CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 19-898/S037

Trade Name: **Pravachol Tablets**

Generic Name: **Pravastatin**

Sponsor: **Bristol-Myers Squibb**

Approval Date: **6/23/2000**

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APPLICATION NUMBER:
NDA 19-898/S037

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APPLICATION NUMBER:
NDA 19-898/S037

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-898/S-037

JUN 23 2000

Bristol-Myers Squibb Pharmaceutical Research Institute
Attention: Fred Henry
Director, Global Regulatory Strategy
P.O. Box 4000
Princeton, NJ 08543

Dear Mr. Henry:

Please refer to your supplemental new drug application dated August 24, 1999, received August 26, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pravachol (pravastatin sodium) Tablets.

We acknowledge receipt of your submissions dated November 3, 1999 and February 25, June 5, 14, 19, and 23 (fax), 2000.

This supplemental new drug application provides for changes to the CLINICAL PHARMACOLOGY, Pharmacokinetics/Metabolism subsection regarding age-related differences in mean AUC and mean cumulative urinary excretion of pravastatin and for the addition of a "Geriatric Use" subsection to the PRECAUTIONS section of the Pravachol package insert.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted June 23, 2000).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 19-898/S-037." Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless

this requirement is waived or deferred. We note that a Written Request (WR) for pediatric studies in patients with heterogygous familial hypercholesterolemia (heFH) was sent to you on August 4, 1999. No specific studies in Frederickson Type IIa and IIb are required. We hereby waive the requirement for pediatric studies in these groups, and we defer submission of the pediatric studies in heFH until March 31, 2002.

Submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Margaret Simoneau, R.Ph., Regulatory Project Manager, at (301) 827-6418.

Sincerely,

/S/

John K. Jenkins, M.D.
Acting Director
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 19-898/S037

APPROVED LABELING

BRISTOL-MYERS SQUIBB

WORLDWIDE REGULATORY SCIENCE

Telefax Transmission Cover Sheet

DATE: June 13, 2000

TO: Margaret Simoneau (fax: 301-827-0878)

FROM: Fred Henry

NO. OF PAGES: 10 (including cover page)

SUBJECT: Pravachol – NDA 19-898 Supplement S-037

MESSAGE:

Dear Margaret,

As per the faxed comments from the medical reviewer and our discussion on Friday, attached is revised Pravachol draft labeling supported by data presented in submission S-037 (geriatric labeling). Changes to the originally submitted draft label are found on page 7.

Please let me know if you have any difficulties with this submission.

Sincerely,

Fred Henry

Labeling acceptable

/S/ 6/13/00

MD

If not properly received, please notify promptly
Lucy Soden at (609) 252-4442
Fax: (609) 252-6000

Acceptable

/S/ 6-21-00

CURRENT INSERT- 5134DIM-11
PRAVACHOL® (pravastatin sodium)

PROPOSED REVISIONS

Bristol-Myers Squibb Company

5134DIM-11 S1-000876-09
516422DIM-02 S1-007869-G1
J4-6301 S1-006111-04

Rx only

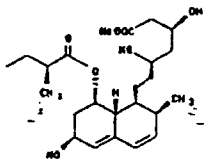
PRAVACHOL®

(pravastatin sodium) Tablets

DESCRIPTION

PRAVACHOL® (pravastatin sodium) is one of a new class of lipid-lowering compounds, the HMG-CoA reductase inhibitors, which reduce cholesterol biosynthesis. These agents are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (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 and 40 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 tablet also contains 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).

CLINICAL PHARMACOLOGY

Cholesterol and triglycerides in the bloodstream circulate as part of lipoprotein complexes. These complexes can be separated by density ultracentrifugation into high (HDL), intermediate (IDL), low (LDL), and very low (VLDL) density lipoprotein fractions. Triglycerides (TG) and cholesterol synthesized in the liver are incorporated into very low density lipoproteins (VLDLs) and released into the plasma for delivery to peripheral tissues. In a series of subsequent steps, VLDLs are transformed into intermediate density lipoproteins (IDLs), and cholesterol-rich low density lipoproteins (LDLs). High density lipoproteins (HDLs), containing apolipoprotein A, are hypothesized to participate in the reverse transport of cholesterol from tissues back to the liver.

PRAVACHOL produces its lipid-lowering effect in two ways. First, as a consequence of its reversible inhibition of HMG-CoA reductase activity, it effects modest reductions in intracellular pools of cholesterol. This results in an increase in the number of LDL-receptors on cell surfaces and enhanced receptor-mediated catabolism and clearance of circulating LDL. Second, pravastatin inhibits LDL production by inhibiting hepatic synthesis of VLDL, the LDL precursor.

Clinical and pathologic studies have shown that elevated levels of total cholesterol (Total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (a membrane transport complex for LDL) promote human atherosclerosis. Similarly, decreased levels of HDL-cholesterol (HDL-C) and its transport complex, apolipoprotein A, are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of Total-C and LDL-C and inversely with the level of HDL-C. Though frequently found in association with low HDL, elevated plasma triglyceride (TG) has not been established as an independent risk factor for coronary heart disease. The independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined. In both normal volunteers and patients with hypercholesterolemia, treatment with PRAVACHOL reduced Total-C, LDL-C, and apolipoprotein B. PRAVACHOL also reduced VLDL-C and TG and produced variable increases in HDL-C and apolipoprotein A. The effects of pravastatin on Lp (a), fibrinogen, and certain other independent biochemical risk markers for coronary heart disease are unknown. Although pravastatin is relatively more hydrophilic than other HMG-CoA reductase inhibitors, the effect of relative hydrophilicity, if any, on either efficacy or safety has not been established.

In the Pravastatin Primary Prevention Study (West of Scotland Coronary Prevention Study – WOS), the effect of improving lipoprotein levels with PRAVACHOL on fatal and nonfatal coronary heart disease (CHD) was assessed in 6595 men, without a previous myocardial infarction, and with LDL-C levels between 156–254 mg/dL (4–6.7 mmol/L). The patients were followed for a median of 4.8 years. In this randomized, double-blind, placebo-controlled study, PRAVACHOL reduced the risk of a first coronary event [either CHD death or nonfatal myocardial infarction (MI)] by 31% [7.9% vs 5.5%, placebo vs PRAVACHOL, p=0.0001; 248 events in the

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CURRENT INSERT- 5154DIM-11
PRAVACHOL® (pravastatin sodium)

PROPOSED REVISIONS

placebo group (CHD death=44, nonfatal MI=204) vs 174 events in the PRAVACHOL group (CHD death=31, nonfatal MI=143)]. PRAVACHOL also decreased the risk for undergoing myocardial revascularization procedures (coronary artery bypass graft surgery or coronary angioplasty) by 37% (2.5% vs 1.7%, p=0.009) and coronary angiography by 31% (4.2% vs 2.8%, p=0.007). Cardiovascular deaths were decreased by 32% (2.3% vs 1.6%, p=0.03) and there was no increase in death from non-cardiovascular causes.

Pharmacokinetics/Metabolism

PRAVACHOL (pravastatin sodium) is administered orally in the active form. In clinical pharmacology studies in man, pravastatin is rapidly absorbed, with peak plasma levels of parent compound attained 1 to 1.5 hours following ingestion. Based on urinary recovery of 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 undergoes extensive first-pass extraction in the liver (extraction ratio 0.66), which is its primary site of action, and the primary site of cholesterol synthesis and of LDL-C clearance. *In vitro* studies demonstrated that pravastatin is transported into hepatocytes with substantially less uptake into other cells. In view of pravastatin's apparently extensive first-pass hepatic metabolism, plasma levels may not necessarily correlate perfectly with lipid-lowering efficacy. Pravastatin plasma concentrations [including: area under the concentration-time curve (AUC), peak (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. This finding of lower systemic bioavailability suggests greater hepatic extraction of the drug following the evening dose. Steady-state AUCs, C_{max} and C_{min} plasma concentrations showed no evidence of pravastatin accumulation following once or twice daily administration of PRAVACHOL (pravastatin sodium) tablets. Approximately 50% of the circulating drug is bound to plasma proteins. Following single dose administration of ^{14}C- pravastatin, the elimination half-life (t½) for total radioactivity (pravastatin plus metabolites) in humans is 77 hours.

Pravastatin, like other HMG-CoA reductase inhibitors, has variable bioavailability. The coefficient of variation, based on between-subject variability, was 50% to 60% for AUC.

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). Since there are dual routes of elimination, the potential exists both for compensatory excretion by the alternate route as well as for accumulation of drug and/or metabolites in patients with renal or hepatic insufficiency.

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 16-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.

Biotransformation pathways elucidated for pravastatin include: (a) isomerization to 6-epi pravastatin and the 3α-hydroxyisomer of pravastatin (SQ 31,906), (b) enzymatic ring hydroxylation to SQ 31,945, (c) ω-1 oxidation of the ester side chain, (d) β-oxidation of the carboxy side chain, (e) ring oxidation followed by aromatization, (f) oxidation of a hydroxyl group to a keto group, and (g) conjugation. The major degradation product is the 3α-hydroxy isomeric metabolite, which has one-tenth to one-fortieth the HMG-CoA reductase inhibitory activity of the parent compound.

In a single oral dose study of pravastatin 20 mg in healthy elderly men aged 65 to 75 years, no statistically significant differences in bioavailability parameters for pravastatin were observed when compared with healthy young men aged 18 to 31 years. However, the mean AUC value for pravastatin was approximately 27% greater in elderly compared with younger men and mean cumulative urinary excretion (CUE) was decreased approximately 19% in the elderly. In a similar study conducted in women, mean AUC for pravastatin was approximately 46% higher in elderly women (65 to 78 years old) compared with younger women (18 to 38 years old) and mean CUE decreased approximately 16% in the elderly. In both studies C_{max}, T_{max} and $T^1/_2$ values were similar in older and younger subjects.

Clinical Studies

PRAVACHOL (pravastatin sodium) is highly effective in reducing Total-C, LDL-C and Triglycerides (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 myocardial infarction.

A single daily dose administered in the evening (the recommended dosing) is as effective as the same total daily dose given twice a day. Once daily administration in the evening appears to be marginally more effective than once daily administration in the morning, perhaps because hepatic cholesterol is synthesized mainly at night. In multicenter, double-blind, placebo-controlled studies of patients with primary hypercholesterolemia, treatment with pravastatin in daily doses ranging from 10 mg to 40 mg consistently and significantly decreased Total-C, LDL-C, TG, and Total-C/HDL-C and LDL-C/HDL-C ratios; modestly decreased VLDL-C and produced variable increases in HDL-C.

Primary Hypercholesterolemia Study
Dose Response of PRAVACHOL®
Once Daily Administration At Bedtime

Dose	Total-C	LDL-C	HDL-C	TG
10 mg	-16%	-22%	+ 7%	-15%
20 mg	-24%	-32%	+ 2%	-11%
40 mg	-25%	-34%	+12%	-24%

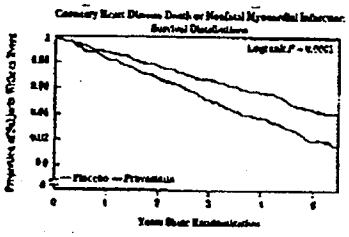
*Mean percent change from baseline after 8 weeks

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)

Prevention of Coronary Heart Disease

In the Pravastatin Primary Prevention Study (West of Scotland Coronary Prevention Study - WOS)[1], the effect of PRAVACHOL on fatal and nonfatal coronary heart disease (CHD) was assessed in 6595 men 45–64 years of age, without a previous MI, and with LDL-C levels between 156–254 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.

