early and rate limiting step in the biosynthetic pathway for cholesterol. In addition, pravastatin reduces VLDL and TG and increases HDL-C.

12.3 Pharmacokinetics

General

Absorption: PRAVACHOL is administered orally in the active form. In studies in man, peak plasma pravastatin concentrations occurred 1 to 1.5 hours upon oral administration. Based on urinary recovery of total radiolabeled drug, the average oral absorption of pravastatin is 34% and absolute bioavailability is 17%. While the presence of food in the gastrointestinal tract reduces systemic bioavailability, the lipid-lowering effects of the drug are similar whether taken with or 1 hour prior to meals.

Pravastatin plasma concentrations, including area under the concentration-time curve (AUC), C_{max}, and steady-state minimum (C_{min}), are directly proportional to administered dose. Systemic bioavailability of pravastatin administered following a bedtime dose was decreased 60% compared to that following an AM dose. Despite this decrease in systemic bioavailability, the efficacy of pravastatin administered once daily in the evening, although not statistically significant, was marginally more effective than that after a morning dose.

The coefficient of variation (CV), based on between-subject variability, was 50% to 60% for AUC. The geometric means of pravastatin C_{max} and AUC following a 20 mg dose in the fasted state were 26.5 ng/mL and 59.8 ng*hr/mL, respectively.

Steady-state AUCs, C_{max}, and C_{min} plasma concentrations showed no evidence of pravastatin accumulation following once or twice daily administration of PRAVACHOL tablets.

Distribution: Approximately 50% of the circulating drug is bound to plasma proteins.

Metabolism: The major biotransformation pathways for pravastatin are: (a) isomerization to 6-epi pravastatin and the 3α-hydroxyisomer of pravastatin (SQ 31,906) and (b) enzymatic ring hydroxylation to SQ 31,945. The 3α-hydroxyisomeric metabolite (SQ 31,906) has 1/10 to 1/40 the HMG-CoA reductase inhibitory activity of the parent compound. Pravastatin undergoes extensive first-pass extraction in the liver (extraction ratio 0.66).

Excretion: Approximately 20% of a radiolabeled oral dose is excreted in urine and 70% in the feces. After intravenous administration of radiolabeled pravastatin to normal volunteers, approximately 47% of total body clearance was via renal excretion and 53% by non-renal routes (i.e., biliary excretion and biotransformation).

Following single dose oral administration of ^{14}C-pravastatin, the radioactive elimination $t_{½}$ for pravastatin is 1.8 hours in humans.

Specific Populations

Renal Impairment: A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SQ 31,906). Compared to healthy subjects with normal renal function, patients with severe renal impairment had 69% and 37% higher mean AUC and C_{max} values, respectively, and a 0.61 hour shorter $t_{½}$ for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945).

Hepatic Impairment: In a study comparing the kinetics of pravastatin in patients with biopsy confirmed cirrhosis (N=7) and normal subjects (N=7), the mean AUC varied 18-fold in cirrhotic patients and 5-fold in healthy subjects. Similarly, the peak pravastatin values varied 47-fold for cirrhotic patients compared to 6-fold for healthy subjects. [See *Warnings and Precautions (5.2)*.]

Geriatric: In a single oral dose study using pravastatin 20 mg, the mean AUC for pravastatin was approximately 27% greater and the mean cumulative urinary excretion (CUE) approximately 19% lower in elderly men (65-75 years old) compared with younger men (19-31 years old). In a similar study conducted in women, the mean AUC for pravastatin was approximately 46% higher and the mean CUE approximately 18% lower in elderly women (65-78 years old) compared with younger women (18-38 years old). In both studies, C_{max}, T_{max}, and $t_{½}$ values were similar in older and younger subjects. [See *Use in Specific Populations (8.5)*.]

Pediatric: After 2 weeks of once-daily 20 mg oral pravastatin administration, the geometric means of AUC were 80.7 (CV 44%) and 44.8 (CV 89%) ng*hr/mL for children (8-11 years, N=14) and adolescents (12-16 years, N=10), respectively. The corresponding values for C_{max} were 42.4 (CV 54%) and 18.6 ng/mL (CV 100%) for children and adolescents, respectively. No conclusion can be made based on these findings due to the small number of samples and large variability. [See *Use in Specific Populations (8.4)*.]

