CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 019898/S-061

Trade Name: **PRAVACHOL**

Generic Name: **Pravastatin Sodium**

Sponsor: **Bristol-Myers Squibb Company**

Approval Date: 05/18/2011

Indications: 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)

Indications:

- 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)

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 19898/S-061

SUPPLEMENT APPROVAL

Bristol-Myers Squibb Company
Attention: Mary Christian, Pharm. D., MBA
Group Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, N.J. 08543

Dear Dr. Christian:

Please refer to your Supplemental New Drug Application (sNDA) dated May 18, 2009, received May 18, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Pravachol (pravastatin sodium) Tablets.

We acknowledge receipt of your amendments dated November 18, 2010, March 11, and May 17, 2011 (by email).

The November 18, 2010, submission constituted a complete response to our November 18, 2009, action letter.

This "Prior Approval" supplemental new drug application provides for changes in the format of the Pravachol package insert in response to the Physician's Labeling Rule (PLR).

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
Division of Drug Marketing, Advertising, and Communications
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 Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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}

Eric Colman, M.D.
Deputy Director
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/

ERIC C COLMAN
05/18/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019898/S-061

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 19898/S-061 **COMPLETE RESPONSE**

Bristol-Myers Squibb Company
Attention: Madhu Anant, Ph.D.
Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, N.J. 08543

Dear Dr. Anant:

Please refer to your supplemental new drug application (sNDA) dated May 18, 2009, received May 18, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pravachol (pravastatin sodium) Tablets.

This supplemental new drug application proposes changes in the format of the Pravachol package insert in response to the Physician's Labeling Rule (PLR).

We have completed the review of your application and have determined that we cannot approve this application in its present form.

The safety information submitted to date is inadequate to update the **ADVERSE REACTIONS** section of the package insert. We refer to our July 10, 2009, email requesting additional information and to the October 8, 2009, telephone conference discussing this request. Additionally, we acknowledge your October 16, 2009, email informing us that the requested information would be submitted for review on February 17, 2010.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

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}

Eric Colman, M.D.
Deputy Director
Division of Metabolism and Endocrine Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-19898	SUPPL-61	BRISTOL MYERS SQUIBB	PRAVACHOL TABLETS

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

/s/

ERIC C COLMAN
11/18/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019898/S-061

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)
- Liver enzyme abnormalities and monitoring: persistent elevations in hepatic transaminase can occur. Monitor liver enzymes before and during treatment. (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: use with fibrate products may increase the risk of adverse skeletal muscle effects. (2.4, 5.1)
- 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

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.**

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.

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 $\geq$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	4.0	1.3	5.2	0.0	3.4	3.9
Fatigue	4.0	1.3	3.3	1.2	2.7	1.9

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
Chest Pain	4.0	2.6	1.9	0.6	2.0	0.7
Influenza						
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
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

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
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.

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)*].

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

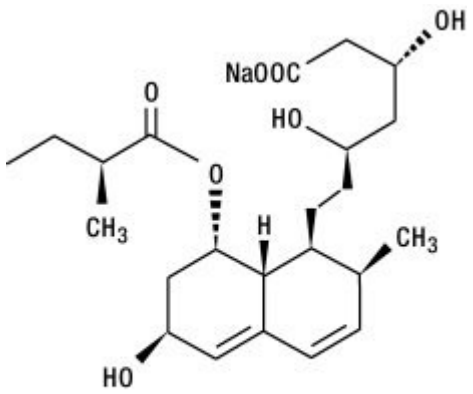
To date, there has been limited experience with overdosage of pravastatin. If an overdose occurs, it should be treated symptomatically with laboratory monitoring and supportive measures should be instituted as required.

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.

12.2 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%
Colestipol 10 g single dose	20 mg single dose	↓47%	↓53%
Cholestyramine 4 g single dose Administered simultaneously Administered 1 hour apart Administered 4 hours apart	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%
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 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 Chain 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

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.

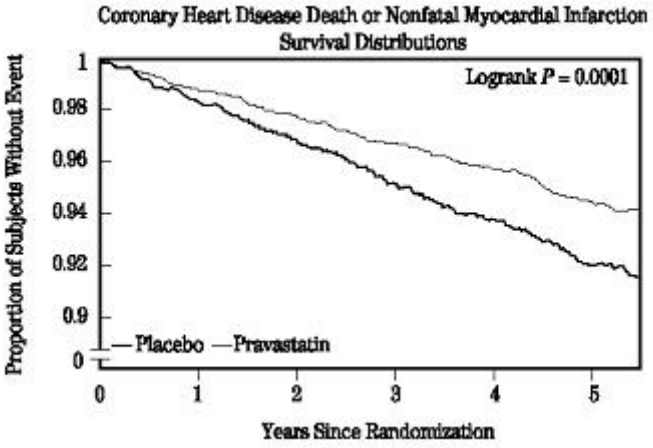
When administered to juvenile rats (postnatal days [PND] 4 through 80 at 5-45 mg/kg/day), no drug related changes were observed at 5 mg/kg/day. At 15 and 45 mg/kg/day, altered body-weight gain was observed during the dosing and 52-day recovery periods as well as slight thinning of the corpus callosum 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. 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

Table 5: LIPID - Primary and Secondary Endpoints

	Number (%) of Subjects			
Event	**Pravastatin 40 mg (N=4512)**	**Placebo (N=4502)**	**Risk Reduction**	***p*-value**
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).

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)

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)
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)
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≤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

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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)*].

Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

1186935A3
Rev May 2011

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/s/

ERIC C COLMAN
05/18/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019898/S-061

MEDICAL REVIEW(S)

MEMORANDUM

RE:	NDA 19-898/S-061, Pravachol Physician's Labeling Rule (PLR) conversion labeling supplement
Re-submission Date:	November 18, 2010
Due Date:	May 18, 2011

Please refer to this reviewer's memo dated November 17, 2009 regarding the original submission of the Pravachol PLR and the requests made to the company in order to harmonize the Adverse Reactions section of the label with other statin labels. The sponsor resubmitted the PLR label 1 year after the original CR action, and the division has made further clinical changes to be consistent with other statins. Notable changes are outlined here:

- The starting dose for renal impairment is 10 mg, but this dosing instruction has been removed from Dosage and Administration for patients with significant hepatic impairment (contraindication) or *a history* of renal or hepatic impairment (no clear justification).
- Adverse event tables have been redrawn to only include those events with an incidence > placebo in at least one dose group. This entailed excluding some events. The sponsor listed those adverse events removed form the tables that have been reported in the postmarketing setting and thought important to remain in the label [i.e., abdominal pain, constipation, urinary abnormality (including dysuria, frequency, nocturia), and dyspnea].
- Cognitive adverse events have been added to Postmarketing Experience (statin class labeling).
- Some fibrate language has been altered to be consistent with other statin labels. The following language was added to: Dosage and Administration, "The combination of statins and fibrates should generally be used with caution."; Warnings and Precautions, "**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.**"; and Drug Interactions, "**For the concurrent therapy of** … **fibrates** … **the risk of myopathy increases**…".

This PLR label is recommended for approval with the agreed-upon changes.

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/s/

JULIE K GOLDEN
05/17/2011

ERIC C COLMAN
05/17/2011

MEMORANDUM

RE:	NDA 19-898/S-061, Pravachol Physician's Labeling Rule (PLR) conversion labeling supplement
Submission Date:	May 18, 2009
Due Date:	November 18, 2009

In order to harmonize the content and format of the Pravachol PLR label with those of other statins recently converted to PLR (i.e., Zocor, Lipitor), we requested updates to the Adverse Reactions section (see Appendix A). These requests were sent to the firm by email July 10, 2009. A telephone conference was held with the firm October 8, 2009 discussing this request, and a follow-up email was received October 16, 2009, informing us that the requested information would be submitted for review on February 17, 2010.

The Clinical Pharmacology staff has also requested that the sponsor submit study synopses to substantiate the information provided in the submitted pravastatin-drug interaction table in Section (b) (4)

Because the requested information will not be available by the PDUFA date, the recommended action on this supplement is Complete Response. The submitted label has been reviewed. Appendix B includes recommended changes that will be incorporated into the revised label updated once the above requested information has been submitted and reviewed.

Appendix A.

Please note that Section 6 and its subheadings are called "Adverse Reactions"; however, it is intended to be a summary of adverse events from the clinical trials, regardless of causality. These sections may involve converting adverse event preferred terms from COSTART to MedDRA in order to include older and newer studies and to update the preferred terms.

Request 1. Update the information under Section 6.1 to include information as described below (highlighted). You can include this information separately under the short-term and long-term trials subsections.

In the PRAVACHOL placebo-controlled clinical trials database of (b) (4) *patients* (b) (4) *with a median treatment duration of* (b) (4) *weeks,* (b) (4) *of patients on PRAVACHOL and* (b) (4) *patients on placebo discontinued due to adverse reactions regardless of causality. The most common adverse reactions that led to treatment discontinuation and occurred at an incidence greater than placebo were:* (b) (4)

Please present adverse experiences reported in ≥2% of patients in placebo-controlled clinical studies, regardless of causality, in a table of short-term and a table of long-term studies. Include columns for placebo and all Pravachol doses individually and combined (if the only pravastatin dose used in the long-term trials was 40 mg then a table with placebo and pravastatin 40 mg only is acceptable; but events regardless of causality, occurring in ≥ 2% of patients should be included).

You should generate a list of adverse events that occurred in < 2% of patients in the long-term trials, similar to the list that is currently after Table 3. Serious, low-frequency adverse events generally will be listed when there is reason to suspect that the drug may have caused the event. Typical reasons to suspect causality for an event include (1) timing of onset or termination with respect to drug use, (2) plausibility in light of the drug's known pharmacology, (3) occurrence at a frequency above that expected in the treated population, and (4) occurrence of an event typical of drug-induced adverse reactions (e.g., liver necrosis, agranulocytosis, Stevens-Johnson syndrome). For serious events that are typical of drug-induced adverse reactions, the occurrence of even a single event could be a basis for inclusion in the list. When none of these reasons exist, however, an event should be excluded from the list. Non-serious, low-frequency adverse events should be listed only when there is strong evidence that the drug caused the event. Such evidence may include, for example, positive challenge/dechallenge tests or rate of occurrence in a large controlled trial that, although low, is markedly imbalanced between drug and control arms. Please provide a brief explanation for inclusion or deletion of terms from the list.

Request 2. Section 6.2 (Postmarketing Experience) may need to be updated, taking the above into consideration.

Request 3. Please provide the following information under 6.3 Pediatric Use:

In a 2-year, double-blind, placebo-controlled study involving (b) (4) *with HeFH (n=214;* (b) (4) *the safety and tolerability profile of pravastatin was generally similar to that of placebo.*

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-19898	SUPPL-61	BRISTOL MYERS SQUIBB	PRAVACHOL TABLETS

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/s/

JULIE K GOLDEN
11/17/2009

ERIC C COLMAN
11/17/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019898/S-061

CHEMISTRY REVIEW(S)

DIVISION OF POST-MARKETING VALUATION
Review of Chemistry, Manufacturing, and Controls

NDA # 19-898 **SUPPLEMENT**: SLR-061 REVIEW DATE: 09-Nov-2009

SUPPLEMENT(S) PROVIDE(S) FOR: proposed revisions to reformat the USP for Pravachol (pravastatin sodium) according to the Physician's Labeling Rule of January 2006.

TYPE of SUPPLEMENT:
☐ SUPAC ☐ CBE-0 ☐ CBE-30 ☒ Prior Approval ☐ Bundled Review ☐ Expedited Review

THE USER FEE GOAL DATE: 18-Nov-2009

SUBMISSION DATE	SUB. TYPE	DOC. DATE	CDER DATE	ASSIGNED DATE
18-May-2009	electronic	18-May-2009	18-May-2009	08-Jun-2009

NAME & ADDRESS OF APPLICANT:

Daniel J. Papa, Director Mature Brands,
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DRUG PRODUCT NAME:

Proprietary:	Pravachol®
Nonproprietary/Established/USAN:	Pravastatin sodium
Code Name/#:	SQ-31000
Chem. Type/Therapeutic Class:	1/S

DESI/PATENT STATUS: N/A

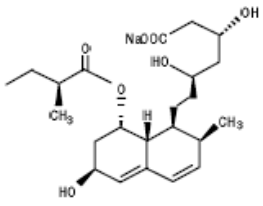
PHARMACOL. CATEGORY/INDICATION: Competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase/Lipid-lowering agent.

DOSAGE FORM: Tablet
STRENGTHS: 10, 20, 40, and 80 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: xx Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA(M.F.), MOLECULAR WEIGHT(M.W.):

Pravastatin sodium

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]]-.



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

SUPPORTING DOCUMENTS: N/A
RELATED DOCUMENTS (if applicable): N/A
CONSULTS: N/A

REMARKS/COMMENTS: (see review notes as well)

Revisions made in the section of Description, Dosage and Administration, Dosage Form and Strength, and Storage appear to be minor and acceptable. These changes are mainly for typographical expressions.

Therefore, from CMC standpoints, this supplement is approved.

CONCLUSIONS & RECOMMENDATIONS: **Approval**

Li-Shan Hsieh, Ph.D., Review Chemist,

James Vidra, Ph.D., Chief of Branch VII

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-19898	SUPPL-61	BRISTOL MYERS SQUIBB	PRAVACHOL TABLETS

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LI SHAN HSIEH
11/10/2009

JAMES D VIDRA
11/10/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019898/S-061

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**19-898**
SERIAL NUMBER:	**061**
SUBMISSION DATE:	**11/18/10**
PRODUCT:	**Pravachol (pravastatin)**
INTENDED CLINICAL POPULATION:	**treatment of hypercholesterolemia**
SPONSOR:	**Bristol-Myers Squibb**
REVIEW DIVISION:	**Division of Metabolism & Endocrinology**
PHARM/TOX REVIEWER:	**Davis-Bruno**
PHARM/TOX SUPERVISOR:	Davis-Bruno
DIVISION DIRECTOR:	**Parks**
PROJECT MANAGER:	**Simoneau**

TABLE OF CONTENTS

APPEARS THIS WAY ON ORIGINAL

EXECUTIVE SUMMARY

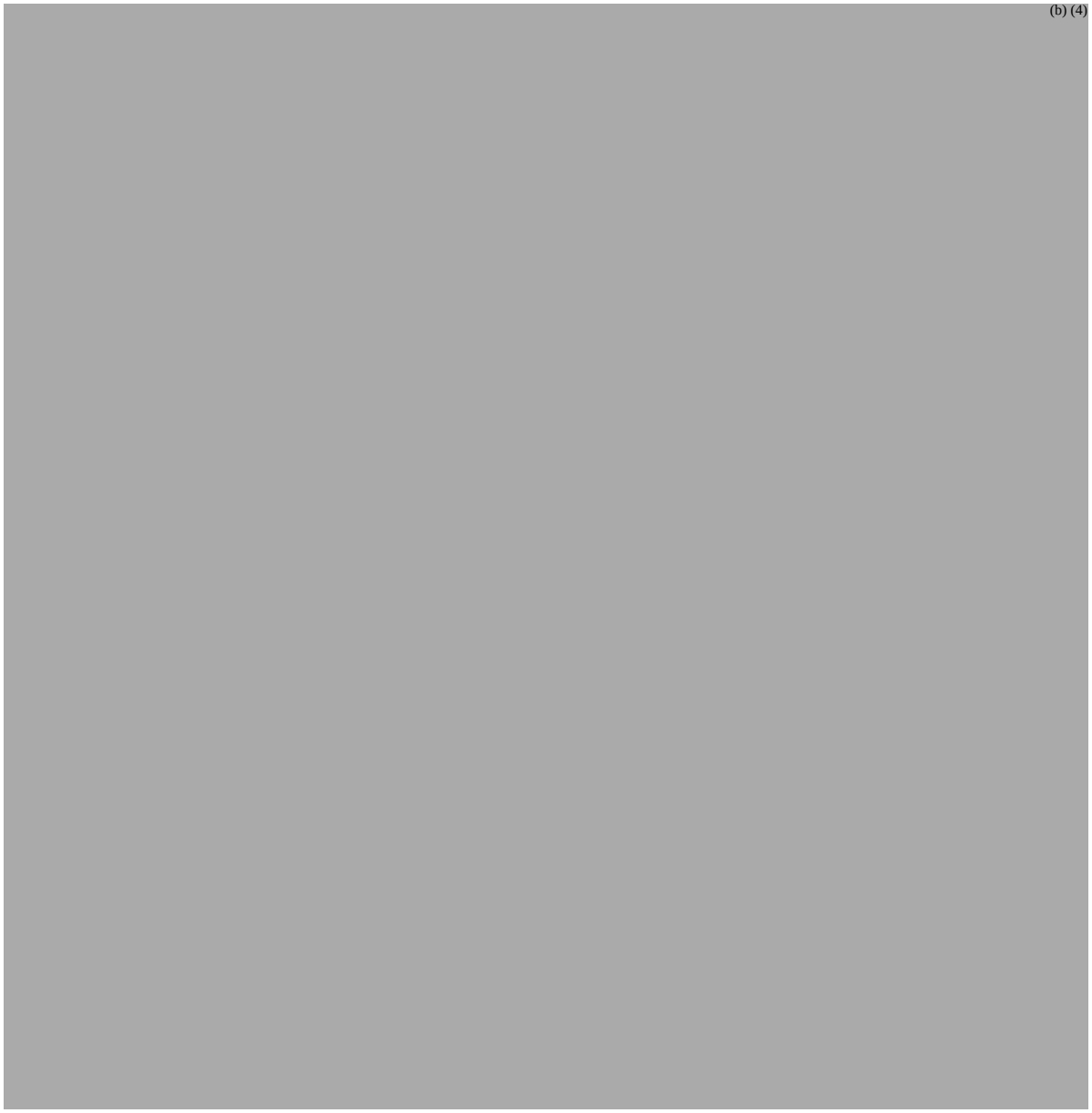
I. Recommendations

A. Recommendation on approvability: approvable pending labeling edits

B. Recommendation for nonclinical studies: none

C. Recommendations on labeling:

(b) (4)



II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: (b) (4)

Labeling Review: The sponsor indicates their intention to update the existing pravstatin label to reflect the findings from a new developmental neurotoxicity and reproductive toxicology study in neonatal rats in conjunction with PLR formatting changes. However there is disagreement regarding the pravastatin-induced effects on offspring mortality, ocular defects, skeletal anomalies and developmental delays in prior reproductive toxicology studies (b) (4) These differences are the focus of this review.