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) vs 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 surgery or coronary angioplasty) 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.

Atherosclerosis and Myocardial Infarction

In the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I)[2] 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, multicentar, controlled clinical trial angiograms were evaluated at baseline and at three years in 264 patients. Although the difference between pravastatin and placebo for the primary endpoint (per-patient change in mean coronary artery diameter) and one of two 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 Regression Growth Evaluation Statin Study (REGRESS)[3], 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 two 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, the Pravastatin, Lipids and Atherosclerosis in the Carotids Study (PLAC II)[4], REGRESS, and the Kuopio Atherosclerosis Prevention Study (KAPS)[5] (combined N=1891) showed that treatment with pravastatin was associated with a statistically significant reduction in the composite event rate of fatal and nonfatal myocardial infarction (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 myocardial infarction.

In the Cholesterol and Recurrent Events (CARE)[6] study the effect of PRAVACHOL, 40 mg daily, on coronary heart disease death and nonfatal MI was assessed in 4159 patients (3583 men and 576 women) who had experienced a myocardial infarction in the preceding 3–20 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 cholesterol of 209 mg/dL. LDL cholesterol levels in this patient population ranged from 101 mg/dL–180 mg/dL (mean = 139 mg/dL). At

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baseline, 84% of patients were receiving aspirin and 82% were taking antihypertensive medications. Treatment with PRAVACHOL significantly reduced the rate of first recurrent coronary events (either CHD death or nonfatal MI) by 24% [274 patients with events (13.3%) in the placebo group vs 212 patients with events (10.4%) in the PRAVACHOL group, p=0.003]. The reduction in risk was consistent in both sexes. The risk of undergoing revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) was significantly reduced by 27% (p<0.001) in the PRAVACHOL treated patients [391 (19.6%) vs 294 (14.2%) patients]. PRAVACHOL also significantly reduced the risk for stroke or transient ischemic attack (TIA) by 26% [124 (6.3%) vs 93 (4.7%) patients, p=0.029]

INDICATIONS AND USAGE
Therapy with lipid-altering agents should be considered in those individuals at increased risk for atherosclerosis-related clinical events as a function of cholesterol level, the presence or absence of coronary heart disease, and other risk factors. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when the response to diet and other nonpharmacological measures alone has been inadequate (see NCEP Guidelines below).

Primary Prevention of Coronary Events
In hypercholesterolemic patients without clinically evident coronary heart disease, PRAVACHOL (pravastatin sodium) is indicated to:
- Reduce the risk of myocardial infarction
- Reduce the risk of undergoing myocardial revascularization procedures
- Reduce the risk of cardiovascular mortality with no increase in death from non-cardiovascular causes

Secondary Prevention of Cardiovascular Events
Atherosclerosis
In hypercholesterolemic patients *with* clinically evident coronary artery disease, including prior MI, PRAVACHOL (pravastatin sodium) is indicated to:
- Slow the progression of coronary atherosclerosis
- Reduce the risk of acute coronary events

Myocardial Infarction
In patients with previous myocardial infarction, and normal (below the 75th percentile of the general population) cholesterol levels, PRAVACHOL is indicated to:
- Reduce the risk of recurrent myocardial infarction
- Reduce the risk of undergoing myocardial revascularization procedures
- Reduce the risk of stroke or transient ischemic attack (TIA)

Hypercholesterolemia and Mixed Dyslipidemia
PRAVACHOL is indicated as an adjunct to diet to reduce elevated Total-C, LDL-C, and TG levels in patients with primary hypercholesterolemia and mixed dyslipidemia (Frederickson Type IIa and IIb)[7].

Prior to initiating therapy with pravastatin, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure Total-C, HDL-C, and TG. For patients with triglycerides (TG) <400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation:

LDL-C = Total -C - HDL-C - ⅙ TG

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

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

The National Cholesterol Education Program's Treatment Guidelines are summarized below.

		LDL Cholesterol mg/dL (mmol/L)	
Definite Atherosclerotic Disease*	Two or more Other Risk Factors**	Initiation Level***	Goal
NO	NO	≥190 (≥4.9)	<160 (<4.1)
NO	YES	≥160 (≥4.1)	<130 (<3.4)
YES	YES or NO	≥130 (≥3.4)	≤100 (≤2.6)

* Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).
** Other risk factors for coronary heart disease (CHD) include: age (males: ≥45 years; females: ≥55 years or premature menopause without estrogen replacement therapy); family history of premature CHD; current cigarette smoking; hypertension; confirmed HDL-C <35 mg/dL (<0.91 mmol/L); and diabetes mellitus. Subtract one risk factor if HDL-C is ≥60 mg/dL (≥1.6 mmol/L).
*** In CHD patients with LDL-C levels 100-129 mg/dL, the physician should exercise clinical judgement in deciding whether to initiate drug treatment.

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

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

As with other lipid-lowering therapy, PRAVACHOL (pravastatin sodium) is not indicated when hypercholesterolemia is due to hyperalphalipoproteinemia (elevated HDL-C). The efficacy of pravastatin has not been evaluated in patients with combined elevated Total-C and hypertriglyceridemia [>500 mg/dL (>5.7 mmol/L)] or in patients with elevated intermediate density lipoproteins as their primary lipid abnormality.

CONTRAINDICATIONS
Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other prod-

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ucts of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they 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 PRECAUTIONS: Pregnancy).**

WARNINGS

Liver Enzymes

HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the US over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

In the largest long-term placebo-controlled clinical trial with pravastatin (Pravastatin Primary Prevention Study; see **Clinical Pharmacology**), the overall incidence of AST and/or ALT elevations to greater than three times the upper limit of normal was 1.05% in the pravastatin group as compared to 0.75% in the placebo group. One (0.03%) pravastatin-treated patient and 2 (0.06%) placebo-treated patients were discontinued because of transaminase elevations. Of the patients with normal liver function at week 12, three of 2375 treated with pravastatin (0.10%) and one of the 2919 placebo patients (0.03%) had elevations of AST greater than three times the upper limit of normal on two consecutive measurements and/or discontinued due to elevations in transaminase levels during the 4.8 years (median treatment) of the study.

It is recommended that liver function tests be performed prior to and at 12 weeks following initiation of therapy or the elevation of dose. Patients who develop increased transaminase levels or signs and symptoms of liver disease should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of three times the upper limit of normal or greater persist, withdrawal of pravastatin therapy is recommended.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see **CONTRAINDICATIONS**). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see **CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism**). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper normal limit, 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. 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 another HMG-CoA reductase inhibitor 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 three reports involving a total of 100 post-transplant patients (24 renal and 76 cardiac) treated for up to two years concurrently with pravastatin 10-40 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 one 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 (see PRECAUTIONS: Drug Interactions). The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

PRECAUTIONS

General

Pravastatin (pravastatin sodium) may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. **Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been**

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reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency: 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). A small increase was seen in mean AUC values and half-life (t½) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever (see **WARNINGS: Skeletal Muscle**).

Drug Interactions

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

Cytochrome P450 3A4 Inhibitors: In vitro and *in vivo* data indicate that pravastatin is not metabolized by cytochrome P450 3A4 to a clinically significant extent. This has been shown in studies with known cytochrome P450 3A4 inhibitors (see diltiazem and itraconazole below). Other examples of cytochrome P450 3A4 inhibitors include ketoconazole, mibefradil, and erythromycin.

Diltiazem – Steady-state levels of diltiazem (a known, weak inhibitor of P450 3A4) had no effect on the pharmacokinetics of pravastatin. In this study, the AUC and C_{max} of another HMG-CoA reductase inhibitor which is known to be metabolized by cytochrome P450 3A4 increased by factors of 3.6 and 4.3, respectively.

Itraconazole – The mean AUC and C_{max} for pravastatin were increased by factors of 1.7 and 2.5, respectively, when given with itraconazole (a potent P450 3A4 inhibitor which also inhibits p-glycoprotein transport) as compared to placebo. The mean t½ was not affected by itraconazole, suggesting that the relatively small increases in C_{max} and AUC were due solely to increased bioavailability rather than a decrease in clearance, consistent with inhibition of p-glycoprotein transport by itraconazole. This drug transport system is thought to affect bioavailability and excretion of HMG-CoA reductase inhibitors, including pravastatin. The AUC and C_{max} of another HMG-CoA reductase inhibitor which is known to be metabolized by cytochrome P450 3A4 increased by factors of 19 and 17, respectively, when given with itraconazole.

Antipyrine: Since concomitant administration of pravastatin had no effect on the clearance of antipyrine, interactions with other drugs metabolized via the same hepatic cytochrome isozymes are not expected.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See **DOSAGE AND ADMINISTRATION: Concomitant Therapy.**)

Warfarin: Pravastatin had no clinically significant effect on prothrombin time when administered in a study to normal elderly subjects who were stabilized on warfarin.

Cimetidine: The $AUC_{0-12\ hr}$ for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.

Cyclosporine: Some investigators have measured cyclosporine levels in patients on pravastatin, and to date, these results indicate no clinically meaningful elevations in cyclosporine levels. In one single-dose study, pravastatin levels were found to be increased in cardiac transplant patients receiving cyclosporine.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C_{max}, and T_{max} for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with *aspirin, antacids* (1 hour prior to PRAVACHOL), *cimetidine, nicotinic acid,* or *probucol,* no statistically significant differences in bioavailability were seen when PRAVACHOL (pravastatin sodium) was administered.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced (p<0.004) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors 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 an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

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, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with

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

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 ($p < 0.01$). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times the human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls ($p < 0.05$). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

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 study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy

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 20x (rabbit) or 240x (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[8] 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.

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**).

Pediatric Use

Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time.

ADVERSE REACTIONS

Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 7.7% of pravastatin-treated patients and 7.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints.

Adverse Clinical Events

All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-

Geriatric Use

Two secondary prevention trials with pravastatin (CARE and LIPID) included a total of 6,593 subjects treated with pravastatin 40 mg for periods ranging up to 6 years. Across these two 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 healthy elderly subjects than in healthy young subjects, but mean C_{max}, T_{max} and $T^1/_2$ values are similar in both age groups and substantial accumulation of pravastatin would not be expected in the elderly (see **CLINICAL PHARMACOLOGY:Pharmacokinetics/Metabolism**).

(See also **PRECAUTIONS: Geriatric Use** section)

treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug:

Body System/Event*	All Events		Events Attributed to Study Drug	
	Pravastatin (N = 900) %	Placebo (N = 411) %	Pravastatin (N = 900) %	Placebo (N = 411) %
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic Rash	4.0*	1.1	1.2	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.6	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	8.2	3.0	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

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In the Pravastatin Primary Prevention Study (West of Scotland Coronary Prevention Study) involving 6595 patients treated with PRAVACHOL (N=3302) or placebo (N=3293) for a median of 4.8 years and in the Cholesterol and Recurrent Events (CARE) study, involving 4159 men and women treated with PRAVACHOL (N=2081) or placebo (N=2078) for an average of 4.9 years the adverse event profile in the PRAVACHOL group was comparable to that of placebo for the duration of the studies.

The following effects have been reported with drugs in this class; not all the effects listed below have necessarily been associated with pravastatin therapy:

Skeletal: myopathy, rhabdomyolysis, arthralgia.

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

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

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

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

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

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

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, and bilirubin; thyroid function abnormalities.

Laboratory Test Abnormalities

Increases in serum transaminase (ALT, AST) values and CPK have been observed (see **WARNINGS**).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with HMG-CoA reductase inhibitors.

Concomitant Therapy

Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is not associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See **WARNINGS: Skeletal Muscle** and **PRECAUTIONS: Drug Interactions**.)