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Drug-Drug Interactions

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}
Cyclosporine 5 mg/kg single dose	40 mg single dose	↑282%	↑327%
Clarithromycin 500 mg BID for 9 days	40 mg OD for 8 days	↑110%	↑128%
Darunavir 600 mg BID/Ritonavir 100 mg BID for 7 days	40 mg single dose	↑81%	↑63%
Colestipol 10 g single dose	20 mg single dose	↓47%	↓53%
Cholestyramine 4 g single dose Administered simultaneously Administered 1 hour prior to cholestyramine Administered 4 hours after cholestyramine	20 mg single dose	 ↓40% ↑12% ↓12%	 ↓39% ↑30% ↓6.8%
Cholestyramine 24 g OD for 4 weeks	20 mg BID for 8 weeks 5 mg BID for 8 weeks 10 mg BID for 8 weeks	↓51% ↓38% ↓18%	↑4.9% ↑23% ↓33%
Fluconazole 200 mg IV for 6 days 200 mg PO for 6 days	 20 mg PO+10 mg IV 20 mg PO+10 mg IV	 ↓34% ↓16%	 ↓33% ↓16%
Kaletra 400 mg/100 mg BID for 14 days	20 mg OD for 4 days	↑33%	↑26%
Verapamil IR 120 mg for 1 day and Verapamil ER 480 mg for 3 days	40 mg single dose	↑31%	↑42%
Cimetidine 300 mg QID for 3 days	20 mg single dose	↑30%	↑9.8%
Antacids 15 mL QID for 3 days	20 mg single dose	↓28%	↓24%
Digoxin 0.2 mg OD for 9 days	20 mg OD for 9 days	↑23%	↑26%
Probucol 500 mg single dose	20 mg single dose	↑14%	↑24%
Warfarin 5 mg OD for 6 days	20 mg BID for 6 days	↓13%	↑6.7%
Itraconazole 200 mg OD for 30 days	40 mg OD for 30 days	↑11% (compared to Day 1)	↑17% (compared to Day 1)
Gemfibrozil 600 mg single dose	20 mg single dose	↓7.0%	↓20%
Aspirin 324 mg single dose	20 mg single dose	↑4.7%	↑8.9%
~~Nicotinic Acid~~Niacin 1 g single dose	20 mg single dose	↓3.6%	↓8.2%
Diltiazem	20 mg single dose	↑2.7%	↑30%

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}
Grapefruit juice	40 mg single dose	↓1.8%	↑3.7%

BID = twice daily; OD = once daily; QID = four times daily

Table 4: Effect of Pravastatin on the Pharmacokinetics of Coadministered Drugs

Pravastatin Dosing Regimen	Name and Dose	Change in AUC	Change in C_{max}
20 mg BID for 6 days	Warfarin 5 mg OD for 6 days Change in mean prothrombin time	↑17% ↑0.4 sec	↑15%
20 mg OD for 9 days	Digoxin 0.2 mg OD for 9 days	↑4.6%	↑5.3%
20 mg BID for 4 weeks 10 mg BID for 4 weeks 5 mg BID for 4 weeks	Antipyrine 1.2 g single dose	↑3.0% ↑1.6% ↑ Less than 1%	Not Reported
20 mg OD for 4 days	Kaletra 400 mg/100 mg BID for 14 days	No change	No change

BID = twice daily; OD = once daily

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p<0.01$). These effects in rats were observed at approximately 12 times the human dose (HD) of 80 mg based on body surface area (mg/m^2) and at approximately 4 times the HD, based on AUC.

In a 2-year study in mice fed pravastatin at doses of 250 and 500 mg/kg/day, there was an increased incidence of hepatocellular carcinomas in males and females at both 250 and 500 mg/kg/day ($p<0.0001$). At these doses, lung adenomas in females were increased ($p=0.013$). These effects in mice were observed at approximately 15 times (250 mg/kg/day) and 23 times (500 mg/kg/day) the HD of 80 mg, based on AUC. In another 2-year study in mice with doses up to 100 mg/kg/day (producing drug exposures approximately 2 times the HD of 80 mg, based on AUC), there were no drug-induced tumors.

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*; a forward mutation assay in L5178Y TK +/− mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a fertility study in adult rats with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance.

13.2 Animal Toxicology and/or Pharmacology

CNS Toxicity

CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day. These effects in dogs were observed at approximately 59 times the HD of 80 mg/day, based on AUC. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

When administered to juvenile rats (postnatal days [PND] 4 through 80 at 5-45 mg/kg/day), no drug related changes were observed at 5 mg/kg/day. At 15 and 45 mg/kg/day, altered body-weight gain was observed during the dosing and 52-day recovery periods as well as slight thinning of the corpus callosum at the end of the recovery period. This finding was not evident in rats examined at the completion of the dosing period and was not associated with any inflammatory or degenerative changes in the brain. The biological relevance of the corpus callosum finding is uncertain due to the absence of any other microscopic changes in the brain or peripheral nervous tissue and because it occurred at the end of the recovery period.