Pregnancy Category: (b) (4) . Pregnancy categories are generally determined in accordance with 21 CFR 201.57 as a function of the clinically relevant nonclinical data, and clinical data if available. The current designation of category X is based on animal developmental findings and the determination that potential human fetal risk outweighs the clinical benefit. Temporarily treating pregnant women for hypercholesterolemia does not have a clinical benefit. There are no well controlled studies in pregnant women. Some live-birth post-marketing reports following exposure to pravachol are without apparent adverse effects, however this data is too limited to provide any definitive conclusions. (b) (4) Therefore the most appropriate Pregnancy Category labeling for this product remains X; the original designation under NDA 190898 approval in 1991. (b) (4) a neonatal rat reproductive development study submitted Oct 2006 that is the focus of this review.

B. Pharmacologic activity: HMG CoA reductase inhibitor; see NDA 19-898 review

C. Nonclinical safety issues relevant to clinical use: findings in developmental reproductive toxicity and a specialized neurodevelopmental and reproductive neonatal rat study indicate adverse effects in myelination consistent with the known mechanism of action of this drug class. A clinical benefit of treating pregnant women for dyslipidemia provides no apparent clinical benefit and an unacceptable risk supporting a contraindication for use during pregnancy as original designated and labeled in the original NDA review.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 19-898
Review number: 5
Sequence number/date/type of submission: 061/IT
Information to sponsor: Yes (X) No ( )
Sponsor and/or agent: Bristol-Myers Squibb
Manufacturer for drug substance: Same

Reviewer name: **Davis-Bruno**
Division name: DMEP
HFD #: 510
Review completion date: April 2011

Drug:
Trade name: pravachol
Generic name: pravastatin

Relevant INDs/NDAs/DMFs: OMD 27, 201; (b) (4)

Drug class: HMG Co A reductase inhibitor

Intended clinical population: hypercholesterolemia

Clinical formulation: **see original NDA review**

Route of administration: oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

[For (b)(2) applications:

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of [NDA number] are owned by [name of sponsor] or are data for which [name of sponsor] has obtained a written right of reference. Any information or data necessary for approval of [NDA number] that [name of sponsor] does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness

for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that [name of sponsor] does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of [NDA number].]

Studies reviewed within this submission: N/A

Studies not reviewed within this submission: **N/A**
Note: For NDA reviews, all section headings should be included.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

2.6.2.2 Primary pharmacodynamics

2.6.2.3 Secondary pharmacodynamics

2.6.2.4 Safety pharmacology

2.6.2.5 Pharmacodynamic drug interactions

2.6.3 PHARMACOLOGY TABULATED SUMMARY

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

2.6.4.2 Methods of Analysis

2.6.4.3 Absorption

2.6.4.4 Distribution

2.6.4.5 Metabolism

2.6.4.6 Excretion

2.6.4.7 Pharmacokinetic drug interactions

2.6.4.8 Other Pharmacokinetic Studies

2.6.4.9 Discussion and Conclusions

2.6.4.10 Tables and figures to include comparative TK summary

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

Reproductive toxicology: Overview from standard reprotox battery in original NDA

Mortality in Teratology and Perinatal/Postnatal with Pravastatin:
Two rat teratology studies were performed. In the first study doses of 4, 20, 100 mg/kg/day were given by oral gavage GD7-17. Mortality PND 0-4 was 0%, 1%, 13% respectively and 9% in controls. In a second study, doses of 500, 1000 mg/kg/day were given and mortality PND 0-4 was 0.8%, 17% respectively and 8% in controls.

In a prenatal/postnatal developmental study, rats were given pravastatin at 0, 10, 100, 1000 mg/kg/day by oral gavage from GD 17-LD21. Neonatal mortality on PND 0-4 was 0, 0, 2.1, 0.5% respectively.

This forms the basis for the label change stating that pravastatin increased mortality in the offspring of rats given 100 mg/kg/day in teratology and perinatal/postnatal development studies.

(b) (4)

The elevation in mean pup mortality per litter in the first teratology study at 100 mg/kg/day (12.6%) is within 2% of the control value (8.3%). At 1000 mg/kg/day the pup morality rate of 17.2% is similar to the 100 mg/kg/day rate suggesting that a 10X increase in dose did not impact the mortality. While it is acknowledged that the increased mortality is not dose-dependent it may be dose-related and 100 mg/kg/day may reflect a threshold for this effect.

Skeletal Abnormalities in Teratology and Perinatal/Postnatal Studies w/Pravastatin:

Two rat teratology studies were performed. In the first study doses of 0, 4, 20, 100 mg/kg/day were given by oral gavage GD7-17. Increased cervical rib splitting (variation) was 2.7%, 2.1%, 3.7%, 6.4% respectively. In addition lumbar rib splitting (variation) was observed at 6.4%, 2.1%, 2.8%, 7.3% and increased sternebrae fusion (malformation)

was observed at 0, 0, 0, 0.9% respectively. In a second study doses of 0, 500, 1000 mg/kg/day were given and increased cervical rib splitting was 0, 1.5%, 3.3%. In addition 14th rib incidence was observed at 7.1%, 4.6%, 9.8 % respectively.

This forms the basis for the label change stating that pravastatin increased skeletal anomalies in the offspring of rats given 100 mg/kg/day in teratology studies.

[redacted] (b) (4) The fetal and litter incidences of extra lumbar rigs (14 ribs) were elevated in all groups in both teratology studies. However since the litter incidences were ~30% in controls and 50% at 1000 mg/kg/day it was considered a background lesion by the sponsor. While it is acknowledged that the increased skeletal anomalies is not dose-dependent it may be dose-related and 100 mg/kg/day may reflect a threshold for this effect.

Visceral Abnormalities in Teratology and Perinatal/Postnatal Studies w/Pravastatin:

The proposed label changes indicated that in perinatal/postnatal developmental studies in rats given 10, 100, 1000 mg/kg/day GD7-LD21 increased [redacted] (b) (4) developmental delays [redacted] (b) (4) at doses of 100 mg/kg/day.

[redacted] (b) (4) microphthamia occurred in the second teratology study where pregnant rats were given 0, 500, 1000 mg/kg/day from GD7-17 which is the period of organogenesis. The incidence of this finding was 0, 0, 1.3% (13.6% litters) where the increase was observed at 1000 mg/kg/day but not at lower doses. Since the control group in the first teratology study showed a higher incidence (15%) by litter than the 1000 mg/kg/day treated group it suggested to the sponsor that this finding was within background levels. Anophthalmia which was considered a more sever expression of microphthalmia was observed at 4 mg/kg/day in the first teratology study which the sponsor attributes to a genetic defect endemic to the strain of rat supplied to the test facility during the interval of the study performance.

[redacted] (b) (4)

Developmental landmark delays (vaginal opening, testes descent and ear separation) occurred at doses of 100 mg/kg/day in peri-natal/postnatal developmental studies where pregnant rats were given Pravastatin by oral gavage GD17-LD21. [redacted] (b) (4)

PRAVASTATIN - Reproductive Toxicology Studies

Naturally Delivered Pups	1ST TERATOLOGY STUDY				2ND TERATOLOGY STUDY		
Dose (mg/kg/day, GD 7-17)	0 mg/kg/day	4 mg/kg/day	20 mg/kg/day	100 mg/kg/day	0 mg/kg/day	500 mg/kg/day	1000 mg/kg/day
Mean % Pups Percent Meeting Criterion							
Separation Ear Auricula							
PND 3	24.5%	26.1%	18.9%	33.6%	3.3%	8.4%	5.5%
PND 5	100%	100%	100%	100%	98.9%	99.0%	98.8%
Testes Descent							
PND 26	9.5%	8.7%	8.3%	15.9%	16.7%	16.0%	14.0%
PND 30	100%	97.8%	97.9%	100%	100%	100%	97.7%
Vaginal Opening							
PND 40	39.5%	37.8%	31.3%	31.8%	72.9%	75.8%	82.5%
PND 48	100%	100%	100%	100%	100%	100%	100%

	PERINATAL/POSTNATAL STUDY		
Naturally Delivered Pups			
Dose (mg/kg/day; GD 17-LD21)	0 mg/kg/day	10 mg/kg/day	100 mg/kg/day	1000 mg/kg/day
Mean % Pups Percent Meeting Criterion				
Separation Ear Auricula				
PND 3	8.9%	8.2%	6.2%	14.7%
PND 5	100%	100%	100%	100%
Testes Descent				
PND 26	12.2%	7.9%	11.8%	6.8%
PND 30	100%	100%	100%	100%
Vaginal Opening				
PND 40	84.0%	85.5%	76.8%	77.3%
PND 48	100%	100%	100%	100%

GD = Gestation Day LD = Lactation Day PND = Postnatal Day

Labeling Review

The sponsor indicates their consent to update the existing pravstatin label to reflect the findings from the developmental neurotoxicity study in rats and that the proposed labeling accurately represents the findings of this study. However there is disagreement regarding the Pravastatin-induced effects on offspring mortality, ocular defects, skeletal anomalies and developmental delays in prior reproductive toxicology studies. (b) (4)

[redacted]

The following is the current approved (June 2005) pregnancy category labeling (S# 058)

Pregnancy Category X.

See **CONTRAINDICATIONS**.

Safety in pregnant women has not been established. Pravastatin was not 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 10X (rabbit) or 120X (rat) the human exposure based on surface area ($mg/meter^2$). Rare reports of congenital anomalies have been received following intrauterine exposure to other HMG-CoA reductase inhibitors. In a review[9] 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 only to exclude a three-to-four-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**), treatment should be immediately discontinued as soon as pregnancy is recognized. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.

Animal fetal/neonatal findings are observed consisting of: increased fetal/neonatal mortality, and skeletal anomalies at >10X therapeutic exposures when rat dams are exposed to drug during organogenesis (GD7-17). When dosing occurs in the peri-/post-natal developmental period from GD17-LD21 in rats, increased pup mortality, microphthalmia (malformation) and developmental delays in vaginal opening, testes decent, separation (unfolding) of the ears are observed at doses ≤ 100 mg/kg/day in the absence of maternal toxicity suggesting that the developmental NOAEL was < 10 mg/kg/day or systemic exposure similar to that achieved with an 80 mg clinic dose based on mg/M^2 comparisons. This suggests that Pravastatin may be developmentally toxic at lower doses than previously acknowledged at least in the rat. Teratogenicity is not observed with Pravastatin in the rat and rabbit. In embryo-fetal development in the rabbit with dosing GD13-18, maternal toxicity is observed at 50 mg/kg/day without any adverse effects on development suggesting a developmental NOAEL=50 mg/kg/day or 10X MRHD based on body surface area comparisons. The results in the rabbit are consistent with the currently approved label.

Studies performed since the marketing approval in 1991 consist of direct dosing neonatal rats PND 4-80 to specifically address neurodevelopmental events (e.g. myelination) which occurs *in utero* in humans but postnatal in the rat. This type of developmental event are not adequately assessed in the standard reproductive toxicity studies described above. Decreased thickness of the corpus callosum was observed at 20X systemic exposure following an 80 mg clinical dose. At higher exposures (40X) this finding in conjunction with decreased relative brain weights and functional alterations in reflex response (acoustical

startle) and learning (watermaze) are observed. Together these studies indicate a perturbation in myelination. The NOAEL of 5 mg/kg/day or 5X systemic exposure following an 80 mg human dose (AUC=281 fasted; 176 ng h/ml with food) was established in the rat neonatal neurodevelopmental study

TABLE 68

PRAVASTATIN SODIUM

Disposition of Orally Administered ^{14}C-Pravastatin (20 mg/kg) in Male and Female Rats (N = 5 per sex)[b]

Parameter	Male	Female
C_{max} (µg-eq./ml)	2	1.5
AUC (µg-eq./ml)	23	16
Biliary Excretion[a] (% of dose)	58	62
Biotransformation Profile in Bile (% of Radioactivity)		
^{14}C-Pravastatin	47	61
Polar Metabolites	22	9
SQ 31,945	6	2
SQ 31,906	10	15
SQ 31,360	2	3
Lactones	2	2
Others	11	8

[a] For bile-duct-cannulated rats, N = 3 per sex. Percentage of dose excreted in 0 to 24 hr.

[b] Reference #88

TABLE 69

PRAVASTATIN SODIUM

Mean Pharmacokinetic Parameters for Pravastatin in the Plasma or Serum of Laboratory Animals After Oral Doses

Species	N	Dose (mg/kg)	T_{max} (hr)	C_{max} (µg/ml)	AUC (µg x hr/ml)
Rat	5	500	0.14	0.85	4.56
Dog	7	12.5	0.9	2.6	9.4
	6	25	1.4	4.1	16.6
	6	50	1.0	16.4	29.6
	2	100	0.8	31.9	54.7
	6	100	1.3	13.4	35.0
	6	200	1.0	44.0	96.0
	6	400	1.2	47.5	134
Rabbit	4	25	0.63	0.24	0.80
	4	100	1.0	1.1	3.70
	4	400	0.88	4.6	13.4
Monkey	3	50	1.2	0.20	0.63
	3	200	0.8	0.67	1.3
	3	800	1.0	2.2	4.8
Man[a]	36	ca. 0.14	1.3	9.2	0.022
		ca. 0.28	1.1	19.0	0.044
		ca. 0.57	1.3	43.0	0.093

[a] For man, the actual doses were 10, 20, and 40 mg.

Table 1: Definitive GLP Reproductive Safety Studies with Pravastatin

Species	Route/Study	Doses Evaluated	Primary Endpoints Evaluated
Rat	Oral/Mating & Fertility[4]	20, 100 & 500 mg/kg for 9 weeks prior to mating (males) and 2 weeks prior to mating through Gestation Day 7 (females)	Mating, fertility, reproductive function, & gestation
Rat	Oral/Embryo-Fetal Development[5,6]	4, 20, 100, 500, & 1000 mg/kg on Gestation Days 7 to 17	Embryo-fetal viability, gender, & body weight; fetal gross external, visceral, & skeletal development
Rabbit	Oral/Embryo-Fetal Development[7]	12.5, 25, & 50 mg/kg on Gestation Days 6 to 18	Embryo-fetal viability, gender, & body weight; fetal gross external, visceral, & skeletal development
Rat	Oral/Perinatal & Postnatal Development[8]	10, 100, & 1000 mg/kg on Gestation Day 17 through Lactation Day 21	Pup viability at birth, post-natal survival, appearance, growth, sexual maturation, sensory perception, motor activity, learning, memory, & reproductive function.

Table 2: Relative Exposures to Pravastatin in Definitive GLP Reproductive and Developmental Safety Studies

Species	Route/Study	Doses (mg/kg)	NOEL/LOAEL Dose[a] (mg/kg)		Multiple of Human Exposures at a dose of 80 mg
Rat	Oral/Fertility[4]	20, 100 & 500	NOEL	500	60 X[b]
Rat	Oral/Embryo-Fetal Development[5,6]	4, 20, 100, 500, & 1000	NOEL	1000	120 X[b]
Rabbit	Oral/Embryo-Fetal Development[7]	12.5, 25, & 50	NOEL	50	10 X[b]
Rat	Oral/Perinatal & Postnatal Development[8]	10, 100, & 1000	NOEL	1000	120 X[b]
Rat	Oral/Developmental Neurotoxicity[12]	5, 15, & 45	NOEL LOAEL	5 15	5 X[c] 19 X[c]

Rat Fertility: No maternal/paternal toxicity and no adverse findings in F1; parental and developmental NOAEL=500 mg/kg/day or 60X systemic exposure following an 80 mg therapeutic dose based on mg/M^2 comparisons.