OVERDOSAGE

To date, there are two reported cases of overdosage with pravastatin, both of which were asymptomatic and not associated with clinical laboratory abnormalities. If an overdose occurs, it should be treated symptomatically and supportive measures should be instituted as required.

DOSAGE AND ADMINISTRATION

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

The recommended starting dose is 10 or 20 mg once daily at bedtime. In primary hypercholesterolemic patients with a history of significant renal or hepatic dysfunction, and in the elderly, a starting dose of 10 mg daily at bedtime is recommended. PRAVACHOL (pravastatin sodium) may be taken without regard to meals.

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. The recommended dosage range is generally 10 to 40 mg administered once a day at bedtime. In the elderly, maximum reductions in LDL-cholesterol may be achieved with daily doses of 20 mg or less.

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PRAVACHOL® (pravastatin sodium)

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In patients taking immunosuppressive drugs such as cyclosporine (see **WARNINGS: Skeletal Muscle**) concomitantly with pravastatin, therapy should begin with 10 mg of pravastatin 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 dose of 20 mg/day.

Concomitant Therapy

The lipid-lowering effects of PRAVACHOL on total and LDL cholesterol are enhanced when combined with a bile-acid-binding resin. 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 also **ADVERSE REACTIONS: Concomitant Therapy.**

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) and bottles of 1000 (NDC 0003-5178-75). 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.

Unimatic® unit-dose packs containing 100 tablets are also available for the **10 mg** (NDC 0003-5154-06) and **20 mg** (NDC 0003-5178-06) potencies.

Storage

Do not store above 86° F (30° C). Keep tightly closed (protect from moisture). Protect from light.

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NO REVISIONS

Bristol-Myers Squibb
Princeton, NJ 08543

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 19-898/S037

MEDICAL REVIEW

NDA #19-898/S-037
Pravachol (pravastatin sodium) tablets
Bristol-Myers Squibb
Date of submission: August 24, 1999
Date of review: June 19, 2000

Medical Team Leader note on geriatric labeling supplement

Background
In accordance with 21CFR201.57(f)(10), the sponsor proposes changes based on the clinical trial experience with pravastatin in elderly (>65 years) patients to the following sections of the package insert:

- Clinical Pharmacology, Pharmacokinetics/Metabolism
- Precautions (add a section "Geriatric Use")

Supportive information
The Biopharmaceutics reviewer has addressed the proposed changes to Clinical Pharmacology in the OCPB review. The single-dose pharmacokinetic data in elderly men and women show small increases in mean AUC for pravastatin in elderly versus non-elderly men and women, small decreases in urinary excretion of pravastatin with no significant differences across the age groups in Tmax and T1/2. Dr. Lubas has reviewed the data on safety and effectiveness of pravastatin that derive from the three studies that support the clinical aspects of this supplement. These studies include #27,201-31, a 32-week placebo-controlled trial in 142 men and women over age 65 with hypercholesterolemia. In addition the safety and efficacy outcomes for the subgroups over age 65 were presented for the CARE and LIPID studies, two large, 5-year, placebo-controlled, secondary prevention studies in patients with average LDL-C levels at baseline. The results of the CARE and LIPID studies were previously submitted to the Agency in support of changes to the pravastatin label. These trials were extensively reviewed and the respective efficacy supplements approved with changes to the Clinical Pharmacology, Indications and Usage, and Precautions sections of the label. Across the two studies, approximately 4700 patients were over age 65 at enrollment, evenly distributed between placebo and pravastatin groups. The dose of pravastatin in both studies was 40 mg daily.

With respect to efficacy, the mean responses in plasma lipids were slightly greater in the older (>65 yrs) than in the younger patients across the CARE and LIPID studies (3-4% mean differences in % change in LDL-C from baseline). Across both studies, as expected, the risk of cardiovascular events was generally greater in the older patients; however, the risk reduction associated with pravastatin therapy across the various primary and non-primary endpoints was for the most part similar in the two age groups. The data on efficacy are summarized in Dr. Lubas' review in tables 1-4.

With respect to safety, in study 27,201-31, there were no marked differences in either the types or frequency of adverse events across the two treatment groups (pravastatin and placebo). There were no cases of myopathy or hepatic disease in this study.

For the CARE and LIPID studies, the sponsor summarized adverse events by body system and age. There were no marked differences in the frequency of any events by body system between the two treatment groups. In addition, there were no differences in the frequency of abnormalities in AST, ALT, or CK between the placebo and pravastatin groups in either the elderly or non-elderly subgroups. As for the shorter study, there were no cases of myopathy or serious liver disease in CARE or LIPID.

Labeling

Dr. Lubas has made suggestions for minor changes to the proposed wording of the Precautions, Geriatric Use section, with which I concur. Most significant was his proposal of the statement that the "...adverse event profile in the elderly was similar to that observed in the overall population." This was altered from a statement that the

The language proposed by Dr. Lubas is, furthermore, in keeping with 21CFR201.57 (f)(10)(ii)(B) calling for comparative statements regarding safety and effectiveness in elderly versus non-elderly patients where the data support such statements. The sponsor has incorporated these changes and the clinical sections of the revised label are acceptable.

Financial disclosure

All of the studies included in this submission were completed prior to February 2, 1999. As such, the sponsor is obligated only to certify that no investigator in any of the three studies had a financial interest in the outcome of the studies or had a proprietary interest in the product. The sponsor has so certified in the submission of June 5, 2000. This was reiterated in a letter dated June 19, 2000 in response to the Division's request for clarification of financial disclosure information.

Conclusions and recommendations

From the large database of elderly patients treated with pravastatin in controlled trials summarized in this application, it appears that the safety and effectiveness of pravastatin are similar in older and younger patients. The lipid altering efficacy may be slightly greater in the elderly, though the clinical significance of this difference is not known and the findings of the subgroup analyses in this regard do not bear mention in labeling. The clinical aspects of the proposed labeling changes have been discussed with the sponsor, and our requested changes have been incorporated into the revised label. The proposed labeling is now accepted and this supplement should be approved.

David G. Orloff, M.D.
Deputy Director/ Med Tm Ldr
DMEDP/CDER/FDA

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NDA 19-898/SE8-037
Pravachol (pravastatin sodium) tablets
Bristol-Myers Squibb Pharmaceutical Research Institute
Category: Lipid-altering drugs
Proposed labeling change: Geriatric Labeling Supplement
Date of submission: August 24, 1999
Date of review: 6/9/00
Documents reviewed: 97.1-97.2

Medical Reviewer: William A. Lubas M.D.-Ph.D. (HFD-510)
Medical Team Leader: David Orloff M.D. (HFD-510)

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INTRODUCTION

Pravachol is a member of the statin lipid-altering class of drugs, which reduce cholesterol synthesis by competitively inhibiting HMG-CoA reductase. It is presently approved for use in individuals at increased risk of atherosclerosis-related clinical events because of cholesterol level, history of coronary heart disease, and other risk factors. In primary prevention trials with hypercholesterolemic subjects without clinically evident coronary heart disease, pravachol has been found to reduce the risk of myocardial infarction, reduce the risk of undergoing myocardial revascularization procedures and reduce the risk of cardiovascular mortality with no increase in death from non-cardiovascular causes. In secondary prevention trials with hypercholesterolemic subjects with clinically evident coronary heart disease, such as prior myocardial infarction, pravachol has been shown to slow the progression of coronary atherosclerosis and to reduce the risk of acute coronary events. In secondary prevention trials in subjects with a previous myocardial infarction but normal cholesterol levels, it has been shown to reduce the risk of recurrent myocardial infarction, reduce the risk of undergoing myocardial revascularization procedures and reduce the risk of stroke or transient ischemic attack. Clinical trials with pravachol have included subjects with an age range of 18 to 90. This labeling supplement reanalyzes efficacy and long-term safety information from three previously reviewed studies, for subjects ≥65 years of age. These studies include Protocol 27,201-31, *Efficacy and Safety of Pravastatin Administered Once Daily in Subjects Over Age 65 with Hypercholesterolemia*, Protocol 27-201-95, *Long term Intervention with Pravastatin in Ischemic Disease (LIPID)*, and Protocol 27,201-67, *Cholesterol and Recurrent Events (CARE)*. The sponsor proposes using the information from these studies to amend the geriatric label.

EFFICACY RESULTS

Protocol 27,201-31, *Efficacy and Safety of Pravastatin Administered Once Daily in Subjects Over Age 65 with Hypercholesterolemia*

This was a randomized double-blind placebo-controlled study of pravastatin or placebo for hypercholesterolemic men (LDL-C >165mg/dL) and women (LDL-C >170mg/dL) aged 65-90. The primary endpoint was percent change from baseline of LDL-C. A total of 142 subjects were randomized 2:1 to 20mg of pravastatin or placebo. If after 8 weeks their LDL-C was still >95 percentile, for age and sex, their dose was increased to 40mg for the next 8 weeks. If their LDL-C was >75 percentile after 16 weeks a bile acid resin could be added. If after 32 weeks their LDL-C was still elevated they could receive either probucol or nicotinic acid for the remainder of the study.

Most patients had a good response to the 20mg dose of pravastain by 8 weeks, so that the average dose at week 16 was 20.4mg. At 16 weeks there was a statistically significant improvement in the lipid profile of subjects compared to controls. There was a 30.9% decrease in LDL-C ($p \leq 0.001$ vs. baseline and placebo), a 21.9% decrease in total cholesterol ($p \leq 0.001$ vs. baseline and placebo), and a 11.3 % increase in HDL-C ($p \leq 0.001$ vs. baseline and $p \leq 0.01$ vs. placebo).

Protocol 27-201-95, *Long term Intervention with Pravastatin in Ischemic Disease (LIPID)*

This was a multi-center, randomized, double-blind, parallel-group, placebo-controlled study of pravastatin in subjects with average total cholesterol (total cholesterol >155mg/dL and <271mg/dL) and a history of myocardial infarction or unstable angina pectoris to determine if cholesterol reduction would result in a reduction of coronary heart disease (CHD) mortality. The primary endpoint was incidence of CHD mortality. The relevant secondary endpoints were incidence of total mortality, incidence of CHD events (including nonfatal myocardial infarction and fatal CHD), incidence of cardiovascular mortality, incidence of myocardial revascularization procedures, incidence of total stroke and non-hemorrhagic stroke, and change in lipid profile. 3,514 or 39% of the 9,014 subjects randomized in this trial were ≥65 years old. Subjects received pravastatin 40mg or matching placebo tablets for a period of up to 5 years.

In elderly subjects, pravastatin produced greater reductions in total cholesterol, triglycerides and LDL cholesterol and a slightly greater increase in HDL cholesterol than in nonelderly subjects (Table 1). Since the study was not powered to detect differences in these subgroups, the clinical and statistical significance of the small differences in the findings in these subgroups is not known.

Table 1
Effect of Pravastatin on the Final Lipid Profile of Subjects in the LIPID Study

Age (years)	% change in total cholesterol		% change in triglycerides		% change in LDL cholesterol		% change in HDL cholesterol	
	Prav [a]	Pbo [a]	Prav	Pbo	Prav	Pbo	Prav	Pbo
<65	-16.7	-5.0	-6.0	1.0	-22.9	-6.1	9.1	5.1
≥65	-19.2	-5.2	-10.0	-1.1	-26.8	-6.2	10.8	4.2

[a] The abbreviations are Prav for pravastatin and Pbo for placebo.