Reference ID: 3090896

Neurobehavioral changes (enhanced acoustic startle responses and increased errors in water-maze learning) combined with evidence of generalized toxicity were noted at 45 mg/kg/day during the later part of the recovery period. Serum pravastatin levels at 15 mg/kg/day are approximately ≥1 times (AUC) the maximum pediatric dose of 40 mg. No thinning of the corpus callosum was observed in rats dosed with pravastatin (≥250 mg/kg/day) beginning PND 35 for 3 months suggesting increased sensitivity in younger rats. PND 35 in a rat is approximately equivalent to an 8- to 12-year-old human child. Juvenile male rats given 90 times (AUC) the 40 mg dose had decreased fertility (20%) with sperm abnormalities compared to controls.

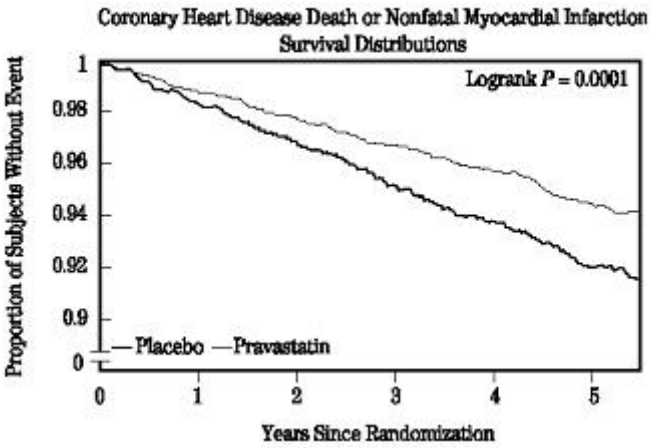
14 CLINICAL STUDIES

14.1 Prevention of Coronary Heart Disease

In the Pravastatin Primary Prevention Study (WOS),[3] the effect of PRAVACHOL on fatal and nonfatal CHD was assessed in 6595 men 45 to 64 years of age, without a previous MI, and with LDL-C levels between 156 to 254 mg/dL (4-6.7 mmol/L). In this randomized, double-blind, placebo-controlled study, patients were treated with standard care, including dietary advice, and either PRAVACHOL 40 mg daily (N=3302) or placebo (N=3293) and followed for a median duration of 4.8 years. Median (25^{th}, 75^{th} percentile) percent changes from baseline after 6 months of pravastatin treatment in Total-C, LDL-C, TG, and HDL-C were −20.3 (−26.9, −11.7), −27.7 (−36.0, −16.9), −9.1 (−27.6, 12.5), and 6.7 (−2.1, 15.6), respectively.

PRAVACHOL significantly reduced the rate of first coronary events (either CHD death or nonfatal MI) by 31% (248 events in the placebo group [CHD death=44, nonfatal MI=204] versus 174 events in the PRAVACHOL group [CHD death=31, nonfatal MI=143], p=0.0001 [see figure below]). The risk reduction with PRAVACHOL was similar and significant throughout the entire range of baseline LDL cholesterol levels. This reduction was also similar and significant across the age range studied with a 40% risk reduction for patients younger than 55 years and a 27% risk reduction for patients 55 years and older. The Pravastatin Primary Prevention Study included only men, and therefore it is not clear to what extent these data can be extrapolated to a similar population of female patients.

Reference ID: 3090896



PRAVACHOL also significantly decreased the risk for undergoing myocardial revascularization procedures (coronary artery bypass graft [CABG] surgery or percutaneous transluminal coronary angioplasty [PTCA]) by 37% (80 vs 51 patients, p=0.009) and coronary angiography by 31% (128 vs 90, p=0.007). Cardiovascular deaths were decreased by 32% (73 vs 50, p=0.03) and there was no increase in death from non-cardiovascular causes.