Rat Embryo-Fetal Development: The initial study assessed oral gavage doses of 4, 20, 100 mg/kg/day from GD7-17. The sponsor states there were no effects in either the Fo or F1 rats and therefore a second study was performed using 500 and 1000 mg/kg/day. (b) (4) [redacted] the increase in non-fostering dams at 1000 mg/kg/day might be suggestive of maternal toxicity and explain the decrease in neonatal survival PND 0-4 in the second study. However confounding maternal toxicity does not explain the increased mortality and skeletal anomalies at lower doses. The NOAEL for pup mortality is 20 mg/kg/day or 2X systemic exposure following an 80 mg clinical dose based on mg/M^2 comparisons. The NOAEL for skeletal variations is 4 mg/kg/day or systemic exposures below those expected from an 80 mg clinical dose based on mg/ M^2 comparisons. Alterations in the sex ratio are observed at all doses. Although not statistically significant, a delay in the acquisition of the avoidance response in males is observed at 100 mg/kg/day which was similarly seen in the Segment 3 study. However this effect is not observed in the Segment 2 study at doses >100 mg/kg/day suggesting that this finding is not dose related.

Findings Study 1	0 mg/kg/day	4 mg/kg/day	20 mg/kg/day	100 mg/kg/day
Cesarean GD 21 Decreased sex ratio M/F	1.09	1.08	0.89	0.80
Live Births				
Birth rate (neonate/conceptuses)	97.5%	96.6%	97.7%	93%
Stillborn	0	1.8%	0.8%	0.8%
Increased cervical rib splitting (variation) Lumbar rib splitting (variation)	2.7% 6.4%	2.1% 2.1%	3.7% 2.8%	6.4% 7.3%
Malformation:Fusion of sternebrae	0	0	0	0.9%
Mortality PND0-4	9%	0%	1%	13%
Acquisition of avoidance response in shuttle box @5 min. M,F	20.6 % 16.5%	24% 22.3%	25.8% 22.4%	17.5% 18.4%

Findings Study 2	0 mg/kg/day	500 mg/kg/day	1000 mg/kg/day
Cesarean GD 21 sex ratio M/F	0.84	0.98	1.29
Live births			
Birth rate	86.8%	92.3%	92.4%
Sex ratio M/F	0.87	0.93	1.13
Malformation: situs inversus of esophagus	0	0	0.9%
Malformation: microphthalmia	0*	0	1.3%
14^{th} rib	7.1%	4.6%	9.8%
Increased cervical rib splitting (variation)	0	1.5%	3.3%
Mortality PPD 0-4 Nonfostering dams	8% 7.7%	0.8% 0	17% 15.4%

* 0.4% brachydactyly + kinky tail

Rabbit Embryo-Fetal Development: Decreased maternal food consumption (-22%) during GD 13-18 at 50 mg/kg/day suggests maternal toxicity in the absence of developmental effects. Developmental NOAEL=50 mg/kg/day or 10X MRHD based on body surface area comparisons.

Rat Perinatal-Postnatal Development: The sponsor notes no effect at 10 and 100 mg/kg/day on Fo or F1 generation rats. At 1000 mg/kg/day maternal toxicity is observed consisting of reduced maternal body weight and food consumption without affecting F1 or F2 generation rats leading the sponsor to suggest a developmental NOAEL=1000 mg/kg/day at systemic exposures 120X those from an 80 mg clinical dose based on body surface area comparisons. However altered sex ratios, increased pup mortality, microphthalmia (malformation) and developmental delays in vaginal opening, testes decent, separation (unfolding) of the ears are observed at doses ≤ 100 mg/kg/day in the absence of maternal toxicity suggesting that the developmental NOAEL was < 10 mg/kg/day or systemic exposure similar to that achieved with an 80 mg clinic dose based on mg/M^2 comparisons.

Findings GD17-LD21	0 mg/kg/day	10 mg/kg/day	100 mg/kg/day	1000 mg/kg/day
Neonatal wt.(g)	5.07	4.99	4.98	4.88
Microphthalmia	0/202	1/255	1/243	0/191
# neonates/dam	202	255	243	191
Male/Female	1.27	0.69*	1.01	0.97
Neonate mortality PND0-4	0	0	2.1%	0.5%
Separation of ear auricular PND3	8.9%	8.2%	6.2%	14.7%
Testes descent PND26	12.2%	7.9%	11.8%	6.8%
Opening vagina PND 40	84%	85.5%	76.8%	77.3%
Acquisition of avoidance response in shuttle box @5 min. M,F	20.9 % 7.4%	25.8% 18.3%	19.6% 16.4%	17.3% 19.1%

Placental transfer and secretion of Pravastatin into milk was examined in pregnant and lactating rats respectively. Pregnant dams were dosed GD 18 with a single dose of 20 mg/kg. The plasma Cmax of 1.35 μg/ml was achieved at 1 h post-dose in the dams whereas in the pups the Cmax was lower (0.4 μg/ml) at the same timepoint. Although Pravastatin is generally considered hydrophilic in nature and more hepatoselective than other statins, pup brain exposure is demonstrated, reaching Cmax=0.46 μg/g 6 h after dosing the dams.

Placental Transfer of ^{14}C-Pravastatin[a]

Selected Data for Tissue Concentrations of Radioactivity After Oral Administration of ^{14}C-Pravastatin (20 mg/kg) to Pregnant (Day 18), Fasting Rats

	Concentration of Radioactivity (µg-eq. of Pravastatin/g or ml)		
	1 hr	6 hr	24 hr
Maternal			
Blood	0.98 (0.7)[b]	0.47 (0.7)	0.16 (0.8)
Plasma	1.35 (1.0)	0.69 (1.0)	0.20 (1.0)
Cerebrum	0.51 (0.4)	0.31 (0.5)	0.15 (0.8)
Liver	15.5 (11.5)	2.83 (4.1)	0.93 (4.7)
Kidney	2.87 (2.1)	1.02 (1.5)	0.51 (2.6)
Fetal			
Blood	0.40 (0.3)	0.31 (0.5)	0.19 (1.0)
Brain	0.32 (0.2)	0.46 (0.7)	0.35 (1.8)
Liver	0.74 (0.6)	1.24 (1.8)	0.72 (3.6)
Kidney	0.53 (0.4)	0.68 (1.0)	0.42 (2.1)
Fetus	0.49 (0.4)	0.57 (0.8)	0.41 (2.1)

a Reference #106
b Figure in ( ) = ratio of concentration in tissue to that in maternal plasma.

Lactating dams were given a single dose of 20 mg/kg Pravastatin on PPD 12 which resulted in peak plasma levels of 0.47 µg/ml one hour after dosing and maximal milk levels of 1.4 µg/ml 24 h post-dosing. This exposure level of Pravastatin is similar to plasma levels achieved in neonatal rats direct dosed with 10 mg/kg/day at PND 7 and 25 mg/kg/day at PND 21.

Mean Concentrations of Radioactivity in Milk and Plasma After Oral Administration of ^{14}C-Pravastatin (20 mg/kg) to Non-Fasting, Lactating Rats[a]

Time (hr)	Concentration of Radioactivity (µg equiv. of Pravastatin/ml)	
	Milk	Plasma
0.5	0.08 (0.18)	0.45
1	0.18 (0.38)	0.47
6	0.79 (2.03)	0.39
24	1.36 (6.48)	0.21
48	0.28 (3.11)	0.09
72	N.D.	N.D.

( ): The ratio of concentration in milk to that in plasma.
N.D.: Not detected.
Limit of Detectability: Milk - 0.10 µg-eq./ml
Plasma - 0.09 µg-eq./ml.

An investigative study (Document Control No. 920002593; 1998) was performed in rats fed a 2% cholesterol diet to remove any contribution of maternal cholesterol synthesis, and then compared Pravastatin and Lovastatin on fetal cholesterol biosynthesis (total, liver, brain) during early (GD11) and late gestation (GD18). Pravastatin was less potent than lovastatin in inhibiting total cholesterol synthesis in GD 11 fetuses. At a teratogenic dose of 900 mg/kg, lovastatin produced 82% inhibition whereas only 39% inhibition was seen with pravastatin at the same dose. Treatment of dams on GD11 with lovastatin produced equivalent inhibition of both fetal liver and brain cholesterol synthesis at doses 50, 100 mg/kg/day however Pravastatin required higher doses; of 300 mg/kg/day to produce a primarily hepatoselective cholesterol inhibition (79% liver compared to 26% in brain) in the fetuses. However when this study was repeated in GD 18 fetuses with 800 mg/kg lovastatin or pravastatin, 80% inhibition of total cholesterol synthesis was observed, with similar inhibition in liver; 61% with lovastatin and 73% with Pravastatin. The greatest difference was in brain cholesterol biosynthesis with 73% inhibition with lovastatin and 54% with Pravastatin. Interestingly Pravastatin and Lovastatin were equipotent inhibitors of cholesterol synthesis in non-gravid female rats with ED_{50}=0.75 mg/kg given by acute oral dosing.

2.6.6.2 Single-dose toxicity

2.6.6.3 Repeat-dose toxicity

2.6.6.4 Genetic toxicology

2.6.6.5 Carcinogenicity

2.6.6.6 Reproductive and developmental toxicology

2.6.6.7 Local tolerance

2.6.6.8 Special toxicology studies –Juvenile studies submitted after the original NDA to assess neurobehavior and reproductive development in neonatal animals

Pravastatin/Atorvastatin: Oral Range-Finding Study of Neurobehavioral Development in Juvenile Rats

Key study findings:

Pravastatin - 50 and 100 mg/kg

1. Decreased body-weight gain (as much as 20% less than controls) from postnatal days (PNDs) 14 to 21 at 50 mg/kg and PNDs 4 to 28 at 100 mg/kg.
2. Increased food consumption (as much as 16% higher than controls) during the first two weeks postweaning (PNDs 28 to 42) in males at 50 mg/kg and the entire three-week postweaning period (PNDs 28 to 48) in males and females at 100 mg/kg.

Pravastatin - 100 mg/kg

1. Two males and four females found dead or euthanatized in moribund condition.
2. Clinical observations of ungroomed and sparse hair coat.
3. Enhanced acoustic startle response on PND 47.

Pravastatin - 500 and 1000 mg/kg

Discontinued on PNDs 5 through 9 due to excessive toxicity (death and morbundity). Clinical signs of black discoloration of the head noted in numerous pups were confirmed as darkened areas of the brain at necropsy.

Atorvastatin - 20 mg/kg

No drug-related changes.

Atorvastatin - 100 mg/kg

1. Seventeen and 12 females found dead or euthanatized in moribund condition.
2. Clinical observations of sparse hair coat in males and females, and dehydration and cold to touch in females.
3. Decreased body-weight gain (as much as 14% less than controls) during the first four weeks of dosing (PNDs 4 to 28).
4. Increased food consumption (as much as 10% higher than controls) during the entire three-week postweaning period (PNDs 28 to 48).
5. Enhanced acoustic startle responses in females on PND 47.

Atorvastatin - 200 mg/kg

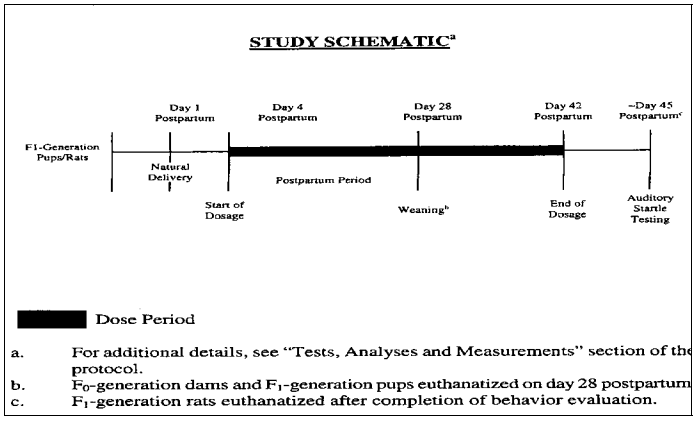
Discontinued on PNDs 5 and 6 due to excessive toxicity (death and morbundity).

- At 50 mg/kg Pravastatin one male was sacrificed moribund and 2 females were found dead. Control incidence of 1 M and F either moribund or found dead. At 20 mg/kg atorvastatin 2M, 2F found dead.
- Based on the mortality and reductions in body weight gain at 100 mg/kg/day a high dose of 45 mg/kg/day was selected as the MTD for juvenile rats for the definitive neonatal study. However the mortality at 50 mg/kg/day suggests that the selected high dose may also exceed the MTD.

Study no.: DN03001, DCN 930004905
Volume #, and page #: IND 27, 201 S494, vol. 265.1;
Conducting laboratory and location: (b) (4)
Date of study initiation: Jan. 2003
GLP compliance: yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: R3925A; 99.7%
Formulation/vehicle: dissolved in reverse osmosis deionized water; 5 ml/kg vol.

Methods

Doses: 50, 100, 500, 1000 mg/kg/day Pravastatin
20, 100, 200 mg/kg/day atorvastatin
from PND 4-42



Pravastatin: Oral Developmental TK Study in Juvenile Rats

Key study findings:

- Systemic exposure to Pravastatin increased dose proportionally PND 7 & 21 but less than the dose increment on PND 42. Cmax was 13-216X higher and AUC 26-197X higher from PND 7 to PND 42 which the sponsor attributes to immature liver capacity.
- Morbidity/mortality (3M, 2F; PND 13-20) was observed at 100 mg/kg/day, a dose that is well tolerated in adult rats, transient mild adverse effects on liver function were evident on PND 21 at ≥25 mg/kg/day. Decreases in body weight gain (~20%) in males during PND 4-14 and females during PND 7-14 compared to controls. This indicates to the sponsor that Pravastatin produces toxic effects in young rats secondary to excessive exposures reflecting the limited capacity of the immature liver to clear Pravastatin. Adult rats given 100 mg/kg/day by oral gavage for 7 days, Pravastatin + major metabolite SQ 31,906 achieved an $AUC_{0\text{-}24h}$ of 1411 ng h/ml in males and 816 ng h/ml in females (Study 9117;1992 SB165, vol. 82.1). This is similar to the exposures achieved in the juvenile rats by PND 42, supporting the sponsor's claim regarding immature liver functional effects at <PND42. Mortality was observed at single incidence in males at 10 and 50 mg/kg/day.
- Drug related clinical chemistry changes occurred at doses ≥10 mg/kg/day. Serum cholesterol was decreased 10-46% at ≥10 mg/kg/day on PND 7 and in females only (35%) at 100 mg/kg/day on PND 21. Increases of 94-240% ALT, alkaline phosphatase (67-103%) on PND 21 in groups given ≥25 mg/kg/day. Decreased triglycerides (48-80%), bilirubin (~40%) and serum protein (12-25%) were also observed. No perturbations in clinical chemistry were observed PND42.

Study no.: DN03056
Volume #, and page #: eCTD
Conducting laboratory and location: (b) (4)
Date of study initiation: 7/03
GLP compliance: Y
QA reports: yes (X) no ( )
Drug, lot #, and % purity: R3925A; 99.7%
Formulation/vehicle: deionized water

Methods

Doses: 10, 25, 50, 100 mg/kg; PND 4-41

Study design: serum concentrations were determined PND 7, 21, 42 along with clinical chemistry including serum cholesterol levels. Body weight was assessed every 3-4 days, survival was monitored daily.

Results

Serum Toxicokinetics

Dose [mg/kg/day]	Day of Study (PND)	Cmax [ng/ml]		AUC(0-T)[a] [ng·h/ml]	
		Male	Female	Male	Female
10	7	1144	1132	6446	6500
	21	438	159	1043	796
	42	88	17	160	249
25	7	2281	3756	17000	18235
	21	969	1354	3569	2858
	42	27	34	134	123
50	7	8924	9292	51096	48943
	21	4599	10879	10004	15322
	42	106	43	298	248
100	7	18128	20564	106425	132159
	21	2179	3612	16103	26915
	42	216	283	741	1241
Dose Ratio	**PND**	**Cmax ratio**		**AUC ratio**	
		Male	**Female**	**Male**	**Female**
1:2.5:5:10	7	1.0:2.0:7.8:1	1.0:3.3:8.2:18.	1.0:2.6:7.9:16.5	1.0:2.8:7.5:20.
	21	1.0:2.2:10.5:	1.0:8.5:68.5:2	1.0:3.4:9.6:15.4	1.0:3.6:19.2:3
	42	1.0:0.3:1.2:2.	1.0:2.0:2.5:16.	1.0:0.8:1.9:4.6	1.0:0.5:1.0:5.0

a. Calculated from time zero to the time of last measurable concentration, up to 24 h.

TABLE 3 (PAGE 1): NECROPSY OBSERVATIONS - SUMMARY - F, GENERATION MALE RATS

DOSE GROUP DOSE (MG/KG/DAY)a		I 0 VEHICLE	II 10 PRAVASTATIN	III 25 PRAVASTATIN	IV 50 PRAVASTATIN	V 100 PRAVASTATIN
TOTAL NUMBER OF RATS DOSED	N	28	100	100	100	100
RATS EVALUATED	N	20	82	80	83	95
FOUND DEAD	N	0	1b	0	1c	2d
MORIBUND EUTHANATIZED	N	0	0	0	0	1e
NOT SELECTED FOR EVALUATION	N	8	18	20	17	15
APPEARED NORMAL	N	20	82	79	81	95
KIDNEYS: RIGHT, PELVIS, MARKED DILATION	N	0	0	1	0	0
STOMACH: CARDIAC REGION, MUCOSAL SURFACE, BLACK AREAS, TOO NUMEROUS TO COUNT	N	0	0	0	1c	0
HEAD: f SPARSE HAIR COAT	N	0	0	0	1	0

a. Postnatal days 4 through 42.
b. Rat 9043 was found dead on postnatal day 28. All tissues appeared normal at necropsy.
c. Rat 9571 was found dead on postnatal day 16.
d. Rats 9924 and 9961 were found dead on postnatal days 13 and 19, respectively. All tissues appeared normal at necropsy.
e. Rat 9764 was euthanatized in moribund condition on postnatal day 20. All tissues appeared normal at necropsy.
f. Clinical observations were confirmed at necropsy.