In both elderly and nonelderly subjects, pravastatin reduced the risk of the primary endpoint, CHD mortality, as well as the following secondary endpoints: total mortality, CHD events (including nonfatal myocardial

infarction and fatal CHD), cardiovascular mortality, and myocardial revascularization procedures. There was no significant improvement in the incidence of total stroke and non-hemorrhagic stroke in elderly subjects. Although, there was a significant improvement observed for all subjects in the incidence of total causes of stroke ($p < 0.05$), and non-hemorrhagic stroke ($p < 0.02$, Table 2).

Table 2
Pravastatin Efficacy in Elderly and Nonelderly Subjects in the LIPID Study

A. Statistical Significance[a] of Relative Risk Reduction

ENDPOINTS	<65 year of age		≥ 65 years of age		All subjects	
	risk reduction	p value	risk reduction	p value	risk reduction	p value
CHD mortality	**-24%**	**.02**	**-24%**	**.009**	**-24%**	**.0004**
total mortality	**-24%**	**.003**	**-21%**	**.003**	**-22%**	**.0001**
CHD events	**-24%**	**.0004**	**-23%**	**.001**	**-24%**	**.0001**
cardiovascular mortality	**-22%**	**.02**	**-26%**	**.002**	**-25%**	**.0001**
myocardial revascularization procedures	**-15%**	**.02**	**-28%**	**.0006**	**-19%**	**.0001**
all cause stroke	-26%	.07	-12%	.35	**-19%**	**.05**
non-hemorrhagic stroke	**-32%**	**.03**	-15%	.24	**.23%**	**.02**

B. Percentage of Subjects in Each Treatment Group

ENDPOINTS	<65 year of age		≥ 65 years of age		All subjects	
	Prav[b]	Pbo[b]	Prav	Pbo	Prav	Pbo
CHD mortality	**127/2771 (4.6%)**	**162/2729 (5.9%)**	**160/1741 (9.2%)**	**211/1773 (11.9%)**	**287/4512 (6.4%)**	**373/4502 (8.3%)**
total mortality	**210/2771 (7.6%)**	**268/2729 (9.8%)**	**288/1741 (16.5%)**	**365/1773 (20.6%)**	**498/4512 (11%)**	**633/4502 (14.1%)**
CHD events	**287/2771 (10.4%)**	**366/2729 (13.4%)**	**270/1741 (15.5%)**	**349/1773 (19.7%)**	**557/4512 (12.3%)**	**715/4502 (15.9%)**
cardiovascular mortality	**143/2771 (5.2%)**	**179/2729 (6.6%)**	**188/1741 (10.8%)**	**254/1773 (14.3%)**	**331/4512 (7.3%)**	**433/4502 (9.6%)**
myocardial revascularization procedures	**392/2771 (14.2%)**	**443/2729 (16.2%)**	**192/1741 (11%)**	**263/1773 (14.8%)**	**584/4512 (12.9%)**	**706/4502 (15.7%)**
all cause stroke	65/2771 (2.4%)	85/2729 (3.1%)	104/1741 (6%)	119/1773 (6.7%)	**169/4512 (3.8%)**	**204/4502 (4.5%)**
non-hemorrhagic stroke	55/2771 **(5.6%)**	79/2729 **(2.9%)**	99/1741 (5.7%)	117/1773 (6.6%)	**154/4512 (3.4%)**	**196/4502 (4.4%)**

[a] **Statistically significant data is in bold print.**

[b] The abbreviations are Prav for pravastatin and Pbo for placebo.

Protocol 27,201-67, *Cholesterol and Recurrent Events (CARE)*
This was a multi-center, randomized, double-blind, parallel-group, placebo-controlled study of pravastatin in subjects with normal cholesterol (total cholesterol <240mg/dL, LDL-cholesterol 115-174mg/dL), who had experienced a previous myocardial infarction within the past 3-20 months, to determine if cholesterol reduction would result in a reduction of coronary heart disease (CHD) events. The primary endpoint was incidence of CHD events (including nonfatal myocardial infarction and fatal CHD). Additional endpoints, which were studied, were incidence of CHD mortality, incidence of total mortality, and incidence of myocardial revascularization procedures. 1,283 or 31% of the 4,159 subjects randomized in this trial were ≥65 years old. Subjects received pravastatin 40mg or matching placebo tablets for a period of up to 5 years.

In elderly subjects, pravastatin produced greater reductions in total cholesterol, triglycerides and LDL cholesterol than in nonelderly subjects, while similar increases in HDL cholesterol were seen for both subgroups (Table 3).

Table 3
Effect of Pravastatin at the 5 Year Visit on the Lipid Profile of Subjects in the CARE Study

Age (years)	% change in total cholesterol		% change in triglycerides		% change in LDL cholesterol		% change in HDL cholesterol	
	Prav[a]	Pbo[a]	Prav	Pbo	Prav	Pbo	Prav	Pbo
<65	-14.8	2.2	7.4	23.2	-26.2	-2.3	12.7	7.8
≥65	-19.1	-1.1	-1.4	4.7	-31.2	-4.6	12.1	8.7

[a] The abbreviations are Prav for pravastatin and Pbo for placebo.

In elderly subjects, pravastatin significantly reduced the risk of the primary endpoint, CHD events, as well as the secondary endpoints, CHD mortality, total mortality and incidence of myocardial revascularization procedures. In nonelderly subjects pravastatin reduced the risk of CHD events and incidence of myocardial revascularization procedures but only the latter was statistically significant with a ($p < 0.001$, Table 4). The increase in CHD and total mortality seen in the nonelderly population is not statistically significant.

Table 4
Pravastatin Efficacy in Elderly and Nonelderly Subjects in the CARE Study

A. **Statistical Significance**[a] of Relative Risk Reduction

ENDPOINTS	<65 year of age		≥ 65 years of age		All subjects	
	risk reduction	p value	risk reduction	p value	risk reduction	p value
CHD events	-13%	.21	**-39%**	**.001**	**-24%**	**.003**
CHD mortality	10%	.59	**-45%**	**.004**	-20%	.10
total mortality	20%	.29	**-30%**	**.02**	-9%	.37
myocardial revascularization procedures	**-25%**	**.001**	**-31%**	**.01**	**-27%**	**.0001**

B. Percentage of Subjects in Each Treatment Group

ENDPOINTS	<65 year of age		≥ 65 years of age		All subjects	
	Prav[b]	Pbo[b]	Prav	Pbo	Prav	Pbo
CHD events	143/1441 (10%)	163/1435 (11%)	**69/640 (11%)**	**111/643 (17%)**	**212/2081 (10%)**	**274/2078 (13%)**
CHD mortality	59/1441 (4%)	53/1435 (4%)	**37/640 (6%)**	**66/643 (10%)**	96/2081 (5%)	119/2078 (6%)
total mortality	103/1441 (7%)	88/1435 (6%)	**77/640 (12%)**	**108/643 (17%)**	180/2081 (9%)	196/2078 (9%)
myocardial revascularization procedures	**221/1441 (15%)**	**287/1435 (20%)**	**73/640 (11%)**	**104/643 (16%)**	**294/2081 (14%)**	**391/2078 (19%)**

[a] **Statistically significant data is in bold print.**
[b] The abbreviations are Prav for pravastatin and Pbo for placebo.

SUMMARY OF REVIEWER'S COMMENTS ON EFFICACY

All three clinical studies presented in this review showed that pravastatin reduced total cholesterol, triglycerides and LDL-cholesterol and increased HDL-cholesterol in elderly subjects compared to placebo. This was true for elderly subjects with normal cholesterol levels (LIPID and CARE) in addition to subjects with hypercholesterolemia Protocol 27,201-31. In the two secondary prevention trials, LIPID and CARE, pravastatin appeared to have a greater effect on the lipid profile in elderly subjects compared to the nonelderly subjects. This may be explained by the slightly higher AUC in elderly subjects. However these studies were not powered to detect differences between the elderly and nonelderly subgroups, so the clinical and statistical significance of the small differences in the findings in these subgroups is not known.

Secondary prevention trials, LIPID and CARE, showed that pravastatin compared to placebo reduced the incidence of CHD mortality, CHD events,

total mortality and myocardial revascularization procedures in elderly subjects. The risk reduction compared to placebo was similar in elderly and nonelderly subgroups in the LIPID study. However in the CARE study the risk reduction was greater in the elderly, and there was an unexplained but not statistically significant increased risk in CHD and total mortality in the nonelderly cohort.

SAFETY RESULTS

Protocol 27,201-31, *Efficacy and Safety of Pravastatin Administered Once Daily in Subjects Over Age 65 with Hypercholesterolemia*

There were no significant differences in the occurrences of adverse events between the pravastatin-treated and placebo groups during the 16-week mono-therapy phase of the study. There was an increase in adverse events of constipation in the placebo group attributed to concomitant resin therapy during the long-term phase of the study. During the initial 16 weeks of the study 3.2% of pravastatin-treated subjects and 2.1% of the subjects on placebo were discontinued because of clinical adverse events. During the rest of the study 10.1% of pravastatin-treated subjects and 19.1% of the subjects on placebo were discontinued because of clinical adverse events or laboratory abnormalities. No deaths and no reports of myopathy, myositis or rhabdomyolysis were seen in this study. The sponsor reports no statistically significant differences in the rate of occurrences of marked laboratory abnormalities between the treatment groups.

Protocol 27-201-95, *Long term Intervention with Pravastatin in Ischemic Disease (LIPID)*

There were fewer endpoint committee-adjudicated deaths reported in the pravastatin-treated elderly subjects (n=288) compared to the placebo group (n=365), consistent with the reduced risk in total mortality observed for pravastatin-treated subjects in this study (Table 2). No increase in serious adverse events or serious adverse drug reactions leading to discontinuation of the study medication was seen in the elderly pravastatin-treated subjects compared to the placebo group. Elderly subjects did experience a slightly higher incidence of serious adverse events in the gastrointestinal, renal/genitourinary, vascular (non-cardiac), respiratory, malignancy, musculoskeletal, dermatological and special senses body systems. In the cases of renal/genitourinary (23.1% vs. 20.5%), and of malignancy (19.3% vs. 16.1%) these events did occur slightly more frequently in the pravastatin-treated group than in the placebo cohort. But when the specific events in each of these subgroups were compared there were no marked differences (>1%) between the elderly pravastatin-treated and placebo cohorts. No elderly subjects discontinued study medication because of CPK elevations, and there was no difference in the rate of occurrence of marked laboratory

abnormalities in AST, ALT or CPK between the treatment groups in the elderly cohort.