14.2 Secondary Prevention of Cardiovascular Events

In the LIPID[4] study, the effect of PRAVACHOL, 40 mg daily, was assessed in 9014 patients (7498 men; 1516 women; 3514 elderly patients [age ≥65 years]; 782 diabetic patients) who had experienced either an MI (5754 patients) or had been hospitalized for unstable angina pectoris (3260 patients) in the preceding 3 to 36 months. Patients in this multicenter, double-blind, placebo-controlled study participated for an average of 5.6 years (median of 5.9 years) and at randomization had Total-C between 114 and 563 mg/dL (mean 219 mg/dL), LDL-C between 46 and 274 mg/dL (mean 150 mg/dL), TG between 35 and 2710 mg/dL (mean 160 mg/dL), and HDL-C between 1 and 103 mg/dL (mean 37 mg/dL). At baseline, 82% of patients were receiving aspirin and 76% were receiving antihypertensive medication. Treatment with PRAVACHOL significantly reduced the risk for total mortality by reducing coronary death (see Table 5). The risk reduction due to treatment with PRAVACHOL on CHD mortality was consistent regardless of age. PRAVACHOL significantly reduced the risk for total mortality (by reducing CHD death) and CHD events (CHD mortality or nonfatal MI) in patients who qualified with a history of either MI or hospitalization for unstable angina pectoris.

Table 5: LIPID - Primary and Secondary Endpoints

	Number (%) of Subjects			
Event	**Pravastatin 40 mg (N=4512)**	**Placebo (N=4502)**	**Risk Reduction**	***p*-value**
Primary Endpoint				
CHD mortality	287 (6.4)	373 (8.3)	24%	0.0004
Secondary Endpoints				
Total mortality	498 (11.0)	633 (14.1)	23%	<0.0001
CHD mortality or nonfatal MI	557 (12.3)	715 (15.9)	24%	<0.0001
Myocardial revascularization procedures (CABG or PTCA)	584 (12.9)	706 (15.7)	20%	<0.0001
Stroke				
All-cause	169 (3.7)	204 (4.5)	19%	0.0477
Non-hemorrhagic	154 (3.4)	196 (4.4)	23%	0.0154
Cardiovascular mortality	331 (7.3)	433 (9.6)	25%	<0.0001

In the CARE[5] study, the effect of PRAVACHOL, 40 mg daily, on CHD death and nonfatal MI was assessed in 4159 patients (3583 men and 576 women) who had experienced a MI in the preceding 3 to 20 months and who had normal (below the 75th percentile of the general population) plasma total cholesterol levels. Patients in this double-blind, placebo-controlled study participated for an average of 4.9 years and had a mean baseline Total-C of 209 mg/dL. LDL-C levels in this patient population ranged from 101 to 180 mg/dL (mean 139 mg/dL). At baseline, 84% of patients were receiving aspirin and 82% were taking antihypertensive medications. Median (25th, 75th percentile) percent changes from baseline after 6 months of pravastatin treatment in Total-C, LDL-C, TG, and HDL-C were −22.0 (−28.4, −14.9), −32.4 (−39.9, −23.7), −11.0 (−26.5, 8.6), and 5.1 (−2.9, 12.7), respectively. Treatment with PRAVACHOL significantly reduced the rate of first recurrent coronary events (either CHD death or nonfatal MI), the risk of undergoing revascularization procedures (PTCA, CABG), and the risk for stroke or TIA (see Table 6).

Reference ID: 3090896

Table 6: CARE - Primary and Secondary Endpoints

	Number (%) of Subjects			
Event	**Pravastatin 40 mg (N=2081)**	**Placebo (N=2078)**	**Risk Reduction**	***p*-value**
Primary Endpoint				
CHD mortality or nonfatal MI[a]	212 (10.2)	274 (13.2)	24%	0.003
Secondary Endpoints				
Myocardial revascularization procedures (CABG or PTCA)	294 (14.1)	391 (18.8)	27%	<0.001
Stroke or TIA	93 (4.5)	124 (6.0)	26%	0.029

[a] The risk reduction due to treatment with PRAVACHOL was consistent in both sexes.

In the PLAC I[6] study, the effect of pravastatin therapy on coronary atherosclerosis was assessed by coronary angiography in patients with coronary disease and moderate hypercholesterolemia (baseline LDL-C range: 130-190 mg/dL). In this double-blind, multicenter, controlled clinical trial, angiograms were evaluated at baseline and at 3 years in 264 patients. Although the difference between pravastatin and placebo for the primary endpoint (per-patient change in mean coronary artery diameter) and 1 of 2 secondary endpoints (change in percent lumen diameter stenosis) did not reach statistical significance, for the secondary endpoint of change in minimum lumen diameter, statistically significant slowing of disease was seen in the pravastatin treatment group (p=0.02).