TABLE 4 (PAGE 1): NECROPSY OBSERVATIONS - SUMMARY - F_1 GENERATION FEMALE RATS

DOSE GROUP DOSE (MG/KG/DAY)a		I 0 VEHICLE	II 10 PRAVASTATIN	III 25 PRAVASTATIN	IV 50 PRAVASTATIN	V 100 PRAVASTATIN
TOTAL NUMBER OF RATS DOSED	N	28	100	100	100	100
RATS EVALUATED	N	20	80	81	80	83
FOUND DEAD	N	0	0	0	0	2b
NOT SELECTED FOR EVALUATION	N	8	20	19	20	17
APPEARED NORMAL	N	20	80	81	78	83
HEAD: c SPARSE HAIR COAT	N	0	0	0	1	0
RIGHT EYE: c CHROMODACRYORRHEA	N	0	0	0	1	0
DEHYDRATION c	N	0	0	0	0	2b

a. Postnatal days 4 through 42.
b. Rats 9925 and 9928 were found dead on postnatal days 17 and 16, respectively. All tissues appeared normal at necropsy.
c. Clinical observations were confirmed at necropsy.

Pravastatin: Oral Study of Developmental Neurotoxicity in Rats

Key study findings:

- NOAEL = 5 mg/kg/day (AUC≤ 1623 ng h /ml) which is 5X higher than systemic exposure following a 80 mg human dose (AUC= 281 ng h/ml in fasted or 176 ng h/ml in non-fasted humans).
- Decreased thickness of the corpus callosum at PND 132 (50 day recovery) in groups given ≥15 mg/kg/day in males (-10%) and females (-12%) at 15 mg/kg/day and at 45 mg/kg/day (-13% and -17% respectively). This finding occurs at exposures ≥ 5506 ng h/ml or 20X systemic exposure following an 80 mg clinical dose (AUC= 281 ng h/ml in fasted).
- Higher magnitude acoustical startle response in rats given 45 mg/kg/day on PND 117-119 (123% M, 88% F higher response magnitude than controls). Increased number of errors in learning (watermaze) in females on PNDs 116 and 117 (83% higher error rate per trial than controls). Decreased absolute and relative brain weights in males (4 and 12% less than controls, respectively) and females (5 and 22% less than controls, respectively) on PND 132. One high dose male and one female were found dead PND 24 and 18 respectively without evidence of toxicity or gross lesion at necropsy (only neurohistopathology was performed). This correlates with mortality seen at 50 mg/kg/day in the dose ranging study (DN03001) with dosing PND 4-42 and suggests that this dose may have exceeded the MTD. Interestingly the TK study using doses of 10, 25, 50, 100 mg/kg/day for PND 4-42 (DN03056) shows mortality only at 100 mg/kg/day despite apparent 4X higher exposure at PND 7 on a dose per dose basis. This would support the sponsor's conclusion that the deaths were not drug related. However it doesn't explain the 4X difference in exposure between studies DNO3056 and this one. The neurobehavioral changes noted at 45 mg/kg/day (AUC=11969 ng h/ml F; AUC=14262 ng h/ml M) occur at 43X systemic exposure achieved at an 80 mg human dose.

Study no.: DN03098
Volume #, and page #: eCTD
Conducting laboratory and location: (b) (4)
Date of study initiation: 10/03
GLP compliance: Y

QA reports: yes (X) no ( )
Drug, lot #, and % purity: R3925A; 99.7%
Formulation/vehicle: deionized water; 5 ml/kg
Methods
Doses: 5, 15, 45 mg/kg; PND 4-80

Study design: PND4 pups were culled to 4 male and 4 female and litters were cross-fostered. PND 7 rats were assigned to one of three subsets: 1) euthanized PND 7/8 for TK in serum liver and brain; 2) evaluated for clinical signs, body weight, food consumption and neuropathologic evaluations (brain weight, morphometry and neurohistology) at the end of recovery PND 132; 3)neuropathologic evaluations completed at the end of dosing PND 8. Microscopic evaluation of the brain, spine, Gasserian ganglia, dorsal root ganglia, dorsal and ventral nerve roots, trigeminal, sciatic, tibial, common peroneal and sural nerves were performed. Specialized stains were used to assess myelin integrity (Luxol fast blue/cresyl violet), axonal/neuronal cytoarchitecture (silver stain) and cellular degeneration (Fluro-Jade B). Subset 2 rats were evaluated during the recovery period (PND 81-132) for motor activity, acoustic startle habituation and water maze learning and retention.

Subset Number	Evaluation	Day of Evaluation (Postnatal)
1	Toxicokinetic Evaluations (21 per sex per dose group)	Day 7
2	FOB (21 per sex per dose group)	Days 85 or 86 and 110 and 111
	Motor Activity (21 per sex per dose group)	Days 85 or 86 and 110 or 111
	Acoustic Startle Habituation[a] (21 per sex per dose group)	Days 88 to 90 and 117 to 119
	Watermaze[a] (21 per sex per dose group)	Days 91 or 92 and 116 or 117
	Brain Weights (21 per sex per dose group) and Neurohistology, and Brain Morphometry (10 per sex per dose group)	Day 132
3	Brain Weights, Neurohistology, and Brain Morphometry (5 per sex per dose group)	Day 81

FOB = Functional Observational Battery.
a. Approximately one half of the rats assigned to Subset 2 underwent acoustic startle and watermaze evaluations on PNDs 88 through 92. The remaining rats underwent these evaluations on PNDs 116 through 119.

Coronal slices parallel the band on a headset.
The brains were divided into multiple coronal slices *via* the following cuts:

Cut #1 – Just posterior to the olfactory bulbs.
Cut #2 - Midway between the optic chiasm and the plane of the first section.
Cut #3 - Just anterior to the optic chiasm.
Cut #4 - Just anterior to the infundibulum.
Cut #5 - Anterior to the posterior edge of the mammillary body.
Cut #6 – Just anterior to the anterior edge of the pons.
Cut #7 – Just anterior to the middle of the cerebellar cortex.
Cut #8 - Through the posterior portion of the cerebellar cortex.
Cut #9 – Through the anterior portion of the medulla.

The block list for the evaluated tissues is as follows:

Paraffin-embedded tissues:
Block 1: Coronal slice through the cerebrum at the level of the optic chiasm.
Block 2: Coronal slice through the cerebrum at the level of the infundibulum.
Block 3: Coronal slice through the cerebrum at the level of the mammillary bodies.
Block 4: Coronal slice through the middle of the cerebellum.
Block 5: Multiple-embedded sections including the olfactory bulbs, two coronal slices through the anterior pole, one coronal slice through the cerebrum at the level of the midbrain, one through the posterior portion of the cerebellum, and one through the medulla oblongata.
Block 6: Longitudinal sections of the Gasserian ganglia and associated trigeminal nerves.
Block 7: Longitudinal sections of the dorsal root ganglia and spinal nerve roots.
Block 8: Cross and longitudinal sections of the spinal cord.

Glycol methacrylate-embedded tissues:
Block 9: Cross sections of the sciatic and tibial nerves.
Block 10: Longitudinal section of the sciatic nerve.
Block 11: Longitudinal sections of the common peroneal (fibular), tibial, and sural nerves.

Highly homologous sections were obtained on the brain slices present in tissue Blocks #1, 2, and 4 (*i.e.* the sections on which morphometric measurements were performed). This was done by preparing step sections on these blocks until specific neuroanatomic structures could be observed within the unstained sections. These landmarks included the following: 1) decussation of the anterior commissure (Block #1), 2) complete separation of the granular layers of the dentate gyrus on the right and left side of the brain, with the hippocampal formation also covering the entire dorsal portion of the thalamus (Block #2), and 3) facial nerve tract and deep cerebellar nuclei (Block #4). This sectioning procedure resulted in multiple sections from each of Blocks #1, #2, and #4.

Results: PND 7 tissue levels in juvenile rats is ~4X higher in female and ~5X higher in male liver compared to serum levels whereas brain levels are 1/10th that of serum.

Composite Toxicokinetic Parameters				
Dose (mg/kg/day)	Cmax (ng/mL or g)		AUC_{0-T}[a] (ng*hr/mL or g)	
	Male	Female	Male	Female
Pravastatin Levels in Serum				
5	257	395	1421	1623
15	1050	1104	5506	6467
45	2478	1663	14262	11969
Pravastatin Levels in Liver				
5	1421	1325	8994	7956
15	5000	6556	27260	33296
45	7961	7259	50131	55981
Pravastatin Levels in Brain				
5	16	37	199	218
15	39	60	499	529
45	110	132	1086	1278

a - T = 24 h; except for the 45 mg/kg/day female serum group where T = 12 h.

Pravastatin - 5 mg/ kg/ day No drug- related changes

Pravastatin - 15 and 45 mg/ kg/ day Decreased body weight gains on PNDs 18 to 21 (19 and 33% less than controls in males and 12 and 33% less than controls in females, respectively). Increased body weight gains in females during the postweaning period (10 and 24% higher than controls on PNDs 31 to 80, respectively, and 14 and 59% higher than controls on PNDs 80 to 132, respectively). After weaning on PND 28 and continuing to study termination on PND 132 increased body weight gains were observed in females at ≥ 15 mg/kg/day and in males at 45 mg/kg/day. Food consumption was increased (10 % M, 17% F) at 4 mg/kg/day during this period. Decreased thickness of the corpus callosum (quantified by microscopic linear measurements) in males (10 and 13% less than controls, respectively) and females (12 and 17% less than controls, respectively) on PND 132.

Dose related decreases in the thickness of the corpus callosa present for PND 132 rats, reaching statistical significance in groups given ≥ 15 mg/kg/day. The thickness of the corpus callosum was measured at the level of the anterior commissure, just posterior to the genu. The mean thickness difference for PND 132 control females is 259 μ while the 45 mg/kg/day group is 215 μ. The rat with the thinnest corpus callosum (180 μ) is a HD female on PND 132. The thickness (quantified by microscopic linear measurements of coronal sections (sections parallel the band on a headset) of the corpus callosum was slightly decreased in males (-10%) and females (-12%) at 15 mg/kg/day and at 45 mg/kg/day (-13% and -17% respectively). This finding occurs at exposures ≥ 5506 ng h/ml or 20X systemic exposure following an 80 mg clinical dose (AUC= 281 ng h/ml in fasted). The finding is not associated with any inflammatory or degenerative change and there is overlap in values between control and treated animals. Although acknowledged as drug related the sponsor contends that the biological significance of this finding is unknown. Historical control reference ranges are not available for this finding. In the current study 9/10 males on PND 132 are within concurrent control range but 7/10 females on PND 132 are outside the concurrent control range.

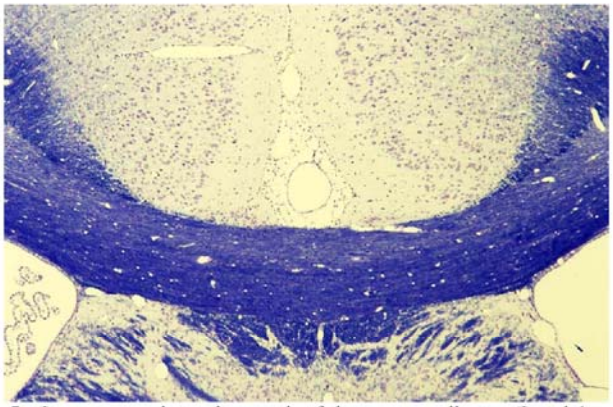


Figure 5: Low power photomicrograph of the corpus callosum (Level 1 section) of a female PND 132 control group rat. This rat had the thickest corpus callosum of all of the rats in the female control group (324 µ). (Rat #3208; luxol fast blue/cresyl violet x 50)

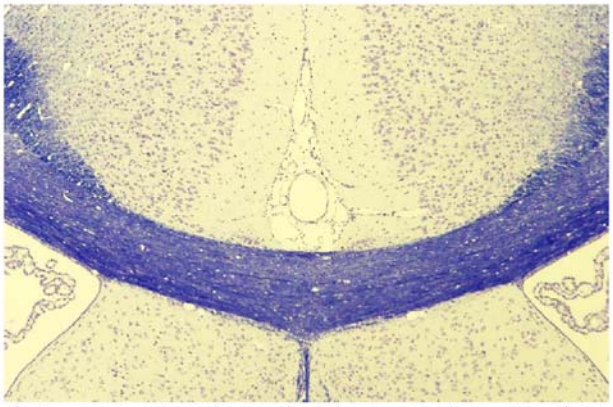


Figure 6: Low power photomicrograph of the corpus callosum (Level 1 section) of a female PND 132 rat in the 45-mg/kg/day group. This rat had the thickest corpus callosum of all of the rats in the female high dose group (252 µ). Contrast this corpus callosum with that of the control group rat shown in Figure 5, above. Other than for being thinner, this corpus callosum is microscopically normal. (Rat #6908; luxol fast blue/cresyl violet x 50)

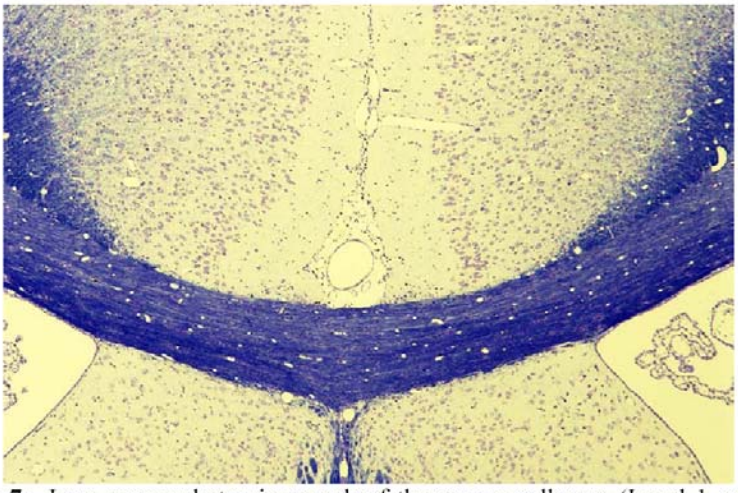


Figure 7: Low power photomicrograph of the corpus callosum (Level 1 section) of a female PND 132 control group rat. This rat was one of five rats in this group with the thinnest corpus callosa (240 µ). (Rat #2506; luxol fast blue/cresyl violet x 50)

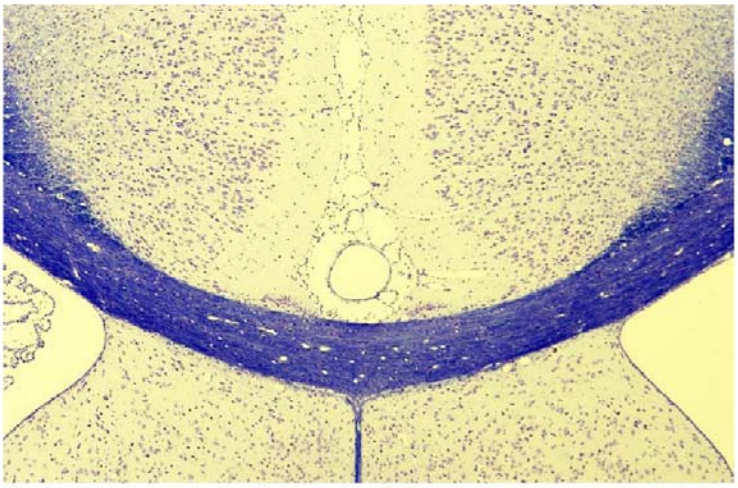


Figure 8: Low power photomicrograph of the corpus callosum (Level 1 section) of a female PND 132 rat in the 45-mg/kg/day group. This rat had the thinnest corpus callosum of all the rats in this female high dose group (180 µ). Other than being thinner, this corpus callosum is microscopically normal. (Rat #7005; luxol fast blue/cresyl violet x 50)

PHOTOMICROGRAPHS (CONTINUED)

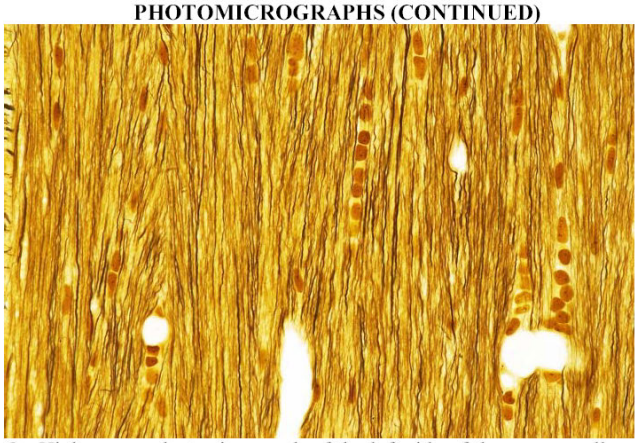


Figure 9: High power photomicrograph of the left side of the corpus callosum (Level 1 section) from a female PND 132 control group rat. This was one of the rats in the control group with the thinnest corpus callosa, but the corpus callosum is, nevertheless, wider than the microscopic field. (Note: This figure is rotated 90^0 from horizontal.) This is the same rat as shown in Figure 7. (Rat #2506; Bielschowsky's x 500)