Protocol 27,201-67, *Cholesterol and Recurrent Events (CARE)*
There were fewer endpoint committee-adjudicated deaths reported in the pravastatin-treated elderly subjects (n=56) compared to the placebo group (n=77), consistent with the reduced risk in total mortality observed for pravastatin-treated subjects in this study (Table 4). No increase in serious adverse events or serious adverse drug reactions leading to discontinuation of the study medication was seen in the elderly pravastatin-treated subjects compared to the placebo group. Elderly subjects did experience a slightly higher incidence of serious adverse events in the gastrointestinal, renal/genitourinary, malignancy, musculoskeletal, dermatological and special senses body systems. In the cases of musculoskeletal (78.4% vs. 75.7%), respiratory (77.8% vs. 75.3%), dermatological (40.6 % vs. 35.3%), and special senses body systems (40.3% vs. 38.1%) these events did occur slightly more frequently in the pravastatin-treated group than in the placebo cohort. When comparing the specific events for each body system there were certain events that occurred more frequently in the pravastatin group. In the musculoskeletal system these events included musculoskeletal pain (67.0% vs. 63.0%), muscle cramps (21.6% vs. 19.6%) and myalgia (8.6% vs. 7.0). For respiratory system events this difference was primarily due to one specific event ie. sinus abnormality (28.9% vs. 24.6%). For dermatological adverse events there was a higher percentage of subjects with pruritis (12.3% vs. 10.0%), ecchymosis (6.1% vs. 4.0%) and hyperkeratosis (3.9% vs. 2.3%). For special senses adverse events there was a higher incidence of subjects with other eye disturbance (13.1% vs. 11.2%), eye surgery (10.5% vs. 8.6%) and lens opacity (5.8% vs. 4.2%). No specific category for cataracts was included in this analysis although it is likely that many of the cases of eye disturbance, eye surgery and lens opacity may be cataract-related. In the previous analysis of the LIPID study these same categories for eye disease were not used so it is hard to make a direct comparison. But if all subjects grouped into cataract related categories in the LIPID study are pooled there is an increased incidence of subjects in the pravastatin-treated cohort (19.5% vs. 16.9%) which was not originally obvious when looking at the individual cataract specified events. Other specific adverse events in these body system groups did not occur more frequently (>1.5% difference) in the elderly pravastatin-treated population compared to the placebo cohort. No elderly subjects discontinued study medication because of CPK elevations. There was no difference in the rate of occurrence of marked laboratory abnormalities in AST, ALT or CPK between the treatment groups in the elderly cohort, but 4 pravastatin-treated subjects did discontinue their medication because of abnormal liver function tests.

SUMMARY OF REVIEWER'S COMMENTS ON SAFETY

The safety review of adverse events in the LIPID and CARE studies show that the incidence of adverse events, as might be expected, is increased in the elderly population in a variety of body systems. It is important, therefore to compare the elderly pravastatin-treated population to their corresponding placebo cohort. When this is done, the results are mixed. No single body system had consistent increases in serious adverse events in both the LIPID and CARE studies. In the LIPID study for example, there was a slight increase in serious adverse events in the renal/genitourinary body system (23.1% vs. 20.5%), and of malignancy (19.3% vs. 16.1%). But an analysis of the individual events in these categories did not identify any specific events responsible for these observed differences. In the CARE study, there was a small increase in serious adverse events in a different set of body systems than had been seen in LIPID. This includes the musculoskeletal (78.4% vs. 75.7%), respiratory (77.8% vs. 75.3%), dermatological (40.6 % vs. 35.3%), and special senses body systems (40.3% vs. 38.1%). However, in the CARE study it is possible to identify certain events that account for most of the observed difference in these body systems. These adverse events include: musculoskeletal pain, muscle cramps, myalgia in the musculoskeletal system; sinus abnormalities in the respiratory system; pruritis, ecchymosis, and hyperkeratosis in the dermatologic system; and other eye disturbance, eye surgery and lens opacity in the special senses. The muscle findings may be significant because statins have been previously associated with myopathy. In addition sinusitis and pruritis have been reported as adverse effects for other statins. The eye findings maybe nonspecific or may suggest an increase in cataract associated disease which was also seen in elderly subjects in the LIPID study. Despite these differences, there were no observed increases in the discontinuation of study medication due to serious adverse events or serious drug reactions in either of these studies. Also, there was no difference in the rate of occurrence of marked laboratory abnormalities in AST, ALT or CPK between the treatment groups in the elderly cohort. In conclusion, while it is not possible to tell with certainty that the adverse event profiles for elderly subjects on pravastatin are the same as the placebo cohort, the observed differences are small and do not appear to substantially impact on usage of the medication.

CONCLUSION OF STUDY RESULTS

1) Pravastatin has been shown to reduce total cholesterol, triglycerides and LDL-cholesterol and to increase HDL-cholesterol in elderly subjects compared to placebo. This change in lipid profile is similar to what had previously been reported for younger subjects.

2) The use of pravastatin as a lipid-altering agent has been shown to be associated with a reduction in CHD mortality, CHD events, total mortality, and myocardial revascularization procedures in elderly subjects.

3) Elderly subjects in the LIPID and CARE studies did experience a slightly higher incidence of adverse events compared to younger subjects. Some adverse events occurred more frequently in the pravastatin-treated elderly subjects but the results were not consistent between the two studies. The observed differences were small and did not appear to substantially impact on usage of the medication. It is not possible, therefore, to tell with certainty whether the adverse event profile for elderly subjects are different from placebo.

LABELING

Sponsor's proposed labeling change

Delete from ADVERSE REACTIONS-

Insert Geriatric Use section under PRECAUTIONS-

Two secondary prevention trials with pravastatin (CARE and LIPID) included a total of 6,593 subjects treated with pravastatin 40mg for periods ranging up to 6 years. In those 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 and overall population were both essentially the same as placebo. Other reported clinical experience has not identified differences in responses to pravastatin between elderly and younger patients.

Mean pravastatin AUC's are slightly higher in healthy elderly subjects than in healthy young subjects, but mean C_{max}, T_{max} and $T_{1/2}$ values are similar in both age groups and substantial accumulation of pravastatin would not be expected in the elderly. (See CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism).

Reviewer's comments:

CHANGE: In those studies

TO: Across the two studies

CHANGE:

TO: The adverse event profile in the elderly was similar to that observed in the overall population.
REASON: See **SUMMARY OF REVIEWER'S COMMENTS ON SAFETY**

RECOMMENDATIONS
This application should be approved pending the appropriate labeling changes.

SIGNATURE PAGE

Reviewed by: /S/

_____ (6/9/2000)
William Lubas, MD-PhD
FDA/CDER/ORM/ODEII/DMEDP
Medical Officer

_____/S/_____ (6/9/2000)
David Orloff, MD
Medical Team Leader
FDA/CDER/ORM/ODEII/DMEDP

cc: Original NDA (NDA Archive DMEDP)
HFD-510/Division File
HFD-510/Lubas/Orloff/Simoneau

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 19-898/S037

CHEMISTRY REVIEWS(S)

CHEMIST'S REVIEW

1. ORGANIZATION CDER/HFD-510 Division of Metabolism and Endocrine Drug Products	**2. NDA #** 19-898 Original NDA approved: 31-OCT-1991
3. NAME AND ADDRESS OF APPLICANT Bristol-Myers Squibb P.O. Box 4000 Princeton, NJ 08543 (Phone): 609-252-4000	**4. SUPPLEMENT** SE8-037-BC 03-NOV-1999 (Rec. 08-NOV-1999)
	5. Name of the Drug PRAVACHOL™
	6. Nonproprietary Name Pravastatin sodium
7. SUPPLEMENT PROVIDES for a waiver of environmental assessment, as a consequence of the revisions to the Pravachol package insert regarding Geriatric use.	**8. AMENDMENT** --

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

14. CHEMICAL NAME AND STRUCTURE

[1S-[1α(βS*,φS*)2α,6α,8β(R*),8α]]-1,2,6,7,8α-hexahydro-β,φ,6-trihydroxy-2-methyl-1-oxobutoxyl)-1-nephthaleneheptanoic acid, monosodium salt

15. COMMENTS None.

16. CONCLUSIONS AND RECOMMENDATIONS The submission requests an EA due to a change in the Pravachol package insert. The sponsor states that the active moiety will not be administered at higher dosage levels or for longer duration than for which it is currently approved.

17. REVIEWER NAME (AND SIGNATURE) **DATE**

COMPLETED 15-DEC-1999

Sharon Kelly, PhD

R/D INITIATED BY

Dec 17, 1999

filename: 19898#037 NDA

DISTRIBUTION: Original: sNDA 19-898 cc: HFD-510 Division File CSO Reviewer

AP

12/17/99

[redacted]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 19-898/S037

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA #	19-898 SE8-037
Drug Name	Pravachol (pravastatin sodium) tablets
Sponsor	Bristol-Myers Squibb
Indication	Geriatric use
Review Documents	Volumes 1.1-1.2 dated August 24, 1999
	SAS datasets included in the original NDA submission
Medical Reviewer	William Lubas, M.D. (HFD-510)
Medical Team Leader	David Orloff, M.D. (HFD-510)

MAY 3 1 2000

The following review has been discussed with the medical reviewer. The sponsor did not submit data for this geriatric NDA supplement review other than those for the CARE study and the LIPID study.

1 BACKGROUND

Pravastatin (Trade name: Pravachol) tablet was originally approved in October 1991for treatment of hypercholesterolemia (increased triglycerides (TG) and low-density lipoprotein-cholesterol (LDL-C)) in patients with mixed dyslipidemia and type IIa and IIb dyslipidemia. Subsequently Bristal-Myers Squibb, Inc. submitted several NDA supplements pursuing new indications such as primary and secondary prevention of coronary artery disease (CAD) etc. In this geriatric supplement, the sponsor is proposing text for "Geriatric Use" subsection under PRECAUTIONS in the Pravachol package insert. Pharmacokinetic data for pravastatin in elderly subjects is proposed for the CLINICAL PHARMACOLOGY section. A statement concerning the elderly under ADVERSE EVENTS is deleted in the draft and is replaced by a reference to the more detailed discussion under Geriatric Use.

This review pertains to evaluation of the more detailed discussion under "Geriatric Use." That is, "Two secondary prevention trials with pravastatin (CARE and LIPID) included a total of 6,593 subjects treated with pravastatin 40mg for periods ranging up to 6 years. ((studies, 36.1% of pravastatin subjects were aged 65 and older and 0.8% 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 profiles in the elderly ((( ). Other reported clinical experience has not identified differences in responses to pravastatin between elderly and younger patients." This review would focus on the evaluation of efficacy. For adverse event profiles and other reported clinical experience, please see Dr. William Lubass's clinical review and evaluation.

Clinical Studies

In this geriatric supplement, the primary support was from the sponsor's extensive clinical trial experience of over 2000 subjects over the age of 65 years who received pravastatin. The clinical data supporting the proposed labeling changes are from (1) protocol#27,201-31, (2) protocol #27,201-67 (LIPID), (3) protocol #27,201-95 (CARE), (4) 4 trials submitted to protocol #27,201-50 (PLAC I), protocol #27,201-26 (PLAC II), protocol #27,201-83 (KAPS), and protocol #27,201-82 (REGRESS), (5) an on-going trial (CV123-166) to be completed in year 2002, and (6) 6 trials from literature publications. Trials in (1)-(4) were submitted as supplement NDAs and were reviewed previously. The numbers of patients who were elderly and were available for cardiovascular events evaluation were 3514 in LIPID, 1283 in CARE, and 271 in (4) the 4 trials combined. The 6 trials from published studies included a total of 137 elderly patients. The sponsor provided information on (4) as the Pravastatin Regression of Atherosclerosis Application Summary and (6) as supportive evidence and would not be commented in this review.

Keywords: Clinical Study, NDA Review, Geriatric Use

2 LABELING

The proposed text of "Geriatric Use" relating to efficacy of pravastatin can be summarized in the following two aspects: reducing cardiovascular events, and modifying lipid profiles. Data supporting these two statements are reviewed below.

2.1 Reducing cardiovascular events

Included are long-term interventions with pravastatin in cholesterol and recurrent events (CARE) study (protocol 27,201-67) and long-term intervention with pravastatin in ischemic disease (LIPID) study (protocol 27,201-95).

Brief Summary from previous NDA reviews

CARE

The CARE study was designed to investigate the effects of pravastatin in preventing recurrent coronary events in subjects with normal cholesterol levels (Total-C <240 mg/dL; LDL-C 115-174 mg/dL) who had experienced a previous myocardio-infarction (MI). In this study, 4159 subjects (576 females and 3583 males) aged 21 to 75 years were randomized to pravastatin 40mg or placebo once daily for a median treatment period of 4.9 years. It has been shown (see NDA# 19-898 S18) that pravastatin treatment is associated with a 24% reduction in risk for the primary endpoint of nonfatal MI or CHD death (p=0.003). For the secondary and tertiary endpoints of fatal CHD and total mortality, pravastatin was associated with risk reductions of 20% (p=0.104) and 9% (p=0.366), respectively.