In the REGRESS[7] study, the effect of pravastatin on coronary atherosclerosis was assessed by coronary angiography in 885 patients with angina pectoris, angiographically documented coronary artery disease, and hypercholesterolemia (baseline total cholesterol range: 160-310 mg/dL). In this double-blind, multicenter, controlled clinical trial, angiograms were evaluated at baseline and at 2 years in 653 patients (323 treated with pravastatin). Progression of coronary atherosclerosis was significantly slowed in the pravastatin group as assessed by changes in mean segment diameter (p=0.037) and minimum obstruction diameter (p=0.001).

Analysis of pooled events from PLAC I, PLAC II,[8] REGRESS, and KAPS[9] studies (combined N=1891) showed that treatment with pravastatin was associated with a statistically significant reduction in the composite event rate of fatal and nonfatal MI (46 events or 6.4% for placebo versus 21 events or 2.4% for pravastatin, p=0.001). The predominant effect of pravastatin was to reduce the rate of nonfatal MI.

14.3 Primary Hypercholesterolemia (*Fredrickson* Types IIa and IIb)

PRAVACHOL is highly effective in reducing Total-C, LDL-C, and TG in patients with heterozygous familial, presumed familial combined, and non-familial (non-FH) forms of primary hypercholesterolemia, and mixed dyslipidemia. A therapeutic response is seen within 1 week, and the maximum response usually is achieved within 4 weeks. This response is maintained during extended periods of therapy. In addition, PRAVACHOL is effective in reducing the risk of acute coronary events in hypercholesterolemic patients with and without previous MI.

A single daily dose is as effective as the same total daily dose given twice a day. In multicenter, double-blind, placebo-controlled studies of patients with primary hypercholesterolemia, treatment with pravastatin in daily doses ranging from 10 to 40 mg consistently and significantly decreased Total-C, LDL-C, TG, and Total-C/HDL-C and LDL-C/HDL-C ratios (see Table 7).

In a pooled analysis of 2 multicenter, double-blind, placebo-controlled studies of patients with primary hypercholesterolemia, treatment with pravastatin at a daily dose of 80 mg (N=277) significantly decreased Total-C, LDL-C, and TG. The 25th and 75th percentile changes from baseline in LDL-C for pravastatin 80 mg were −43% and −30%. The efficacy results of the individual studies were consistent with the pooled data (see Table 7).

Treatment with PRAVACHOL modestly decreased VLDL-C and PRAVACHOL across all doses produced variable increases in HDL-C (see Table 7).

Table 7: Primary Hypercholesterolemia Studies: Dose Response of PRAVACHOL Once Daily Administration

Dose	Total-C	LDL-C	HDL-C	TG
Mean Percent Changes From Baseline After 8 Weeks[a]				
Placebo (N=36)	−3%	−4%	+1%	−4%
10 mg (N=18)	−16%	−22%	+7%	−15%
20 mg (N=19)	−24%	−32%	+2%	−11%
40 mg (N=18)	−25%	−34%	+12%	−24%
Mean Percent Changes From Baseline After 6 Weeks[b]				
Placebo (N=162)	0%	−1%	−1%	+1%
80 mg (N=277)	−27%	−37%	+3%	−19%

[a] A multicenter, double-blind, placebo-controlled study.

[b] Pooled analysis of 2 multicenter, double-blind, placebo-controlled studies.

In another clinical trial, patients treated with pravastatin in combination with cholestyramine (70% of patients were taking cholestyramine 20 or 24 g per day) had reductions equal to or greater than 50% in LDL-C. Furthermore, pravastatin attenuated cholestyramine-induced increases in TG levels (which are themselves of uncertain clinical significance).

14.4 Hypertriglyceridemia (*Fredrickson* Type IV)

The response to pravastatin in patients with Type IV hyperlipidemia (baseline TG >200 mg/dL and LDL-C <160 mg/dL) was evaluated in a subset of 429 patients from the CARE study. For pravastatin-treated subjects, the median (min, max) baseline TG level was 246.0 (200.5, 349.5) mg/dL (see Table 8.)

Table 8: Patients with *Fredrickson* Type IV Hyperlipidemia Median (25^{th}, 75^{th} percentile) % Change from Baseline

	Pravastatin 40 mg (N=429)	**Placebo (N=430)**
TG	−21.1 (−34.8, 1.3)	−6.3 (−23.1, 18.3)
Total-C	−22.1 (−27.1, −14.8)	0.2 (−6.9, 6.8)
LDL-C	−31.7 (−39.6, −21.5)	0.7 (−9.0, 10.0)
HDL-C	7.4 (−1.2, 17.7)	2.8 (−5.7, 11.7)
Non-HDL-C	−27.2 (−34.0, −18.5)	−0.8 (−8.2, 7.0)

14.5 Dysbetalipoproteinemia (*Fredrickson* Type III)

The response to pravastatin in two double-blind crossover studies of 46 patients with genotype E2/E2 and *Fredrickson* Type III dysbetalipoproteinemia is shown in Table 9.