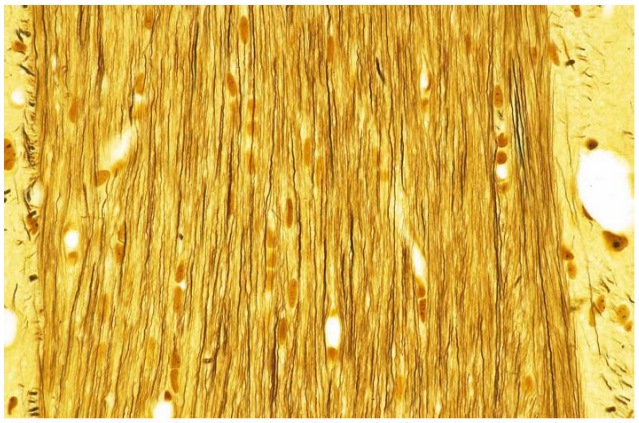


Figure 10: In contrast with Figure 9, this is a high power photomicrograph of the left side of the corpus callosum (Level 1 section) from the PND 132 female rat in the 45-mg/kg/day dose group that had the thinnest corpus callosum (and the same rat as shown in Figure 8). Other than for being thinner, there are no apparent structural changes. (Rat #7005; Bielschowsky's x 500)

Corpus Callosum Thickness (μ)	0 mg/kg/day		5 mg/kg/day		15 mg/kg/day		45 mg/kg/day	
	M	F	M	F	M	F	M	F
PND 81	247±20	242±10	ND	ND	ND	ND	242±21	218±23
PND 132	288±49	259±28	278±36	253±30	258±21	228**±14	250±20	215**±24

Pravastatin - 45 mg/ kg/ day Clinical observations of ungroomed coat, chromorhinorrhea, and/ or excess salivation in males and females. One male and female were found dead on PND 24 and 18 respectively without evidence of toxicity at gross necropsy. Increased body-weight gains in males during the postweaning period (9% higher than controls on PNDs 31 to 80 and 18% higher than controls on PNDs 80 to 132). Increased food consumption in males and females on PNDs 28 to 132 (10 and 17% higher than controls, respectively). Enhanced acoustic startle response in males and females on PNDs 117 to 119 (123 and 88% higher response magnitude than controls, respectively). Increased number of errors in learning (watermaze) in females on PNDs 116 and 117 (83% higher error rate per trial than controls). Decreased absolute and

relative brain weights in males (4 and 12% less than controls, respectively) and females (5 and 22% less than controls, respectively) on PND 132. One male and one female were found dead PND 24 and 18 respectively without evidence of toxicity or gross lesion at necropsy.

TABLE 23 (PAGE 2): TERMINAL BODY WEIGHTS AND ORGAN WEIGHTS AND RATIO (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - SUMMARY - F1 GENERATION MALE RATS

DOSE GROUP		I	II	III	IV
DOSE (MG/KG/DAY)a		0 (VEHICLE)	5	15	45
SUBSET 2 (NECROPSIED ON POSTNATAL DAY 132)					
RATS TESTED	N	21	21	21	21
TERMINAL BODY WEIGHT	MEAN±S.D.	610.0 ± 46.7	622.5 ± 53.6	616.5 ± 61.1	669.4 ± 73.3**
BRAIN	MEAN±S.D.	2.33 ± 0.09	2.31 ± 0.10	2.27 ± 0.06*	2.23 ± 0.07**
BRAIN (%)	MEAN±S.D.	0.384 ± 0.030	0.373 ± 0.028	0.371 ± 0.034	0.336 ± 0.042**

ALL WEIGHTS WERE RECORDED IN GRAMS (G). RATIOS (%) = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) X 100.
a. Postnatal day 4 through postnatal day 80.
* Significantly different from the vehicle control group value ($p \leq 0.05$).
** Significantly different from the vehicle control group value ($p \leq 0.01$).

TABLE 24 (PAGE 2): TERMINAL BODY WEIGHTS AND ORGAN WEIGHTS AND RATIO (%) OF ORGAN WEIGHT TO TERMINAL BODY WEIGHT - SUMMARY - F1 GENERATION FEMALE RATS

DOSE GROUP		I	II	III	IV
DOSE (MG/KG/DAY)a		0 (VEHICLE)	5	15	45
SUBSET 2 (NECROPSIED ON POSTNATAL DAY 132)					
RATS TESTED	N	21	21	21	21
TERMINAL BODY WEIGHT	MEAN±S.D.	308.7 ± 37.0	322.9 ± 28.6	339.8 ± 40.3*	377.4 ± 47.3**
BRAIN	MEAN±S.D.	2.11 ± 0.09	2.11 ± 0.10	2.08 ± 0.06	2.01 ± 0.09**
BRAIN (%)	MEAN±S.D.	0.690 ± 0.077	0.658 ± 0.053	0.618 ± 0.066**	0.540 ± 0.070**

ALL WEIGHTS WERE RECORDED IN GRAMS (G). RATIOS (%) = (ORGAN WEIGHT/TERMINAL BODY WEIGHT) X 100.
a. Postnatal day 4 through postnatal day 80.
* Significantly different from the vehicle control group value ($p \leq 0.05$).
** Significantly different from the vehicle control group value ($p \leq 0.01$).

Enhanced acoustic startle responses on PNDs 117-119 in males and females (123% & 88% higher response magnitude) and decreased absolute (-4%M, -5%F) and relative (-12%M, -22%F) brain weights on PND 132 in rats given 45 mg/kg/day (AUC ≥ 11969 ng h/ml). Females given 45 mg/kg/day had increased number of errors (83% higher error rate vs. controls) in a watermaze learning task on PNDs 116 and 117. The neurobehavioral changes noted at 45 mg/kg/day occur at 43X systemic exposure achieved at an 80 mg human dose.

TABLE 17 (PAGE 1): ACOUSTIC STARTLE HABITUATION - SUMMARY - F1 GENERATION MALE RATS

SUBSET 2												
DOSE GROUP		I			II			III			IV	
DOSE (MG/KG/DAY)a		0 (VEHICLE)			5			15			45	
RESPONSE MAGNITUDE												
NUMBER OF RATS	N	11			10			11			10	
POSTNATAL DAY 88, 89 OR 90:												
BLOCK 1	MEAN ± S.D.	175.71	±	94.10	167.96	±	82.76	187.85	±	114.71	251.52	± 109.42
BLOCK 2	MEAN ± S.D.	115.43	±	75.02	95.14	±	87.40	135.07	±	106.06	215.05	± 93.98
BLOCK 3	MEAN ± S.D.	94.96	±	65.66	65.42	±	37.18	89.92	±	67.21	128.25	± 67.83
BLOCK 4	MEAN ± S.D.	77.92	±	55.36	69.34	±	36.90	86.21	±	78.48	117.82	± 72.61
BLOCK 5	MEAN ± S.D.	86.19	±	60.06	84.62	±	43.32	95.40	±	86.17	126.19	± 96.08
AVERAGE	MEAN ± S.D.	110.036	±	54.355	96.490	±	45.689	118.891	±	86.026	167.760	± 80.330
NUMBER OF RATS	N	10			11			10			11	
POSTNATAL DAY 117, 118 OR 119:												
BLOCK 1	MEAN ± S.D.	173.52	±	62.08	208.57	±	134.17	208.94	±	167.81	262.34	± 142.91
BLOCK 2	MEAN ± S.D.	94.56	±	57.26	137.61	±	113.68	142.21	±	117.26	195.69	± 173.17
BLOCK 3	MEAN ± S.D.	72.24	±	37.86	124.50	±	90.35	101.44	±	70.30	188.32	± 136.73
BLOCK 4	MEAN ± S.D.	66.31	±	35.90	109.16	±	102.73	66.57	±	41.82	198.02	± 135.45
BLOCK 5	MEAN ± S.D.	68.30	±	39.86	117.74	±	76.18	71.06	±	36.12	213.32	± 139.45
AVERAGE	MEAN ± S.D.	94.990	±	37.305	139.527	±	81.349	118.050	±	80.404	211.536	± 136.252*

DATA WERE RECORDED IN GRAMS (G).
BLOCK = TEN CONSECUTIVE TRIALS
RESPONSE MAGNITUDE = PEAK RESPONSE - BASELINE RESPONSE
AVERAGE = AVERAGE RESPONSE MAGNITUDE FOR 5 BLOCKS (50 TRIALS)
a. Postnatal day 4 through postnatal day 80.
* Significantly different from the vehicle control group value ($p \leq 0.05$).

TABLE 18 (PAGE 1): ACOUSTIC STARTLE HABITUATION - SUMMARY - F1 GENERATION FEMALE RATS

SUBSET 2												
DOSE GROUP		I			II			III			IV	
DOSE (MG/KG/DAY)a		0 (VEHICLE)			5			15			45	
RESPONSE MAGNITUDE												
NUMBER OF RATS	N	10			10			11			11	
POSTNATAL DAY 88, 89 OR 90:												
BLOCK 1	MEAN ± S.D.	91.75	±	63.83	64.91	±	23.84	107.04	±	38.86	116.81	± 54.02
BLOCK 2	MEAN ± S.D.	96.78	±	98.88	59.40	±	25.95	60.76	±	34.86	89.66	± 63.84
BLOCK 3	MEAN ± S.D.	76.30	±	91.35	44.46	±	24.76	55.07	±	26.16	85.10	± 39.73
BLOCK 4	MEAN ± S.D.	44.39	±	28.32	30.42	±	14.71	47.97	±	24.46	85.67	± 51.18
BLOCK 5	MEAN ± S.D.	37.76	±	26.38	38.37	±	18.24	52.66	±	12.84	70.42	± 36.85
AVERAGE	MEAN ± S.D.	69.390	±	49.133	47.510	±	15.680	64.709	±	20.815	89.527	± 38.814
NUMBER OF RATS	N	11			11			10			10	
POSTNATAL DAY 117, 118 OR 119:												
BLOCK 1	MEAN ± S.D.	94.62	±	52.62	85.60	±	37.66	101.80	±	56.51	131.45	± 103.56
BLOCK 2	MEAN ± S.D.	68.64	±	62.41	65.77	±	31.48	90.34	±	63.92	126.00	± 90.77
BLOCK 3	MEAN ± S.D.	43.24	±	29.18	54.59	±	25.71	66.74	±	45.54	110.22	± 81.12
BLOCK 4	MEAN ± S.D.	39.37	±	18.24	50.65	±	31.22	62.32	±	47.16	97.70	± 60.14
BLOCK 5	MEAN ± S.D.	42.61	±	15.65	38.76	±	21.80	55.48	±	45.30	77.12	± 37.09
AVERAGE	MEAN ± S.D.	57.745	±	28.192	59.064	±	21.732	75.330	±	46.663	108.500	± 69.767*

DATA WERE RECORDED IN GRAMS (G).
BLOCK = TEN CONSECUTIVE TRIALS
RESPONSE MAGNITUDE = PEAK RESPONSE - BASELINE RESPONSE
AVERAGE = AVERAGE RESPONSE MAGNITUDE FOR 5 BLOCKS (50 TRIALS)
a. Postnatal day 4 through postnatal day 80.
* Significantly different from the vehicle control group value ($p \leq 0.05$).

TABLE 19 (PAGE 1): WATERMAZE PERFORMANCE - SUMMARY - F1 GENERATION MALE RATS

DOSE GROUP		I	II	III	IV
DOSE (MG/KG/DAY)a		0 (VEHICLE)	5	15	45
SUBSET 2 - POSTNATAL DAY 91 OR 92					
SESSION 1b	N	10	11	10	11
TRIALS TO CRITERION	MEAN±S.D.	8.9 ± 2.2	8.7 ± 2.9	7.9 ± 1.7	9.2 ± 2.8
ERRORS PER TRIAL	MEAN±S.D.	0.32 ± 0.14	0.31 ± 0.11	0.28 ± 0.08	0.39 ± 0.18
LATENCY TRIAL 2c	MEAN±S.D.	9.2 ± 2.6	9.4 ± 4.4	7.6 ± 3.9	11.5 ± 4.4
FAILED TO LEARN d	N(%)	0(0.0)	0(0.0)	0(0.0)	1(9.1)
SESSION 2b	N	10	11	10	10
TRIALS TO CRITERION	MEAN±S.D.	5.5 ± 0.7	5.8 ± 1.5	6.5 ± 1.9	5.7 ± 1.6
ERRORS PER TRIAL	MEAN±S.D.	0.08 ± 0.12	0.12 ± 0.19	0.08 ± 0.10	0.07 ± 0.12
LATENCY TRIAL 1c	MEAN±S.D.	8.0 ± 4.7	7.0 ± 3.3	8.4 ± 5.9	7.7 ± 5.7
SUBSET 2 - POSTNATAL DAY 116 OR 117					
SESSION 1b	N	11	10	11	10
TRIALS TO CRITERION	MEAN±S.D.	7.5 ± 2.8	7.1 ± 1.4	7.4 ± 1.6	8.9 ± 3.1
ERRORS PER TRIAL	MEAN±S.D.	0.25 ± 0.10	0.33 ± 0.19	0.29 ± 0.07	0.34 ± 0.19
LATENCY TRIAL 2c	MEAN±S.D.	13.5 ± 11.8	13.7 ± 15.5	13.2 ± 5.6	11.1 ± 6.2
FAILED TO LEARN d	N(%)	1(9.1)	0(0.0)	0(0.0)	0(0.0)
SESSION 2b	N	10	10	11	10
TRIALS TO CRITERION	MEAN±S.D.	6.0 ± 2.2	6.3 ± 1.9	5.6 ± 1.0	5.6 ± 1.0
ERRORS PER TRIAL	MEAN±S.D.	0.08 ± 0.18	0.08 ± 0.12	0.08 ± 0.12	0.08 ± 0.11
LATENCY TRIAL 1c	MEAN±S.D.	8.7 ± 8.7	7.9 ± 5.5	7.5 ± 5.0	8.5 ± 5.0

a. Postnatal day 4 through postnatal day 80.
b. Sessions 1 (Learning Phase) and 2 (Retention Phase) of testing were separated by a one-week interval.
c. The latency was recorded in seconds.
d. Rat did not meet the criterion in Session 1 (Learning Phase); values for Session 2 (Retention Phase) were excluded from group

TABLE 20 (PAGE 1): WATERMAZE PERFORMANCE - SUMMARY - F1 GENERATION FEMALE RATS

DOSE GROUP		I	II	III	IV
DOSE (MG/KG/DAY)a		0 (VEHICLE)	5	15	45
SUBSET 2 - POSTNATAL DAY 91 OR 92					
SESSION 1b	N	11	11	10	10
TRIALS TO CRITERION	MEAN±S.D.	7.4 ± 1.5	8.3 ± 1.8	7.6 ± 2.5	7.2 ± 1.8
ERRORS PER TRIAL	MEAN±S.D.	0.38 ± 0.15	0.32 ± 0.18	0.34 ± 0.31	0.32 ± 0.14
LATENCY TRIAL 2c	MEAN±S.D.	16.5 ± 6.3	14.5 ± 11.4	16.4 ± 15.8	13.4 ± 5.2
FAILED TO LEARN	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
SESSION 2b	N	11	11	10	10
TRIALS TO CRITERION	MEAN±S.D.	5.4 ± 0.5	6.4 ± 2.0	6.3 ± 2.1	5.7 ± 1.9
ERRORS PER TRIAL	MEAN±S.D.	0.08 ± 0.11	0.14 ± 0.19	0.08 ± 0.12	0.10 ± 0.22
LATENCY TRIAL 1c	MEAN±S.D.	14.0 ± 7.0	15.3 ± 10.8	10.7 ± 5.2	14.5 ± 10.0
SUBSET 2 - POSTNATAL DAY 116 OR 117					
SESSION 1b	N	10	10	11	11
TRIALS TO CRITERION	MEAN±S.D.	7.1 ± 2.2	8.2 ± 2.0	8.4 ± 2.6	8.4 ± 2.0
ERRORS PER TRIAL	MEAN±S.D.	0.23 ± 0.07	0.29 ± 0.14	0.33 ± 0.09	0.42 ± 0.23**
LATENCY TRIAL 2c	MEAN±S.D.	9.9 ± 3.8	13.6 ± 7.5	13.7 ± 5.1	14.6 ± 12.9
FAILED TO LEARN	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
SESSION 2b	N	10	10	11	11
TRIALS TO CRITERION	MEAN±S.D.	5.7 ± 1.0	5.8 ± 1.2	5.6 ± 1.3	6.0 ± 1.3
ERRORS PER TRIAL	MEAN±S.D.	0.12 ± 0.16	0.13 ± 0.19	0.09 ± 0.19	0.17 ± 0.19
LATENCY TRIAL 1c	MEAN±S.D.	10.4 ± 5.9	13.6 ± 10.2	13.8 ± 15.9	10.5 ± 6.9

a. Postnatal day 4 through postnatal day 80.
b. Sessions 1 (Learning Phase) and 2 (Retention Phase) of testing were separated by a one-week interval.
c. The latency was recorded in seconds.
** Significantly different from the vehicle control group value (p≤0.01).