LIPID

The LIPID study was designed to determine whether treatment with pravastatin would reduce CHD mortality in subjects with a history of MI or unstable angina pectoris and with cholesterol levels typical for patients with CHD (Total-C 155-275 mg/dL). In this study, 9014 subjects (1516 females and 7498 males) aged 31 to 75 years were randomized to pravastatin 40mg or placebo once daily for a mean treatment period of 5.1 years in the pravastatin group and 4.9 years in the placebo group. It has been shown (see NDA# 19-898 S32) that pravastatin treatment is associated with a 24% reduction in risk for the primary endpoint of CHD mortality (p=0.0004). Significant risk reductions ranging from 19% to 29% were also realized for the secondary endpoints: total mortality (p<0.0001), CHD death or nonfatal MI (p<0.0001), all cause stroke (p=0.0477).

Demography and Baseline Features

In general, demography and baseline features (including hypertension, diabetes, aspirin use, lipid profiles, body mass index, and smoking status) were comparable between pravastatin and placebo within each age category (<65 years and ≥ 65 years) in both the CARE and the LIPID trials. There were some differences between the non-elderly (<65 years) and the elderly (≥ 65 years): slightly more females were observed in the elderly subjects (18% vs. 12% in CARE; 20% vs. 15% in LIPID), more subjects had a history of hypertension (47.8% vs. 40.3% in CARE; 45.3% vs. 39.4% in LIPID) or diabetes (18.6% vs. 12.1% in CARE; 10.2% vs. 7.7% in LIPID), less subjects were current smokers (8.0% vs. 19.8% in CARE; 10.9% vs. 26.2% in LIPID), and baseline triglycerides were lower in the elderly (148.6 mg/dL vs. 158.7 mg/dL in CARE; 152.4 mg/dL vs. 164.9 mg/dL in LIPID).

Baseline characteristics were also compared between CARE and LIPID in elderly subjects (≥ 65 years). As shown in Table 1, among the elderly, there were more subjects in CARE who had a history of diabetes (19% vs. 10%), PTCA (percutaneous transluminal coronary angioplasty) (29% vs. 8%) than those in LIPID, and narrower baseline ranges with lower mean values for Total-C, LDL-C and TG compared to those in LIPID.

Table 1. Comparison of baseline characteristics in elderly subjects (≥65 years) for CARE and LIPID Trials†

Baseline Features	CARE		LIPID	
	Pravastatin (n=640)	Placebo (n=643)	Pravastatin (n=1741)	Placebo (n=1773)
Mean age in yrs (SD)	68.8 (2.9)	68.9 (2.9)	68.8 (2.7)	68.8 (2.7)
Male (%)	81%	82%	80%	80%
Female (%)	19%	18%	20%	20%
Body Mass Index (SD)	26.9 (4.2)	26.9 (4.1)	26.3 (3.6)	26.2 (3.5)
Hypertension (%)	50%	46%	45%	45%
Diabetes (%)	18%	19%	10%	10%
Current smoker (%)	8%	9%	11%	11%
PTCA[a] (%)	28%	30%	8%	8%
CABG[b] (%)	28%	34%	30%	30%
Total-C[c] mg/dL (SD)	207.7 (17.3)	207.9 (17.3)	217.0 (31.6)	217.1 (31.4)
LDL-C[d] mg/dL (SD)	138.1 (14.3)	137.9 (14.3)	148.7 (28.6)	149.4 (28.4)
HDL-C[e] mg/dL (SD)	40.3 (9.4)	40.0 (9.5)	37.5 (9.3)	37.9 (9.4)
TG[f] mg/dL (SD)	147.0 (58.2)	150.1 (56.0)	154.9 (75.4)	150.0 (70.5)

† From the sponsor's Table 11.3.1A and Table 11.3.1B of volume 1.
[a]PTCA: percutaneous transluminal coronary angioplasty.
[b]CABG: coronary artery bypass graft.
[c]Total-C: total cholesterol.
[d]LDL-C: low-density lipoprotein – cholesterol.
[e]HDL-C: high-density lipoprotein – cholesterol.
[f]TG: triglycerides.

2.1.1 Reducing cardiovascular events (< 65 years vs. ≥ 65 years)

This reviewer summarizes efficacy on cardiovascular related events based on the intent-to-treat patients (see Table 2 below), which differed slightly from the sponsor's report (see Table 11.3.2.1 and 11.3.2.2 of volume 1).

Table 2. Effect of pravastatin on cardiovascular events between the young(<65) and the elderly(≥ 65 years)†

	<65 years		≥ 65 years		Homogeneity	RR (95%CI)
	Pravastatin	Placebo	Pravastatin	Placebo	(B&D test)	(≥ 65 years)
CARE (N=4159)	**(n=1441)**	**(n=1435)**	**(n=640)**	**(n=643)**		
CHD mortality or non-fatal MI	9.9%	11.4%	10.8%	17.3%	0.053	.63 (.47, .83)
Death	7.2%	6.1%	12.0%	16.8%	0.012	.72 (.55, .94)
CHD death	4.1%	3.7%	5.8%	10.3%	0.011	.57 (.39, .83)
Non-fatal MI: Def&Prob	8.9%	10.7%	8.4%	12.1%	0.370	.70 (.50, .97)
Fatal MI: Def&Prob	10.3%	12.5%	10.6%	16.2%	0.195	.66 (.50, .88)
LIPID (N=9014)	**(n=2771)**	**(n=2729)**	**(n=1741)**	**(n=1773)**		
CHD mortality or non-fatal MI	10.4%	13.4%	15.5%	19.7%	0.974	.79 (.68, .91)
Death	7.6%	9.8%	16.5%	20.6%	0.906	.80 (.70, .92)
CHD death	4.6%	5.9%	9.2%	11.9%	0.923	.77 (.64, .94)
CVD mortality	5.2%	6.6%	10.8%	14.3%	0.658	.75 (.63, .90)
Fatal or non-fatal MI	6.7%	9.5%	8.6%	11.5%	0.667	.75 (.62, .92)

† from the electronic dataset of CARE and LIPID

In the CARE study, 31% of subjects were at least 65 years of age at study entry. Effect of pravastatin appeared to differ between the non-elderly and the elderly, as shown in the column of Breslow and Day's test for homogeneity, except with non-fatal MI event alone or with fatal MI event alone. Although the

number of subjects was more than twofold with the non-elderly than with the elderly, the observed effect of pravastain was less profound with CHD mortality or non-fatal MI, with non-fatal MI alone, and with fatal MI alone in those subjects who were <65 years than those who were ≥ 65 years. Effect of pravastatin was shown deteriorated numerically with death, or with CHD death. When the elderly subgroup was evaluated, risk reduction with pravastatin relative to placebo was in the range of 28% to 43%.

Different pattern was seen with the LIPID study. There was 39% of subjects who were at least 65 years of age at study entry. It was observed that effect of pravastatin was quite consistent between the non-elderly and the elderly, although the magnitude of risk reduction was less compared to those seen in the CARE study. On average, risk reduction in the elderly ranges from 20% to 25% on cardiovascular related adverse event.

2.1.2 Subgroup by gender

This reviewer further evaluated the effect of pravastatin between females and males in the elderly subjects. The rationale of this investigation was to explore any gender difference in the cardiovascular related event in this subgroup. Results are summarized in Table 3 below.

Table 3. Effect of pravastatin on cardiovascular events between females and males in elderly subjects[†]

	Female		Male		Homogeneity	RR (95%CI)
	Pravastatin	Placebo	Pravastatin	Placebo	(B&D test)	(adjusted)
CARE [N=1283 (31%)]	**(n=120)**	**(n=113)**	**(n=520)**	**(n=530)**		
CHD mortality or non-fatal MI	9.2%	14.2%	11.2%	17.9%	0.891	.58 (.42, .80)
Death	9.2%	8.0%	12.7%	18.7%	0.218	.68 (.50, .93)
CHD death	5.0%	4.4%	6.0%	11.5%	0.192	.54 (.36, .82)
Non-fatal MI: Def&Prob	8.3%	15.0%	8.5%	11.5%	0.489	.67 (.46, .96)
Fatal MI: Def&Prob	9.2%	17.7%	11.0%	15.9%	0.452	.62 (.45, .85)
LIPID [(N=3514 (39%)]	**(n=355)**	**(n=361)**	**(n=1386)**	**(n=1412)**		
CHD mortality or non-fatal MI	14.4%	17.2%	15.8%	20.3%	0.677	.75 (.63, .89)
Death	13.2%	13.9%	17.4%	22.3%	0.278	.76 (.64, .91)
CHD death	6.8%	8.9%	9.8%	12.7%	0.986	.75 (.60, .93)
CVD mortality	8.5%	10.5%	11.4%	15.3%	0.730	.72 (.59, .89)
Fatal or non-fatal MI	9.0%	10.5%	8.5%	11.7%	0.524	.73 (.58, .91)

[†] from the electronic dataset of CARE and LIPID

Among the elderly, there were about one-fifth female subjects (18% in CARE and 20% in LIPID). From Table 3, it is noted that pravastatin benefit was not seen in the elderly female on death or on CHD death in the CARE study. Such heterogeneity was not detected using Breslow and Day's test, possibly due to small sample sizes. Risk reduction after adjusting for gender difference may not be meaningful given the observed heterogeneity seen. With CHD mortality or non-fatal MI, non-fatal MI alone, or fatal MI alone, the adjusted risk reduction ranges from 33% to 42%. In contrast, effect of pravastatin was consistently slightly smaller in female elderly than in male elderly in the LIPID study. Risk reduction after adjusting for gender difference in LIPID ranges from 24% to 28%.

2.2 Modifying lipid profiles in elderly

Protocol 27,201-31 "The efficacy and safety of SQ31,000 in the treatment of hypercholesterolemia in patients over age 65"

This randomized double-blind study was divided into a 16-week short-term placebo-controlled period, followed by a 79-week long-term treatment phase. Following a lipid-lowering, drug withdrawal, and

dietary stabilization period of at least 6-week, 142 hypercholesterolemic subjects (men: LDL-C > 165 mg/dL; women: LDL-C > 170 mg/dL) were randomized to pravastatin 20mg (n=93) or placebo (n=48) once daily for 8-week. The trial was completed in September, 1987. Pravastatin dose may be doubled in subjects whose LDL-C was above the 95th percentile for age and sex after 8-week of treatment, or whose LDL-C remained above the 75th percentile after 16-week of treatment. Concomitant medication may be added, a bile acid-binding resin if after 16-week treatment dosage had been doubled and LDL-C remained above the 75th percentile, or probucol or nicotinic acid if after 32-week treatment LDL-C was persistently elevated.

Table 4. Mean percent change from baseline in Lipids and Lipoproteins after 16-week of treatment[†]

Timepoint	Treatment	N	Total-C	LDL-C	HDL-C	TG
Baseline (mg/dL)	Pravastatin	93	272.2	199.0	50.4	142.6
	Placebo	48	278.7	207.9	45.9	155.5
Week-16 (% change)	Pravastatin	90	-21.9a	-30.9a	+11.3b	-16.7b
	Placebo	47	+0.9	+0.6	+3.6c	-4.2

[†] The sponsor's table 11.1 of volume 1.
Source: Final study report for protocol 27,201-31, Bristol-Myers Squib Company; June 22, 1992.
[a] $p \leq 0.001$ vs. baseline and placebo
[b] $p \leq 0.001$ vs. baseline and $p \leq 0.01$ vs. placebo
[c] $p \leq 0.05$ vs. baseline

Change from baseline in LDL-C after 16-week of double-blind treatment was the primary efficacy endpoint. According to the sponsor, percents change from baseline in total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were all statistically significant in pravastatin treated subjects and was the case in HDL-C in placebo treated subjects, see Table 4 above. After 16 weeks of treatment, pravastatin was shown to significantly reduce the level of LDL-C, Total-C, and TC and significantly increase the level of HDL-C compared to placebo.