Table 9: Patients with *Fredrickson* Type III Dysbetalipoproteinemia Median (min, max) % Change from Baseline

	Median (min, max) at Baseline (mg/dL)	Median % Change (min, max) Pravastatin 40 mg (N=20)
Study 1		
Total-C	386.5 (245.0, 672.0)	−32.7 (−58.5, 4.6)
TG	443.0 (275.0, 1299.0)	−23.7 (−68.5, 44.7)
VLDL-C[a]	206.5 (110.0, 379.0)	−43.8 (−73.1, −14.3)
LDL-C[a]	117.5 (80.0, 170.0)	−40.8 (−63.7, 4.6)

Table 9: Patients with *Fredrickson* Type III Dysbetalipoproteinemia Median (min, max) % Change from Baseline

	Median (min, max) at Baseline (mg/dL)	Median % Change (min, max) Pravastatin 40 mg (N=20)
HDL-C	30.0 (18.0, 88.0)	6.4 (−45.0, 105.6)
Non-HDL-C	344.5 (215.0, 646.0)	−36.7 (−66.3, 5.8)
[a] N=14		
	Median (min, max) at Baseline (mg/dL)	Median % Change (min, max) Pravastatin 40 mg (N=26)
Study 2		
Total-C	340.3 (230.1, 448.6)	−31.4 (−54.5, −13.0)
TG	343.2 (212.6, 845.9)	−11.9 (−56.5, 44.8)
VLDL-C	145.0 (71.5, 309.4)	−35.7 (−74.7, 19.1)
LDL-C	128.6 (63.8, 177.9)	−30.3 (−52.2, 13.5)
HDL-C	38.7 (27.1, 58.0)	5.0 (−17.7, 66.7)
Non-HDL-C	295.8 (195.3, 421.5)	−35.5 (−81.0, −13.5)

14.6 Pediatric Clinical Study

A double-blind, placebo-controlled study in 214 patients (100 boys and 114 girls) with heterozygous familial hypercholesterolemia (HeFH), aged 8 to 18 years was conducted for 2 years. The children (aged 8-13 years) were randomized to placebo (N=63) or 20 mg of pravastatin daily (N=65) and the adolescents (aged 14-18 years) were randomized to placebo (N=45) or 40 mg of pravastatin daily (N=41). Inclusion in the study required an LDL-C level >95th percentile for age and sex and one parent with either a clinical or molecular diagnosis of familial hypercholesterolemia. The mean baseline LDL-C value was 239 mg/dL and 237 mg/dL in the pravastatin (range: 151-405 mg/dL) and placebo (range: 154-375 mg/dL) groups, respectively.

Pravastatin significantly decreased plasma levels of LDL-C, Total-C, and ApoB in both children and adolescents (see Table 10). The effect of pravastatin treatment in the 2 age groups was similar.

Table 10: Lipid-Lowering Effects of Pravastatin in Pediatric Patients with Heterozygous Familial Hypercholesterolemia: Least-Squares Mean % Change from Baseline at Month 24 (Last Observation Carried Forward: Intent-to-Treat)[a]

	Pravastatin 20 mg (Aged 8-13 years) N=65	Pravastatin 40 mg (Aged 14-18 years) N=41	Combined Pravastatin (Aged 8-18 years) N=106	Combined Placebo (Aged 8-18 years) N=108	95% CI of the Difference Between Combined Pravastatin and Placebo
LDL-C	−26.04[b]	−21.07[b]	−24.07[b]	−1.52	(−26.74, −18.86)
TC	−20.75[b]	−13.08[b]	−17.72[b]	−0.65	(−20.40, −13.83)
HDL-C	1.04	13.71	5.97	3.13	(−1.71, 7.43)
TG	−9.58	−0.30	−5.88	−3.27	(−13.95, 10.01)
ApoB (N)	−23.16[b] (61)	−18.08[b] (39)	−21.11[b] (100)	−0.97 (106)	(−24.29, −16.18)

[a] The above least-squares mean values were calculated based on log-transformed lipid values.

[b] Significant at $p \leq 0.0001$ when compared with placebo.

The mean achieved LDL-C was 186 mg/dL (range: 67-363 mg/dL) in the pravastatin group compared to 236 mg/dL (range: 105-438 mg/dL) in the placebo group.