Neurohistopathology:
Minimal nerve fiber degeneration within peripheral nerves, spinal cord or brain which generally involve short segments of one to several nerve fibers and are characterized by areas filled with myelin and/or axonal debris (H&E, LFB or toluidine), by fragmented axons (silver stain) or by bright yellow staining with Fluoro-Jade. The most common region of degeneration in the brain is the trapezoid body of the brainstem. PND 81 rats given 45 mg/kg/day had increased minimal nerve fiber degeneration in sciatic and tibial nerves (3/5 M, 1/5 F) compared to control (2/5 M, 0 F). Evaluations at PND 132 shows a similar effect in the 45 mg/kg/day treated groups were the incidence of minimal nerve degeneration was slightly increased in females (4/10 M, 7/10 F) compared to controls (5/10M, 6/10 F). One PND 132 male rat in the 45 mg/kg/day group had a minimal degree of hydrocephalus (lateral ventricle expansion) which was considered a background alteration. One PND 132 male rat in the same group had dorsal root ganglia mineralization.

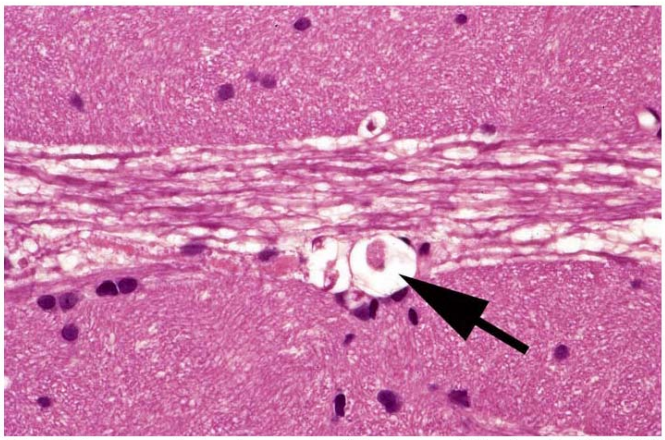


Figure 11: High power photomicrograph of the trapezoid body of a PND 132 male rat in the control group. The arrow points to a small ball of myelin and/or axonal debris. This is sometimes referred to as a "digestion chamber." Minimal nerve fiber degeneration is common in the trapezoid body of rats. (Rat #3303; H&E x 500)

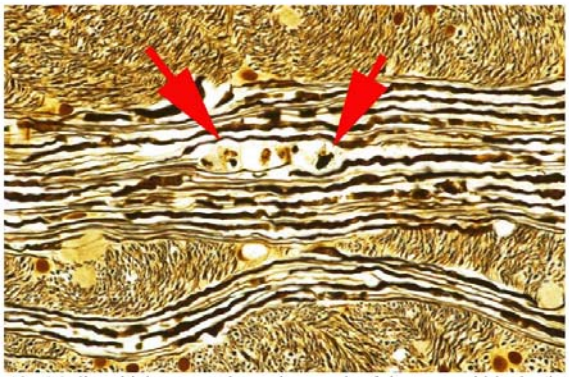


Figure 12: Medium-high power photomicrograph of the trapezoid body (in the ventral pontine region) of a PND 132 male rat in the 45-mg/kg/day dose group. The red arrows point to fragments of axonal (and possibly also myelin) debris. This micrograph is included merely to show the different appearances of nerve fiber degeneraton with different stains. (Rat #7403; Bielschowsky's x 250)

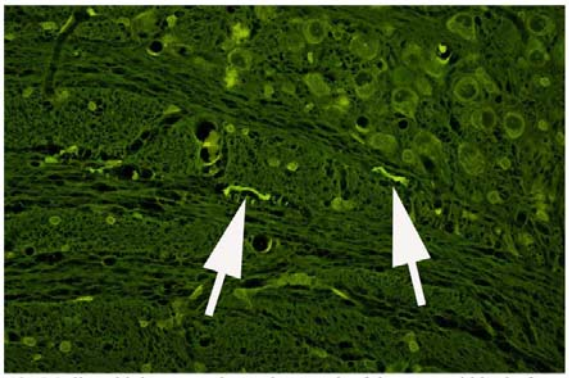


Figure 13: Medium-high power photomicrograph of the trapezoid body from a PND 132 female rat in the 45-mg/kg/day dose group. The white arrows point to small segments of axons that stain intensely with the Fluoro-Jade B stain, indicating axonal (nerve fiber) degeneration. (Rat #7106; Fluro-Jade B x 312)

Minimal Nerve Fiber Degeneration	0 mg/kg/day		5 mg/kg/day		15 mg/kg/day		45 mg/kg/day	
	M	F	M	F	M	F	M	F
Day 81								
Spinal nerve root	1/5							
Sciatic nerve							2/5	
Tibial nerve	1/5						1/5	1/5
Total	2						3	1
Day 132								
Trapezoid body	3/10						3/10	
Sciatic nerve	1/10							
Tibial nerve	1/10						1/10	
Cerebellar cortex-purkinje dendrite + staining		2/10						
Cervical spine								2/10
Peroneal/sural nerve		1/10						
Trapezoid body-axon + staining Nerve degeneration		6/9 3/9						5/10 2/9
Total	5	6					4	7
Dorsal root ganglia mineralization							1/10	
Minimal hydrocephalus							1/10	
Optic nerve chiasm unilateral optic tract atrophy moderate	1/10							

A single female given 45 mg/kg/day had slight bilateral dilation of the renal pelvis. The sponsor does not consider this drug related because it lies within historical control data for this variation [n=25 studies 2001-2004 with 6/659=0.9% evaluated F1 females had slight or greater dilation of the renal pelvis range 0-1%]

A statistically significant increase in the average age of preputial separation occurred at 45 mg/kg/day (PND 46.9 compared to control PND 45.4) representing a 3% difference. The sponsor does not consider this drug related because the value is within the historical range for the test lab [n=25 studies 2001-2001 preputial separation assessed in 647 control males range PND 44.5-49.2, mean PND 46.9]

Pravastatin: Oral study of reproductive development in rats

Key study findings: Essentially this is a fertility study in juvenile rats (male & female) The NOAEL for reproductive toxicity was <5 mg/kg/d in males and 45 mg/kg/day in females

Treated Males

- Seminiferous tubular dilatation was observed in treated rats given ≥ 5 m/k/d. The background incidence of this finding is not reported in the historical control ata.
- Pravastatin ≥ 15 mg/kg/day increases in body weight gain (15 and 19% greater than controls respectively) during PND 94-143. Statistically significant transient decreases in body weight gain were observed in males given 5 m/k/d (PND 11-14; 14-18) and 45 m/k/d (PND 28-31). .
- Pravastatin 45 mg/kg/day was associated with
  - ungroomed coat
  - preweaning period PND 14-21 decreases of <20% in body weight gain compared to controls
  - postweaning PND 45-59 increases of >9% body weight gain compared to controls
  - 9% increase in food consumption during PND 28-80 and 11% increase in the post dose period PND 98-140 compared to controls which correlates to the increased body weight gain observed post-weaning
  - Minimal decreases in fertility (84 and 87% fertile compared to 100% controls during the first cohabitation and recovery -second cohabitation periods respectively). Fertility (87%) remained reduced compared to 100% in controls following a 9-week drug free recovery period whereas with the exception of 2 rats with grade 5 bilateral tubular degeneration (historical control incidence 4/409=0.97%; range 0-10%) the cause of infertility was not apparent from sperm or testicular histopathology. The fertility appeared to recover in some but not all rats.
  - Decreased (12.5% less than controls) motile sperm were observed at the end of dosing PND 81 Increased abnormal (morphologic) sperm (15% compared to 4%in controls) were observed PND 81.

Treated females

- Pravastatin at ≥5 mg/kg/day resulted in increased maternal body weight gain of 14, 12, 20% compared to controls and food consumption (9, 12, 16% compared to controls) on GD 0-20. In females given 5 m/k/d an increase in body weight gain was observed (PND 59-63; 73-77) however decreases at 15 m/k/d PND 14-18 were observed
- Pravastatin 45 mg/kg/d resulted in reduced body weight gain by 19% compared to control PND 14-21 and increased body weigh gain by 20% compared to controls from PND 49-80. Increased food consumption by 12% compared to controls was observed during PND 28-77 (postweaning dosing period)
- Pravastatin ≥15 mg/kg/day resulted in clinical observations of ungroomed coat
- No drug related effects on reproductive development or function were observed in females at doses up to 45 mg/kg/day

Study no.: DNO5016

Volume #, and page #: 288.1-288.4
Conducting laboratory and location: (b) (4)
Date of study initiation: 2/22/05
GLP compliance: Y
QA reports: yes (X) no ( )
Drug, lot #, and % purity: Mayaguez lot # H623G (aka Sankyo lot # TT213) 94.6% pure

Methods

Doses: 5, 15, 45 mg/kg/day

Species/strain: Sprague-Dawley rat

Number/sex/group and study design: 63/sex/group control; 3 subsets of dosing group rats were used. Males were dosed PND 4-80: **Subset 1**: 28/sex/group were designated for TK and euthanized PND 7/8, **Subset 2**: 10/sex/group for repro organ morphology evaluation and euthanized PND 81; **Subset 3**: 25/sex/group designated for functional evaluations (sexual maturation, estrus, mating and fertility) and cohabitated with untreated rats following the last dose on PND 80. The untreated females mated with Subset 3 males and Subset 3 females mated with untreated males were euthanized and cesarean sectioned on GD 20 and offspring were evaluated for gross alterations. Due to altered sperm endpoints and reduced fertility in the 45 mg/kg/day males at the completion of the dosing period, Subset 3 males were continued on study for 9 weeks after dosing cessation (at least one spermatogenic cycle) and placed in cohabitation with an additional group of untreated females on PND 143. Untreated females from this second mating trial were euthanized and cesarean sectioned on GD20 and their offspring evaluated for gross alterations. Males were euthanized PND 170-172 and evaluated for repro histopath and sperm parameters after the 9 week recovery.

Route, formulation, volume, and infusion rate: 5 ml/kg in deionized water oral gavage

Parameters and endpoints evaluated:

Subset Number	Evaluation	Day of Evaluation (Postnatal)
1	Toxicokinetics (28 rats/sex/dose group)	Day 7
2	End-of-Dose Necropsy, Reproductive Organ Weights, Sperm Evaluations, and Histopathology (10 rats/sex/dose group)	Day 81
3[a]	Female Sexual Maturation - Vaginal Patency (First Day)	Day 28
	Male Sexual Maturation - Preputial Separation (First Day)	Day 39
	Estrous Cycling Evaluations	Days 60 to 80
	Mating & Fertility Evaluations (First Day of Cohabitation)	Days 80 and 143
	Caesarean-Sectioning Observations & Fetal Gross External Evaluations (First Day of Evaluation)	Days 100 and 163
	Male Necropsy, Reproductive Organ Weights, and Sperm Evaluations	Days 170 to 172

a. 25 rats assigned/sex/dose group.

Results

F0 In-life: No drug related mortalities or morbidity were observed. Increased incidences of ungroomed coat were observed in males given 45 m/k/d and females at ≥ 15 m/k/d.

No effect on body weight was observed in males given 5 m/k/d. Drug related increases in body weight gain were observed at higher doses in males and in females at all doses. The body weight gains at 5 and 15 m/k/d were noted during the postdose/gestational phase (15% greater than controls in males at 15 m/k/d on PND 94-143 and 14% and 12% greater than controls in females at 5 and 15 m/k/d on GD 0-20. The increases at 45 m/k/d occurred during the dosing/premating phase (9% greater than controls in males on PND 45-59; 20% greater than controls in females on GD 0-20). Drug related changes in the 45 m/k/d group of both genders included decreases in body weight gain during the preweaning period (19-20% less than controls on PND 14-21). Statistically significant transient decreases in body weight gain were observed in males given 5 m/k/d (PND 11-14; 14-18) and 45 m/k/d (PND 28-31). In females given 5 m/k/d an increase in body weight gain was observed (PND 59-63; 73-77) however decreases at 15 m/k/d PND 14-18 were observed.

PROTOCOL MBA00087: PRAVASTATIN: ORAL STUDY OF REPRODUCTIVE DEVELOPMENT IN RATS (SPONSOR'S STUDY NUMBER: DN05016)

TABLE 21 (PAGE 1): MATERNAL BODY-WEIGHT CHANGES - GESTATION - SUMMARY - F_1 GENERATION FEMALE RATS MATED WITH UNTREATED MALE RATS

DOSE GROUP		I	II	III	IV
DOSE (MG/KG/DAY)a		0(VEHICLE)	5	15	45
SUBSET 3					
RATS TESTED	N	25	25	25	25
PREGNANT	N%	25(100.0)	24(96.0)	25(100.0)	24(96.0)
BODY-WEIGHT CHANGE (G)					
DAYS 0 - 4	MEAN±S.D.	+18.5 ± 5.5	+21.0 ± 8.3	+22.3 ± 6.4	+22.3 ± 6.3
DAYS 4 - 7	MEAN±S.D.	+12.1 ± 4.6	+12.9 ± 4.0	+14.0 ± 5.2	+14.0 ± 5.2
DAYS 7 - 11	MEAN±S.D.	+19.9 ± 11.6	+24.0 ± 4.7	+24.2 ± 5.9	+25.2 ± 5.4
DAYS 11 - 14	MEAN±S.D.	+14.9 ± 12.3	+18.2 ± 7.9	+17.3 ± 5.6	+19.0 ± 3.8
DAYS 14 - 18	MEAN±S.D.	+47.2 ± 9.5	+53.0 ± 6.0*	+51.2 ± 9.9	+53.2 ± 6.2*
DAYS 18 - 20	MEAN±S.D.	+29.2 ± 10.4	+32.8 ± 7.4	+30.2 ± 10.6	+36.6 ± 7.7**
DAYS 0 - 20	MEAN±S.D.	+141.8± 32.7	+162.0± 20.1*	+159.1± 27.6*	+170.4± 21.0**

THIS TABLE IS RESTRICTED TO PREGNANT RATS
DAYS = DAYS OF GESTATION
a. Postnatal Days 4 through 80.
* Significantly different from the vehicle control group value ($p \leq 0.05$).
** Significantly different from the vehicle control group value ($p \leq 0.01$).

There were no effects on food consumption in males at 5 or 15 m/k/d. Drug related increases in food consumption corresponded to increases in body weight gain in males given 45 m/k/d (9% greater than controls PND 28-80 and 11% greater than controls PND 98-140) and in females at all doses an generally occurred during gestation. However the increases in food consumption at 45 m/k/d occurred from weaning through the end of dosing (12% greater than controls on PND 28-77) and continued during gestation (F2?; 16% greater than controls on GD 0-20).

Treated males mated with untreated females resulted in a decreased fertility index based on the number of pregnancies per number of mated rats of: 100, 96, 96, 87% at 0, 5, 15, 45 mg/kg/day respectively.
In untreated female rats mated with treated males there was an increase in resorptions with drug treatment: 12, 37.5, 56.5**($p<0.01$), 47.6* ($p<0.05$)% given 0, 5, 15, 45 mg/kg/day respectively. This was similarly observed in untreated females mated with treated males that had caesarian deliveries GD20 where postimplantation loss expressed as % resorptions were 1.4, 2.9, 4.6, 3.3 conceptuses/litter in 0, 5, 15, 45 mg/kg/day respectively.

Toxicokinetics	AUC 0-24 (µg h/ml) PND 7	
Dose (mg/kg/day)	Male	Female
5	2.05	2.9
15	8.42	6.00
45	28.6	41.3

Exposure in females was less than dose proportional at LD, MD and greater than dose proportional at HD. Male exposure was dose proportional

Necropsy: A 12.5% decrease in sperm motility compared to the control and a moderate increase in the number of abnormal sperm (15% compared to 4% controls) noted in rats dosed 45 m/k/d from PND 4-80 (subset 2) noted in the Peer Reviewed Pathologist Report. The pathologist claims theses abnormalities were attributed to 3/10 rats of which 2/3 had bilateral histopathological testes changes (grade 5 tubular degeneration, grade 3 tubular dilatation). The 3rd rat had moderate decreases in sperm motility (49% motile compared to 89% in controls).

Additional testicular findings in subset 2 were a one 5 m/k/d rat with grade 4 unilateral (presumed right based on correlative small epididymis gross pathology) tubular degeneration and one 15 m/k/d rat with grade 3, unilateral tubular dilatation (presumed left, based on enlarged testis gross pathology). For the left testis with tubular dilatation the sperm count an dmotility from the left epididymis and vas derens were within normal range but there was a slight increase in abnormal sperm (9% compared to upper range of 6.5% in controls).