2.2.1 Modifying lipid profiles (< 65 years vs. ≥ 65 years)

This reviewer plotted the plasma lipids level over time between pravastatin treated subjects and placebo treated subjects for those subjects who were less than 65 years at study entry and for those subjects who were at least 65 years of age at study entry. Total cholesterol level during the study period can be found in Figure 1 (CARE) and Figure 2 (LIPID). Figures 3 (CARE) and 4 (LIPID) are for the triglycerides. Figures 5 (CARE) and 6 (LIPID) are for LDL-C levels, and Figures 7 (CARE) and 8 (LIPID) are for HDL-C levels.

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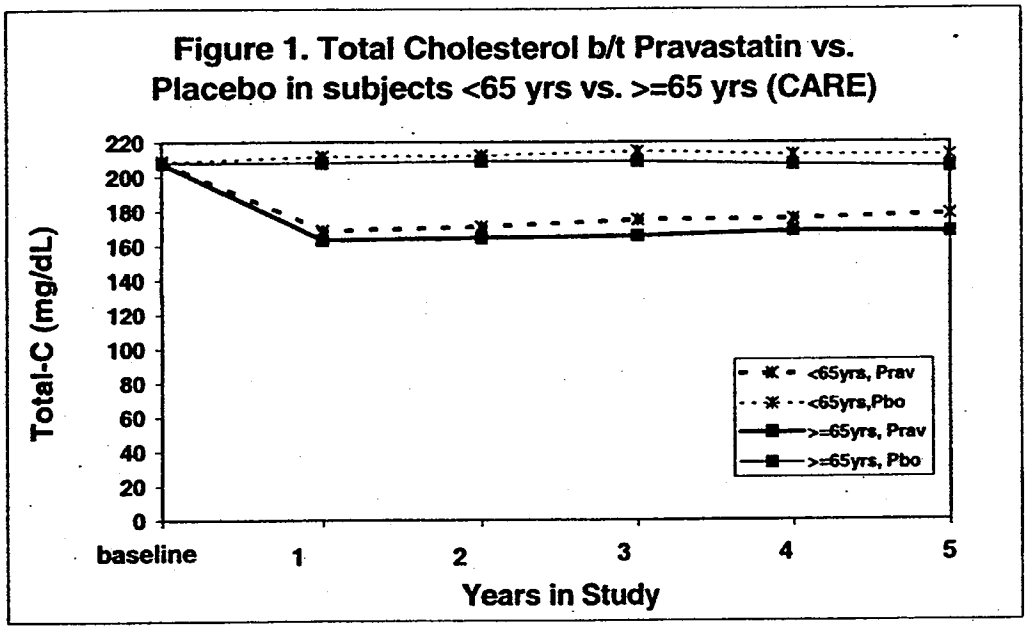
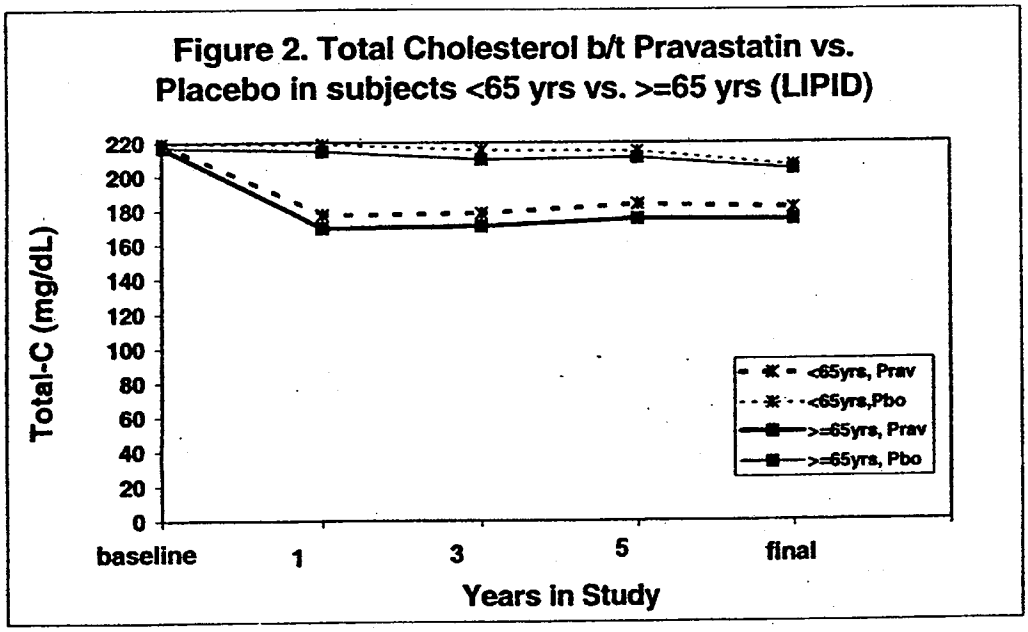
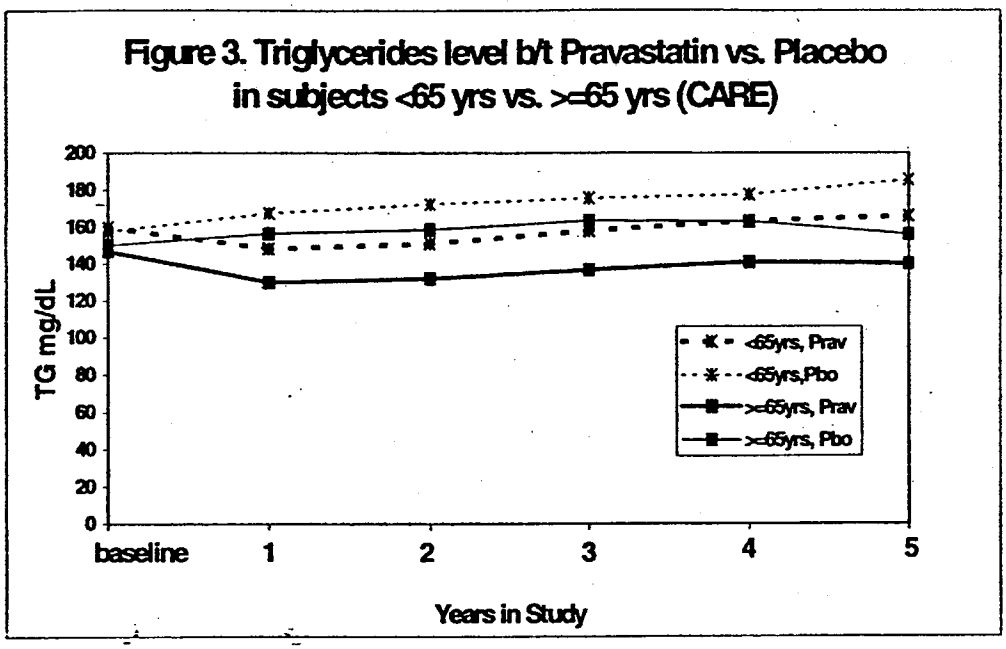
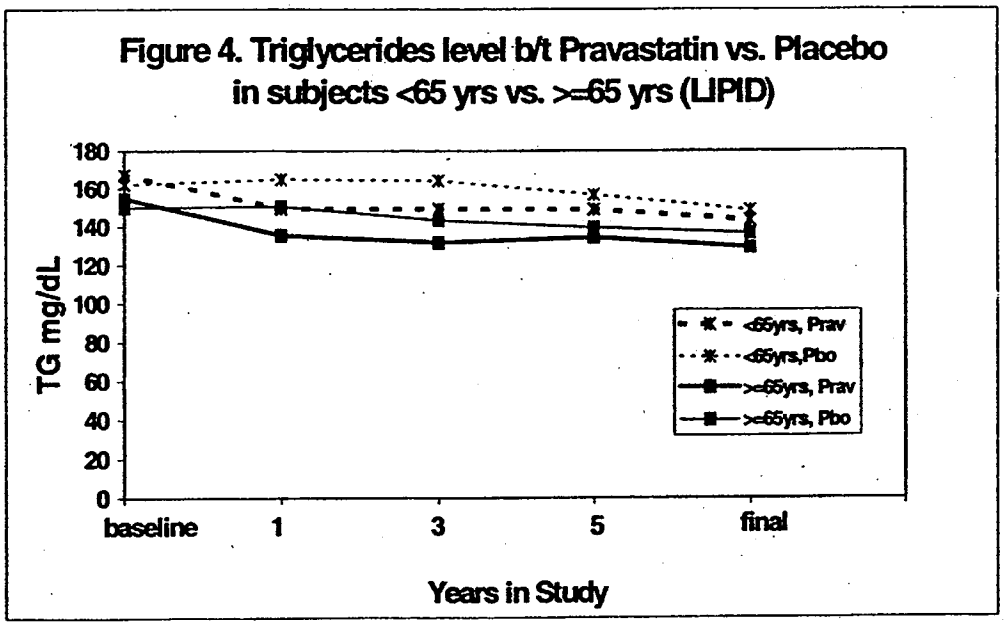