The safety and efficacy of pravastatin doses above 40 mg daily have not been studied in children. The long-term efficacy of pravastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

15 REFERENCES

1. Fredrickson DS, Levy RI, Lees RS. Fat transport in lipoproteins - An integrated approach to mechanisms and disorders. *N Engl J Med*. 1967;276: 34-44, 94-103, 148-156, 215-225, 273-281.

2. Manson JM, Freyssinges C, Ducrocq MB, Stephenson WP. Postmarketing surveillance of lovastatin and simvastatin exposure during pregnancy. *Reprod Toxicol*. 1996;10(6):439-446.

3. Shepherd J, Cobbe SM, Ford I, et al, for the West of Scotland Coronary Prevention Study Group (WOS). Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med*. 1995;333:1301-1307.

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

5. Sacks FM, Pfeffer MA, Moye LA, et al, for the Cholesterol and Recurrent Events Trial Investigators (CARE). The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med*. 1996;335:1001-1009.

6. Pitt B, Mancini GBJ, Ellis SG, et al, for the PLAC I Investigators. Pravastatin limitation of atherosclerosis in the coronary arteries (PLAC I): Reduction in atherosclerosis progression and clinical events. *J Am Coll Cardiol*. 1995;26:1133-1139.

7. Jukema JW, Bruschke AVG, van Boven AJ, et al, for the Regression Growth Evaluation Statin Study Group (REGRESS). Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic man with normal to moderately elevated serum cholesterol levels. *Circ*. 1995;91:2528-2540.

8. Crouse JR, Byington RP, Bond MG, et al. Pravastatin, lipids, and atherosclerosis in the carotid arteries: Design features of a clinical trial with carotid atherosclerosis outcome (PLAC II). *Control Clin Trials*. 1992;13:495-506.

9. Salonen R, Nyyssonen K, Porkkala E, et al. Kuopio Atherosclerosis Prevention Study (KAPS). A population-based primary preventive trial of the effect of LDL lowering on atherosclerotic progression in carotid and femoral arteries. *Circ*. 1995;92:1758-1764.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

PRAVACHOL® (pravastatin sodium) Tablets are supplied as:

10 mg tablets: Pink to peach, rounded, rectangular-shaped, biconvex with a “P” embossed on one side and “PRAVACHOL 10” engraved on the opposite side. They are supplied in bottles of 90 (NDC 0003-5154-05). Bottles contain a desiccant canister.

20 mg tablets: Yellow, rounded, rectangular-shaped, biconvex with a “P” embossed on one side and “PRAVACHOL 20” engraved on the opposite side. They are supplied in bottles of 90 (NDC 0003-5178-05). Bottles contain a desiccant canister.

40 mg tablets: Green, rounded, rectangular-shaped, biconvex with a “P” embossed on one side and “PRAVACHOL 40” engraved on the opposite side. They are supplied in bottles of 90 (NDC 0003-5194-10). Bottles contain a desiccant canister.

80 mg tablets: Yellow, oval-shaped tablet with “BMS” on one side and “80” on the other side. They are supplied in bottles of 90 (NDC 0003-5195-10). Bottles contain a desiccant canister.

16.2 Storage

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Keep tightly closed (protect from moisture). Protect from light.

17 PATIENT COUNSELING INFORMATION

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever [see *Warnings and Precautions (5.1)*].

It is recommended that liver enzyme tests be performed before the initiation of PRAVACHOL, and thereafter when clinically indicated. All patients treated with PRAVACHOL should be advised to promptly report any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice [see *Warnings and Precautions (5.2)*].

Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

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Rev ~~May 2011~~TBD

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019898Orig1s062

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:

Reference ID: 3093395

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

Reference ID: 3093395

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:

Best Available Copy

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) (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.*