Table 1. Sperm parameters (mean ± standard deviation) and histopathological findings i the testes of rats dosed with pravastatin on PNDs 4 - 80

Pravastatin dose (mg/kg/day)	0	5	15	45
Number of rats examined	10	10	10	10
Epididymal/vas deferens sperm parameters				
Caudal sperm count (10^6 /per gram cauda)	1043± 172	791± 273	1063± 263	954± 369
Percent motile sperm	89.1± 9.9	92.9 ±2.9	92.0± 5.0	76.6±23.7[a]
Percent abnormal sperm	4.4 ±1.7	3.7 ±1.2	5.1 ±2.6	14.6 ±26.1
Testis Histopathology*				
Tubular dilatation (grade 3)	0	0	1u	1b
Tubular degeneration (grade 4 or 5)	0	1u	0	1b

* Number of rats with findings, u = unilateral, b = bilateral

a - Excludes rat 8201 for which the morphology sample had insufficient number of sperm to adequately evaluate this parameter.

Table 2: Mating and fertility evaluation in rats dosed with pravastatin on PND 4 – 80 at end of dosing and at the end of a 9-week recovery period

Pravastatin dose (mg/kg/day)	0	5	15	45
End of Dosing				
Number of rats examined	25	25	25	25
Rats that mated	25	25	25	25
Rats that sired (fertility index)	25 (100%)	24 (96%)	23 (92%)	21 (84%)
End of Recovery				
Number of rats examined	24	25	25	25
Rats that mated	23	25	25	23
Rats that sired (fertility index)	23 (100%)	24 (96%)	24 (96%)	20 (87%)

F0 Male Rats Necropsy Findings								
	0		5		15		45 m/k/d	
	M	F	M	F	M	F	M	F
Right Kidney pelvis slight-moderate dilatation	2/35	0/35	0/35	0/35	6/35	0/35	4/35	1/35
Testes flaccid	1/35		1/35		2/35		3/35	
Liver accessory median lobe							1/35	
Left Axilla Mass		0/35		0/35		0/35		1/35

Sperm assessment and testicular pathology of Subset 3 rats at the end of 9 Wk recovery
A single rat in each of the 15 and 45 m/k/d groups at the end of dosing and 1 rat in each treated group at the end of 9 week recovery had seminiferous tubule dilatation which was generally unilateral in the absence of other fertility or sperm morphology/motility changes with had normal seminiferous epithelium morphology.

Table 3: Sperm parameters (mean ± standard deviation) and histopathological changes in the testes at the end of the recovery period.

Pravastatin dose (mg/kg/day)	0	5	15	45
Number of rats examined	25	25	25	25
Epididymal/vas deferens sperm parameters[a]				
Caudal sperm count (10^6 /per gram cauda)	934± 345	878 ±403	1025±365	975 ±482
Percent motile sperm	94.2 ±4.1	93.9±4.5[b]	93.1±7.3[b]	94.3±5.0[b]
Percent abnormal sperm[c]	5.9±2.3	5.6 ±2.7	8.0 ±14.4	6.9 ±2.8
Testis Histopathology*				
Tubular dilatation (grade 3)	0	1u	1u	1u
Tubular degeneration (grade 5)	1u	1b	2uu	2ub

* Number of rats with findings, u = unilateral, b = bilateral

a - Excludes rats 903 (Group I) and 4102 (Group II) that were euthanatized on PNDs 114 and 148, respectively.

b - Excludes rats 4202 (Group II), 6402 (Group III), 7503, and 8502 (Group IV) for which the motility samples had insufficient number of sperm to adequately evaluate this parameter.

c - Excludes three Group I, three Group II, three Group III, and two Group IV rats for which the morphology samples were damaged during processing.

The sponsor states, no drug related changes in caesarean sectioning or gross fetal alterations at any dose. In litters of untreated dams mated with treated males, early resorptions and postimplantation loss were statistically increased at 15 and 45 m/k/d in the first mating trial and decreased at 45 m/k/d in the second mating trial. This corresponds to the fertility index (# pregnancies/number of rats mated) which was reduced to 84% in the 45 m/k/d group compared to controls (100%). This is attributed to the failure of 4/25 males to mate. At the end of recovery the animals were mated again and one control and 2/4 of the prior failures to sire from the 45 m/k/d group (87% fertile vs. 100% controls) in mating 1, again failed to mate. This is within the historical control range for infertility. The sponsor doesn't consider these observations drug related because they aren't dose dependent, values are within historical controls and the number of live fetuses/litter (another index of resorptions) in treated groups were comparable to controls.

Correlating testicular pathology with sperm parameters is difficult because many of the testicular lesions were unilateral and sperm parameters were only measured from the left epididymis and vas deferens. Therefore in subset 2 there was correlation between testicular histopathology and altered sperm parameters for the 2 animals with bilateral changes (tubular dilatation grade 3 and tubular degeneration grade 5) from the 45 m/k/d group. In subset 3 where fertility was measured at dosing termination and again after 9 week recovery the fertility index was similar. However rats failed to mate on each

occasion. There was poor correlation between animals failing to mate and animals with testicular changes or fertility failure.

F_1 physical development: From the 0, 5, 15, 45 mg/kg/day treated groups; 23-25 (n=326-369 fetuses), 24 (n=362-388 fetuses), 24-25 (n=355-380 fetuses), 20-24 (n=297-382 fetuses) litters respectively were evaluated postnatal days 4-80. All were without gross external findings. One fetus sired by a 15 m/k/d male in the first mating trial had multiple head malformations (open eyelids, depressed eye bulge, protruding tongue) and body (craniorrachischisis-fissure of skull and spine and short trunk). Since this was a single occurrence restricted to the MD and all subsequent fetuses sired by the same male were unremarkable this was considered not drug related by the sponsor.

Untreated females mated with treated males delivered by caesarian section on GD 20 had live male fetuses with decreased body weights: 3.88; 3.71*; 3.72*; 3.66** given 0, 5, 15, 45 mg/kg/day respectively. The sponsor does not consider these observations as drug related because the differences are 5% of controls, not dose dependent and reduction may reflect the slightly larger litter sizes in the treatment versus control groups (14.8-15.1 live fetuses/litter compared to 14.2 for controls). Female fetal body weights were unremarkable.

PROTOCOL MBA00087: PRAVASTATIN: ORAL STUDY OF REPRODUCTIVE DEVELOPMENT IN RATS (SPONSOR'S STUDY NUMBER: DN05016)

TABLE 14 (PAGE 1): SPERM MOTILITY, COUNT, AND DENSITY - SUMMARY - F_1 GENERATION MALE RATS

SUBSET 2												
DOSAGE GROUP		I			II			III			IV	
DOSAGE (MG/KG/DAY)a		0 (VEHICLE)			5			15			45	
RATS TESTED	N	10			10			10			10	
VAS DEFERENS SPERM MOTILITY												
NUMBER MOTILE	MEAN±S.D.	329.4	±	133.3	374.3	±	124.0	315.0	±	109.2	242.8 [9]e	± 77.9
MOTILE PERCENT	MEAN±S.D.	89.1	±	9.9	92.9	±	2.9	92.0	±	5.0	76.6 [9]e	± 23.7
STATIC COUNT (NONMOTILE)	MEAN±S.D.	31.4	±	20.7	26.5	±	9.3	27.4	±	20.2	99.8 [9]e	± 145.2
TOTAL COUNT b	MEAN±S.D.	360.8	±	121.0	400.8	±	127.2	342.4	±	117.4	342.6 [9]e	± 127.8
CAUDA EPIDIDYMAL SPERM COUNT												
SPERM COUNT c	MEAN±S.D.	88.3	±	16.1	70.6	±	23.2	83.3	±	19.6	82.7	± 34.6
SPERM DENSITY d	MEAN±S.D.	1043.26	±	172.16	791.18	±	272.70	1063.23	±	263.13	954.19	± 369.03

a. Postnatal Days 4 through 80.
b. Sum of number motile and static count. Groups of five fields were evaluated until a sperm count of at least 200 was achieved c 20 fields were evaluated.
c. Sperm count used in the calculation of sperm density. Ten fields were evaluated.
d. The sperm density was calculated by dividing the sperm count by the volume in the image area (34.3 x 10^{-6} mL), multiplying by 2 (dilution factor) and multiplying by 10^{-6} to obtain the sperm concentration. The calculated sperm concentration value (rounded to 1 decimal place) was multiplied by 50 (volume) and divided by the weight of the left cauda epididymis (see Appendix 11 for the weight of the left cauda epididymis) to obtain the sperm density. The calculated value will vary by approximately 0.8% from the Computer Automated Sperm Analysis because the digital image evaluated is slightly smaller (4 pixels) than the actual field causing a slight underestimate of the actual volume and an overestimate of the concentration.
e. Excludes rat 8201 for which the motility sample had insufficient number of sperm to adequately evaluate this parameter.

PROTOCOL MBA00087: PRAVASTATIN: ORAL STUDY OF REPRODUCTIVE DEVELOPMENT IN RATS (SPONSOR'S STUDY NUMBER: DN05016)

TABLE 14 (PAGE 2): SPERM MOTILITY, COUNT, AND DENSITY - SUMMARY - F_1 GENERATION MALE RATS

SUBSET 3														
DOSAGE GROUP		I			II			III			IV			
DOSAGE (MG/KG/DAY)a		0 (VEHICLE)			5			15			45			
RATS TESTED	N	25			25			25			25			
INCLUDED IN ANALYSES	N	24b			24b			25			25			
VAS DEFERENS SPERM MOTILITY														
NUMBER MOTILE	MEAN±S.D.	330.4	±	89.7	377.0	±	126.4	358.9	±	128.8	357.8	±	125.8	
					[23]f			[24]f			[23]f			
MOTILE PERCENT	MEAN±S.D.	94.2	±	4.1	93.9	±	4.5	93.1	±	7.3	94.3	±	5.0	
					[23]f			[24]f			[23]f			
STATIC COUNT (NONMOTILE)	MEAN±S.D.	20.7	±	15.4	23.4	±	16.1	26.7	±	29.8	20.9	±	16.6	
					[23]f			[24]f			[23]f			
TOTAL COUNT c	MEAN±S.D.	351.1	±	95.1	400.3	±	128.6	385.6	±	132.1	378.7	±	129.3	
					[23]f			[24]f			[23]f			
CAUDA EPIDIDYMAL SPERM COUNT														
SPERM COUNT d	MEAN±S.D.	117.6	±	45.3	114.9	±	58.4	131.6	±	53.1	122.8	±	70.2	
SPERM DENSITY e	MEAN±S.D.	933.91	±	345.36	877.54	±	403.40	1024.77	±	364.84	975.15	±	482.22	

a. Postnatal Days 4 through 80.
b. Excludes rats 903 (Group I) and 4102 (Group II) that were euthanatized on Postnatal Days 114 and 148, respectively.
c. Sum of number motile and static count. Groups of five fields were evaluated until a sperm count of at least 200 was achieved c 20 fields were evaluated.
d. Sperm count used in the calculation of sperm density. Ten fields were evaluated.
e. The sperm density was calculated by dividing the sperm count by the volume in the image area (34.3×10^{-6} mL), multiplying by 2 (dilution factor) and multiplying by 10^{-6} to obtain the sperm concentration. The calculated sperm concentration value (rounded to 1 decimal place) was multiplied by 50 (volume) and divided by the weight of the left cauda epididymis (see Appendix 11 for the weight of the left cauda epididymis) to obtain the sperm density. The calculated value will vary by approximately 0.8% from the Computer Automated Sperm Analysis because the digital image evaluated is slightly smaller (4 pixels) than the actual field causing a slight underestimate of the actual volume and an overestimate of the concentration.
f. Excludes rats 4202 (Group II), 6402 (Group III), 7503, and 8502 (Group IV) for which the motility sample had insufficient number of sperm to adequately evaluate this parameter.

Based on further analysis of the cauda epididymal sperm morphology in F1 males given 45 m/k/d statistically significant increases in absent sperm heads (14.2±23.3 given 45 m/k/d versus control 3.5±1.4) were the most common abnormal sperm morphology observed. Following 9 weeks recovery sperm counts motility and morphology were comparable from 45 m/k/d and controls although broken flagellum (2.2±2.1 given 45 m/k/d versus controls 0.5±0.7) was minimally elevated during recovery.

PROTOCOL MBA00087: PRAVASTATIN: ORAL STUDY OF REPRODUCTIVE DEVELOPMENT IN RATS (SPONSOR'S STUDY NUMBER: DN05016)

TABLE 26 (PAGE 1): CAESAREAN-SECTIONING OBSERVATIONS - SUMMARY - F_1 GENERATION FEMALE RATS MATED WITH UNTREATED MALE RATS

DOSE GROUP DOSE (MG/KG/DAY)a		I 0(VEHICLE)	II 5	III 15	IV 45
SUBSET 3					
RATS COHABITED	N	25	25	25	25
RATS MATED	N	25	24	25	25
PREGNANT	N(%)	25(100.0)	24(96.0)	25(100.0)	24(96.0)
RATS PREGNANT AND CAESAREAN-SECTIONED ON DAY 20 OF GESTATION	N	25	24	25	24
CORPORA LUTEA	MEAN±S.D.	16.1 ± 2.4	18.2 ± 3.0*	16.8 ± 3.1	17.7 ± 2.2
IMPLANTATIONS	MEAN±S.D.	15.6 ± 2.3	16.9 ± 1.9	15.9 ± 3.1	16.7 ± 1.9
% PREIMPLANTATION LOSS	MEAN±S.D.	3.2 ± 5.7	6.4 ± 9.1	5.2 ± 7.5	5.5 ± 5.8
LITTER SIZES	MEAN±S.D.	14.8 ± 3.2	16.2 ± 1.7	15.2 ± 2.9	15.9 ± 1.6
LIVE FETUSES	N	369	388	380	382
	MEAN±S.D.	14.8 ± 3.2	16.2 ± 1.7	15.2 ± 2.9	15.9 ± 1.6
DEAD FETUSES	N	0	0	0	0
RESORPTIONS	MEAN±S.D.	0.8 ± 2.2	0.7 ± 0.8	0.7 ± 0.8	0.8 ± 0.8
EARLY RESORPTIONS	N	16	17	16	18
	MEAN±S.D.	0.6 ± 1.5	0.7 ± 0.8	0.6 ± 0.8	0.8 ± 0.8
LATE RESORPTIONS	N	4	0	2	0
	MEAN±S.D.	0.2 ± 0.8	0.0 ± 0.0	0.1 ± 0.3	0.0 ± 0.0
DAMS WITH ANY RESORPTIONS	N(%)	8(32.0)	12(50.0)	13(52.0)	13(54.2)
DAMS WITH ALL CONCEPTUSES RESORBED	N(%)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
DAMS WITH VIABLE FETUSES	N(%)	25(100.0)	24(100.0)	25(100.0)	24(100.0)
DAMS WITH NORMAL PLACENTAE	N(%)	25(100.0)	24(100.0)	25(100.0)	24(100.0)

a. Postnatal Days 4 through 80.
* Significantly different from the vehicle control group value ($p \leq 0.05$).

PROTOCOL MBA00087: PRAVASTATIN: ORAL STUDY OF REPRODUCTIVE DEVELOPMENT IN RATS (SPONSOR'S STUDY NUMBER: DN05016)

TABLE 27 (PAGE 1): LITTER OBSERVATIONS (CAESAREAN-DELIVERED FETUSES) - SUMMARY - F_1 GENERATION FEMALE RATS MATED WITH UNTREATED MALE RATS

DOSE GROUP DOSE (MG/KG/DAY)a		I 0(VEHICLE)	II 5	III 15	IV 45
SUBSET 3					
LITTERS WITH ONE OR MORE LIVE FETUSES	N	25	24	25	24
IMPLANTATIONS	MEAN±S.D.	15.6 ± 2.3	16.9 ± 1.9	15.9 ± 3.1	16.7 ± 1.9
LIVE FETUSES	N	369	388	380	382
	MEAN±S.D.	14.8 ± 3.2	16.2 ± 1.7	15.2 ± 2.9	15.9 ± 1.6
LIVE MALE FETUSES	N	182	179	180	211
% LIVE MALE FETUSES/LITTER	MEAN±S.D.	50.4 ± 12.9	46.1 ± 14.2	47.0 ± 14.5	55.0 ± 12.5
LIVE FETAL BODY WEIGHTS (GRAMS)/LITTER	MEAN±S.D.	3.55 ± 0.47	3.61 ± 0.22	3.54 ± 0.30	3.50 ± 0.32
MALE FETUSES	MEAN±S.D.	3.63 ± 0.50	3.71 ± 0.22	3.65 ± 0.32	3.58 ± 0.34
FEMALE FETUSES	MEAN±S.D.	3.47 ± 0.43	3.51 ± 0.25	3.46 ± 0.31	3.41 ± 0.31
% RESORBED CONCEPTUSES/LITTER (POSTIMPLANTATION LOSS)	MEAN±S.D.	5.2 ± 14.8	4.0 ± 4.7	4.2 ± 4.8	4.3 ± 4.4

a. Postnatal Days 4 through 80.