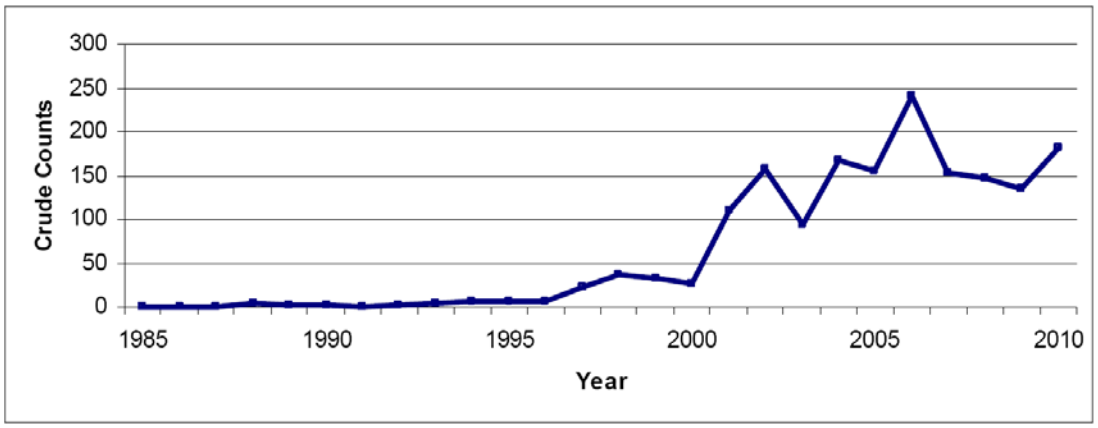
DMEP consulted OSE and requested that a review of AERS and the published literature be conducted to further assess the effect of statins on cognition. In 2002, OSE had performed a review of 279 statin reports associated with transient memory loss. This review had been requested by DMEP in response to 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), Amnestic 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:

Reference ID: 3093395

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.

Reference ID: 3093395

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)

[redacted]

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.

Reference ID: 3093395

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)

(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 ~~10 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:**

Reference ID: 3093395

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, 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*, or ~~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

*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 inhibitor~~s~~ 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 Cmax
10 mg, SD	Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	No change	No change
10 mg QD for 4 days	Fosamprenavir 1400 mg BID, 14 days	↓27%	↓18%
10 mg QD for 4 days	Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	No change	No change

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}
Darunavir 600 mg BID/Ritonavir 100 mg BID for 7 days	40 mg single dose	↑81%	↑63%
Kaletra 400 mg/100 mg BID for 14 days	20 mg OD for 4 days	↑33%	↑26%

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}
20 mg OD for 4 days	Kaletra 400 mg/100 mg BID for 14 days	No change	No change

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 Boceprevir Telaprevir Nefazodone	~~Avoid~~ Contraindicated 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 $AUC_{0\text{-last}}$, and simvastatin acid $AUC_{0\text{-last}}$ 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, boceprevir, 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 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 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	~~Avoid~~ Contraindicated with lovastatin
Gemfibrozil Cyclosporine	Avoid with lovastatin
~~Gembibrozil~~ ~~Other fibrates~~ ~~Lipid-lowering doses (≥1 g/day) of nicacin~~ ~~Cyclosporine~~ Danazol Diltiazem Verapamil	Do not exceed 20 mg lovastatin daily
Amiodarone ~~Verapamil~~	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 (≥ 1g/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-strengthÞ for 4 days	40 mg single dose	1.94	1.57
Cyclosporine	16	Not describedß	10 mg QD for 10 days	5- to 8-fold	NDà
	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 acide	
Diltiazem	10	120 mg BID for 14 days	20 mg	3 57è	

* 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

Þ 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

ß 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.

Reference ID: 3093395

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/s/

AMY G EGAN
02/27/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019898Orig1s062

OTHER REVIEW(S)

Division of Metabolic & Endocrine Drug Products

Labeling Review

Application Number: NDA 19-898/S-062

Name of Drug: Pravachol (pravastatin) Tablets

Sponsor: Bristol-Myers Squibb

Submission Date: September 27, 2011, submission; Final PI: February 17, 2012 (email)

Background and Summary:

Pravachol is indicated:

- Primary Prevention of Coronary Events
- Secondary Prevention of Cardiovascular Events
- Hyperlipidemia

It is supplied in the tablet dose strengths of 10, 20, 40 and 80 mg.

The last approved labeling supplement, S-061, was approved on May 18, 2011. This "Prior Approval" supplemental new drug application provided for changes in the format of the Pravachol package insert in response to the Physician's Labeling Rule (PLR).

Supplement-062 is a "Prior Approval" supplemental new drug application that provides for revisions to the **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS** sections of the Highlights of Prescribing Information section and changes to the **DOSAGE AND ADMINISTRATION**, **WARNINGS AND PRECAUTIONS**, **ADVERSE REACTIONS**, **DRUG INTERACTIONS**, **CLINICAL PHARMACOLOGY,** and **PATIENT COUNSELING INFORMATION** sections of the Full Prescribing Information sections of the Pravachol (pravastatin) 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 PI submitted by email on February 17, 2012, was accepted by Dr. Egan. The PI identifier number is 1292354A0. Agency will issue an approval letter on this submission.

Reviewed by: M.A. Simoneau, R.Ph., Regulatory Project Manager/February 23, 2012
(See appended electronic signature page)

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/s/

MARGARET A SIMONEAU
02/23/2012