F_2 findings: not provided

2.6.6.9 Discussion and Conclusions

2.6.6.10 Tables and Figures

2.6.7 TOXICOLOGY TABULATED SUMMARY

OVERALL CONCLUSIONS AND RECOMMENDATIONS

A complete battery of reprotoxicity studies was performed with Pravastatin to support the original NDA filing. There is no evidence of teratogenicity or other adverse effects on reproductive function at parental exposures that were 60-120 times systemic exposure in rats and 10 times in rabbits following an 80 mg human dose based on body surface area. However a review of these reproductive toxicity studies suggests some evidence of developmental toxicity. The sponsor suggests that Pravastatin is relatively hydrophilic and hepato-selective in its distribution compared to other statins and this may explain its lack of teratogenicity. Distribution into the liver is reported to occur via an anion transporter. However exposure of the fetal/neonatal neurologic tissues to Pravastatin can be demonstrated by indirect exposure in milk or transfer across the placenta following dosing pregnant rats, or by direct dosing rat neonates.

Fetal exposures to Pravastatin were demonstrated following a single 20 mg/kg dose to pregnant rats on Gestation Day 18 (GD18). There is relatively low placental transfer of Pravastatin but there is slow fetal clearance based on whole body autoradiography. Excretion of Pravastatin into maternal milk was 6.5X higher than plasma following administration of 20 mg/kg to female rats on Lactation Day 12 corresponding to a milk Cmax=1.4 µg/ml at 24h post-dose. This maximal concentration in milk is similar to plasma levels achieved by direct dosing neonates at 10-15 mg/kg/day PND 7-21 where some neurodevelopmental findings were observed.

(b) (4)

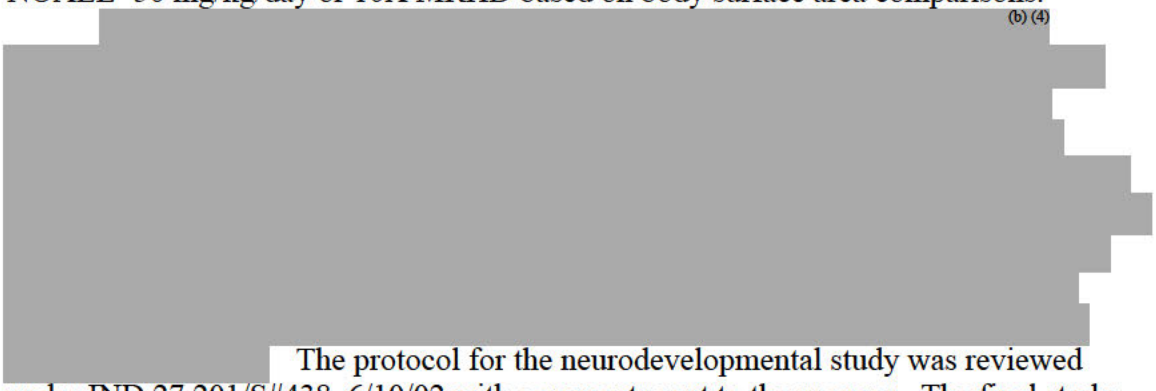
a review of the supporting studies shows an increase in non-fostering dams at 1000 mg/kg/day which is suggestive of maternal toxicity and could explain the decrease in neonatal survival PND 0-4 during the embryo-fetal developmental studies. This does not explain the developmental toxicity evident by increased mortality and skeletal anomalies at lower doses. The NOAEL for neonatal pup mortality is 20 mg/kg/day or 2X systemic exposure following an 80 mg clinical dose based on mg/M^2 comparisons. The NOAEL for skeletal variations is 4 mg/kg/day at systemic exposures below those expected from an 80 mg clinical dose based on mg/ M^2 comparisons. Alterations in the sex ratio are observed at all doses.

In perinatal-postnatal development in the rat the sponsor notes no effect at 10 and 100 mg/kg/day on Fo or F1 generation rats. At 1000 mg/kg/day maternal toxicity is observed consisting of reduced maternal body weight and food consumption without affecting F1 or F2 generation rats suggesting a developmental NOAEL=1000 mg/kg/day at 120X systemic exposures from an 80 mg clinical dose based on body surface area. However altered sex ratios, increased pup mortality, microphthalmia (malformation) and developmental delays in vaginal opening, testes decent, separation (unfolding) of the ears are observed at doses ≤ 100 mg/kg/day in the absence of maternal toxicity suggesting that the developmental NOAEL was < 10 mg/kg/day or systemic exposure similar to that

achieved with an 80 mg clinic dose based on mg/M^2 comparisons. This suggests that Pravastatin may be developmentally toxic at lower doses than previously acknowledged at least in the rat.

In embryo-fetal development in the rabbit, maternal toxicity is observed at 50 mg/kg/day without any adverse effects on development suggesting a developmental NOAEL=50 mg/kg/day or 10X MRHD based on body surface area comparisons.

(b) (4)



The protocol for the neurodevelopmental study was reviewed under IND 27,201/S#438, 6/10/02 with comments sent to the sponsor. The final study report is reviewed in this submission.

The postnatal neurodevelopmental data consist of studies DN03001 (range-finding), DN03056 (toxicokinetics) and the definitive study DN03098. The dose range finding study indicates morbidity/mortality at 50 mg/kg/day. The toxicokinetic study indicates morbidity/mortality at 100 mg/kg/day in both genders and at lower doses in males (10, 50 mg/kg/day). In both studies, rats were dosed from PND 4-42. In the definitive study (dosing PND4-80) one male and one female were found dead PND 24 and 18 respectively given 45 mg/kg/day without evidence of toxicity or gross lesions at necropsy. This correlates with mortality seen in the previous studies. However it doesn't explain the 4X difference in exposure between studies DNO3056 and DN03098 on PND 7. The sponsor attributes the increased exposure (~30-fold) PND7 compared to PND 42 or later to immature liver function and hence drug clearance. Exposures at PND 42 are similar to adult levels at the same dose. In the toxicokinetic study, a 20% decrease in body weight gain is seen at 100 mg/kg/day prior to PND21 and increased liver enzymes at $\geq$ 25 mg/kg/day at PND21 were observed.

In the definitive neurodevelopmental assessment of neonates following direct dosing, decreased thickness of the corpus callosum at the PND 132 (after 50 day recovery) in groups given $\geq$15 mg/kg/day was observed: in males (-10%) and females (-12%) at 15 mg/kg/day and at 45 mg/kg/day (-13% M and -17% F respectively). This finding occurs at exposures $\geq$ 5506 ng h/ml or 20X systemic exposure following an 80 mg clinical dose (AUC= 281 ng h/ml in fasted). The sponsor indicates that the clinical relevance of this finding is unclear. The NOAEL for this finding is 5 mg/kg/day (AUC$\leq$1623 ng h /ml) which is 5X higher than systemic exposure following an 80 mg human dose (AUC=281 fasted or 176 ng h/ml nonfasted). However a 4-fold difference in exposures is seen in neonatal rats across studies during early exposure (PND7) suggesting significant variability. Therefore the robustness of this apparent 5-fold safety margin established during the recovery phase (PND 132) may be tenuous.

The corpus callosum is a thick bundle of nerve fibers containing myelinated and unmyelinated axons which function in the transfer of information between the cerebral

hemispheres. Fibers of the future corpus callosum are derived from neuroblasts when the human fetus is in the first trimester (gestation week 12-18). At 5 months the fetus has in general the adult structure. Initial formation occurs in the genu and the body, progressing posteriorly. The anterior genu and rostrum develops last, folding back under the genu. The collosum thickens with increasing myelination. The appearance of a thin corpus callosum at the anterior commissure just posterior to the genu is consistent with the established association between lower CNS cholesterol and myelination by HMG CoA reductase inhibitors (statins).

Since the measurement of the thickness of the corpus callosum was only performed in one region (anterior commissure just posterior to the genu) it is unknown if the effect was present throughout the structure. Established functional cortical nerve fiber tracts project onto specific regions of the corpus callosum. The motor cortex sends fibers through the rostrum and genu in the anterior of the corpus callosum, the somatosensory cortex projects fibers through the anterior half of the corpus callosum and axons arising from auditory regions pass through the posterior 2/3rd of the corpus callosum and the dorsal splenium (most posterior portion). Axons from the limbic cortex also form the posterior region of the corpus callosum. Axons from visual cortices occupy the largest fraction of the cortical mantle pass through the largest portion of the corpus callosum; the fibers are present throughout the splenium and extend into the body and anterior portion. It would be useful to correlate neural variations in regions of the corpus callosum to the functional neurobehavioral findings in acoustical startle and the water maze assessments however since it is unknown if the reduced thickness of the corpus callosum extends beyond the region examined (just posterior to the genu) this would be speculative.

A higher magnitude acoustical startle response in rats given 45 mg/kg/day on PND 117-119 (123% M, 88% F higher response magnitude than controls) was observed in the neurodevelopmental study. Delayed acquisition of an avoidance response was observed in Segment 2 & 3 rat studies at 100 mg/kg/day (12X human exposure at 80 mg/day based on body surface area) although this did not reach statistical significance. Increased number of errors in learning (watermaze) in females on PNDs 116 and 117 (83% higher error rate per trial than controls) were observed. Decreased absolute and relative brain weights in males (4 and 12% less than controls, respectively) and females (5 and 22% less than controls, respectively) on PND 132 were also observed. The neurobehavioral changes noted at 45 mg/kg/day (AUC=11969 ng h/ml F; AUC=14262 ng h/ml M) occur at 43X systemic exposure achieved at an 80 mg human dose.

Further insight can be obtained from gene knockout mouse models. Inactivation of HMGCoA reductase gene expression is lethal during embryonic development and cannot be developed. Other enzymes in cholesterol biosynthesis can be inactivated without causing mortality. Squalene synthase (SQS) is the first step in sterol biosynthesis. A squalene synthethase gene mutant (Fdft1) mouse model has been developed which is characterized by severely perturbed myelin synthesis (Nature Neuroscience 8:468-475, 2005). The severely disturbed myelin synthesis in the SQS mice is suggested to be a result of SQS deficient oligodendrocytes; the producers of cholesterol in normal brain white matter. Mutant oligodendrocytes survive by using cholesterol from neighboring wild type cells of other types. Any myelin made has levels close to normal demonstrating that cholesterol availability is the critical prerequisite and a limiting factor of myelin membrane growth during brain maturation. These animals largely lacked SQS

specific signals in the white matter such as the corpus callosum. The corpus callosum and cerebellar white matter showed a marked reduction of myelin staining in mutant mice. Most axons showed abnormally thin myelin sheaths or were unmyelinated although the architecture of the existing myelin appeared normal. The gray matter areas showed little change in myelin thickness in contrast. Weight gain and breeding performance lagged behind the wild-type mice. All mutant mice developed motor functional deficits at 2 weeks of age coinciding with the known peak of CNS myelination in wild-type mice. The deficits included ataxia, initiation tremor and impaired control of hindlimb movements. Mutants that survived past one month rarely died prematurely suggesting that older animals had overcome a critical period in this disorder. The trembling phenotype mutant mice improved with age although myelin thickness in the white matter was still below the controls.

Congenital agenesis (absence or partial/incomplete) of the corpus callosum was considered a rare occurrence in humans. However with the advent of MRI the frequency of occurrence has changed. As a congenital defect it can occur as an isolated condition or in combination with other cerebral abnormalities including Arnold-Chiari malformation, Dandy-Walker syndrome, holoprosencephaly, Anderman syndrome, schizencephaly and in females Aicardi's syndrome. Midline facial defects can also be associated. The CNS midline defect holoprosencephaly has been seen in animals given inhibitors of cholesterol biosynthesis (e.g. statins) and of Sonic Hedgehog (Shh) signal transduction. Heterozygous mutations in Shh are the most common genetic finding in familial holoprosencephaly.

The effects of corpus callosum agenesis the disorder range from subtle to severe depending on the associated brain abnormalities. Mental capacity may be normal with mild compromise of skills requiring matching of visual patterns or the most severe may have intellectual deficits, seizures, hydrocephalus and spasticity. Split-brain surgery for treatment of intractable seizures in adults was initiated in the 1960s. This surgery specifically severs the corpus callosum. Patients appear to tolerate this procedure well, suggesting that this region is not the only mechanism of intercerebral communication. Recently autosomal recessive hereditary spastic paraplegia with thin corpus callosum has been mapped to chromosome 15 and associated with a mutation in the spastin gene. An in vitro study in Cos-7 and HeLa cells provided evidence of the mutated spastin gene in altered microtubule dynamics. When partial or complete agenesis of the corpus callosum occurs as an independent event it is diagnosed in the 2nd decade of human life. Therefore it is not entirely surprising that the thinning noted in the neurodevelopmental study was observed in the sexually mature, male and female rats following recovery. The sponsor considers the clinical relevance of the rat corpus callosum thinning uncertain.

In a recent review of 52 term pregnancies with first-trimester statin exposure reported in AERS 1987-2001, 14 cases of Pravastatin are reported without infant anomalies. However this is not conclusive evidence.

In addition to the neurobehavioral assessment in neonatal animals there is a correlative study with the same doses that evaluates fertility (DNO5016). This is the only study that has not been previously reviewed. Female rats from this study exhibit increased body weight gain at ≥ 5 mg/kg/day but did not exhibit any drug related adverse findings at the highest dose tested of 45 mg/kg/day. Treated neonatal males had increased body weight gain at ≥ 15 mg/kg/day as well as seminiferous tubule dilatation at

≥ 5 mg/kg/day. The later exceeds historical control incidence. Higher doses of 45 mg/kg/day were associated with minimal decreases in fertility of 84% and 87% compared to 100% controls during the first and second cohabitation period respectively. Reduced fertility remained during the 9-week recovery period at 87% in these animals. Two of these rats contributing to the reduced fertility index had grade 5 bilateral seminiferous tubular degeneration. Motile sperm was decreased by 13% compared to controls at the end of dosing and 15% increased abnormal headless sperm were observed in treated males compared to 4% in controls at the end of dosing. At the end of the 9-week recovery 2% of these males had broken sperm flagellum compared to 0.5% in controls.

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/s/

KAREN L DAVIS BRUNO
04/29/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019898/S-061

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Memo to File

Clinical Pharmacology Review

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	19-898/S-061
Submission Date	May 18, 2009
Brand Name	PRAVACHOL®
Generic Name	Pravastatin sodium
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
Team Leader	Sally Y. Choe, Ph.D.
OCP Division	Division of Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Bristol-Myers Squibb Company
Submission Type; Code	Labeling supplement; S
Formulation; Strength(s)	Oral immediate release tablet: 15, 20, 40, and 80 mg
Indication	Adjunct to diet to treat patients with hypercholesterolemia

The sponsor submitted this supplement to change the PRAVACHOL® approved labeling to the Physician's Labeling Rule (PLR) format. However, the sponsor cannot submit the requested pravastatin safety data for this supplement until February 17, 2010, which will pass the PDUFA date for this review cycle. Additionally, the sponsor needs to submit the relevant study synopses to substantiate the validity of the submitted pravastatin-drug interaction table in Section (b) (4) of the proposed PLR labeling. Hence, the review of this supplement cannot be completed until submissions of the above-mentioned information.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-19898	SUPPL-61	BRISTOL MYERS SQUIBB	PRAVACHOL TABLETS

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/s/

S. W. JOHNNY W LAU
11/17/2009

SALLY Y CHOE
11/17/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019898/S-061

OTHER REVIEW(S)

Division of Metabolic & Endocrine Drug Products

Labeling Review

Application Number: NDA 19-898/S-061

Name of Drug: Pravachol (pravastatin) Tablets

Sponsor: Bristol-Myers Squibb

Submission Date: November 18, 2010 resubmission/May 17, 2011 (email and submission)

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-060, was approved on February 28, 2007. This "Prior Approval" supplemental new drug application provides for changes in the format of the Pravachol package insert in response to the Physician's Labeling Rule (PLR).

Review:

Supplement-061 was originally submitted on May 18, 2009, and received a Complete Response letter on November 18, 2009. On November 18, 2010, the sponsor resubmitted the application.

Conclusion:

The members of the reviewing team for this PLR labeling conversion are: Drs. Colman, Amy Egan, and Julie Golden for Clinical; Sally Choe and Johnny Lau for Clinical Pharmacology; and Karen Davis-Bruno for Pharm/Toxicology. PI identifier number 1186935A3 Rev May 2011. Agency will issue an approval letter on this submission.

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

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/s/

MARGARET A SIMONEAU
05/18/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 019898/S-061

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-898/S-061 **PRIOR APPROVAL SUPPLEMENT**

Bristol-Myers Squibb Company
Attention: Daniel J. Papa
Director, Global Regulatory Sciences
P.O. Box 4000 (Mailstop D12-02)
Princeton, NJ 08543-4000

Dear Mr. Papa:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Pravachol (pravastatin sodium) Tablets

NDA Number: 19-898

Supplement number: S-061

Date of supplement: May 18, 2009

Date of receipt: May 18, 2009

This supplemental application proposes changes in the format of the Pravachol package insert in response to the Physician's Labeling Rule.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 17, 2009 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be November 18, 2009.

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

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

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

Sincerely,

{See appended electronic signature page}

Margaret Simoneau, M.S., R.Ph.
Regulatory Project Manager
Division of Metabolism and Endocrine Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Margaret Simoneau
5/29/2009 01:45:53 PM