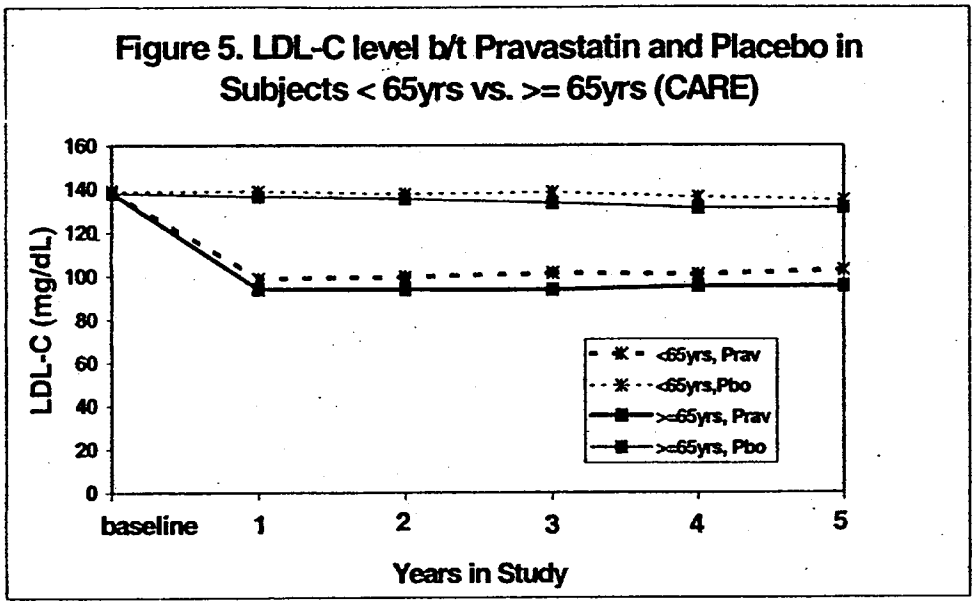


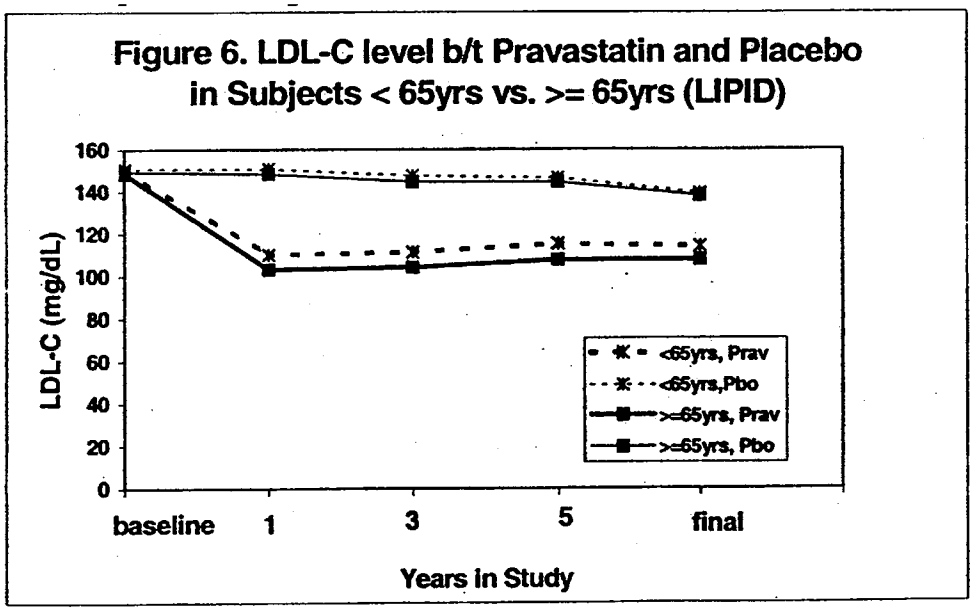
It appeared that elderly subjects tended to have lower total cholesterol level than those non-elderly subjects with pravastatin and with placebo. In both studies, the elderly subgroup had numerically greater reductions with pravastatin in total cholesterol level than with the non-elderly subjects, as shown in Figure 1 (CARE) and Figure 2 (LIPID).



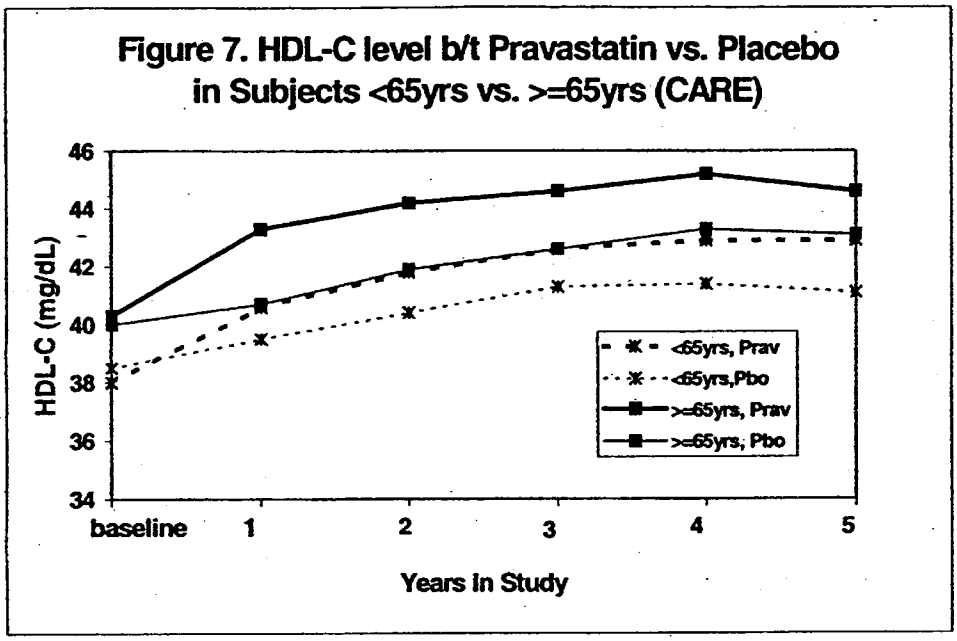


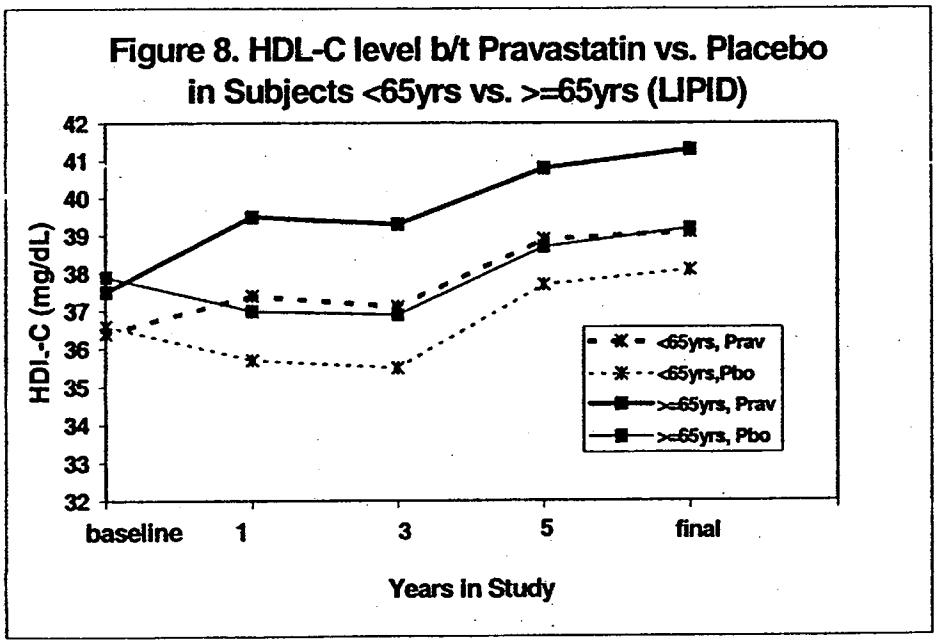
From Figure 3 (CARE) and Figure 4 (LIPID), elderly subjects tended to have lower triglyceride level than those non-elderly subjects with pravastatin and with placebo. In the CARE study, the elderly subgroup had numerically greater reductions with pravastatin in triglyceride level than with the non-elderly subjects, such differences were similar between the elderly and the non-elderly in the LIPID study.





For LDL-C, elderly subjects tended to have lower low-density lipoprotein cholesterol level than those of non-elderly subjects with pravastatin and with placebo. In both studies, the elderly subgroup had numerically greater reductions with pravastatin in low-density lipoprotein cholesterol level than with the non-elderly subjects, as shown in Figure 5 (CARE) and Figure 6 (LIPID).





From Figure 7 (CARE) and Figure 8 (LIPID), elderly subjects tended to have higher high-density lipoprotein cholesterol level than those non-elderly subjects with pravastatin and with placebo. In both the CARE and LIPID studies, the elderly subgroup had numerically greater increase with pravastatin in high-density lipoprotein cholesterol level than with the non-elderly subjects.

2.3 Dropout rates

More subjects discontinued the trial earlier in the CARE trial than in the LIPID trial. Percents of subjects who dropped out earlier than expected were somewhat higher in the elderly (~35% with pravastatin and ~39% with placebo in CARE; ~23% with pravastatin and ~26% with placebo in LIPID) than in the non-elderly (~31% with pravastatin and ~33% with placebo in CARE; ~17% with both treatment groups in LIPID).

3 ONGOING STUDY

Reviewer Comments on prospectively defined Geriatric study

This prospectively defined large study aiming at elderly of 70 to 82 years of age at randomization would provide important efficacy results on reduction of cardiovascular events in this subgroup of the elderly (≥65 years). It is emphasized that current labeling may be further modified if additions and/or revisions to the existing labeling from this prospectively studied trial are deemed necessary. It is noted that current geriatric use contained only 0.8% subjects who were 75 years or older.

4 SUMMARY

Guidance for Industry on "Content and Format for Geriatric Labeling" dated December 11, 1998 stated that "Supplements that lessen or remove WARNINGS, PRECAUTIONS, or CONTRAINDICATIONS relative to the geriatric population should be supported by data." In this submission, summary on "The beneficial effect of pravastatin in elderly subjects in **reducing cardiovascular events** and in **modifying lipid profiles** was similar to that seen in non-elderly subjects" was primarily based on subset data seen in the CARE (1283 elderly patients) and the LIPID (3514 elderly patients) studies, other studies consisting small number of elderly patients, and publications. According to this reviewer's evaluation, risk reduction on cardiovascular events (CHD mortality or non-fatal MI, all-cause mortality, fatal MI or non-fatal MI, CHD mortality) was mostly attributed to the elderly in the CARE trial, in which effect was not as profound in the non-elderly subjects. The magnitude of risk reduction was similar between the elderly and the non-elderly in the LIPID trial, but was less compared to those seen in the CARE study. It appeared that observations from the subset data of geriatric patients support the beneficial effect in reducing cardiovascular events of CHD events and total mortality. About 1/5 of the elderly subjects were females. Pravastatin effect seen in the elderly was consistent between male and female in the LIPID trial, but was more profound in male than in female in the CARE trial.

For the modifying effect on lipids and lipoproteins, this reviewer observed that effect of pravastatin on the lipid and lipoprotein profiles between the CARE and the LIPID studies were similar between the elderly and the non-elderly.

/S/

Sue-Jane Wang, Ph.D. May, 24, 2000
Senior Mathematical Statistician

Concur: S. Edward Nevius, Ph.D. /S/ 5/31/00
Division Director, HFD-715

Todd Sahlroot, Ph.D. /S/ 5/31/00
Team Leader of HFD-510

cc:
Archival NDA 19-898 SE8-037
HFD-510/Div. File
HFD-510/WLubas, DOrloff,
HFD-510/Ms. Simmnaeu, CSO
HFD-715/Division file, ENevius, JSahlroot, SWang
HFD-715/Chron

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This review consists of 11 pages, which includes 4 reviewer summary table, 8 Reviewer figures.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 19-898/S037

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JUN 22 2000

Clinical Pharmacology and Biopharmaceutics Review	
NDA:	**19-898**
Generic	**Pravastatin**
(Brand®)	**Pravachol®**
Sponsor	**Bristo-Myers Squibb**
Submission Date:	**08-24-1999**
Type of Submission:	**Supplement (SE8-037)**
Reviewer:	**Xiaoxiong (Jim) Wei, M.D., Ph.D.**

Synopsis

On August 24, 1999 Bristol-Myers Squibb (BMS) submitted this supplement to their approved NDA 19-898 for Pravachol® tablets for geriatric use. To support their proposed labeling for Pravachol® use in elderly subjects for CLINICLA PHARMACOLOGY section, the sponsor re-submitted two pharmacokinetic studies, which were submitted previously to the Agency as part of the original NDA for pravastatin.

The study of age on Pravachol® pharmacokinetics in a single oral dose study of Pravachol 20 mg in healthy subjects indicated that the mean AUC values for elderly men (65 –75 years), was about 27% greater compared with young men aged 19 to 31 years. The mean AUC for elderly women (65 to 78 years old) was 46% greater compared with young women. However, Cmax, T1/2 values were similar in older and young subjects in both genders.

Clinical Pharmacology/Pharmacokinetics

Is there any difference in pharmacokinetics of pravastatin between elderly and young subjects?

The following two studies were submitted previously to the Food and Drug Administration as part of the New Drug Application (NDA) for pravastatin. Later, the sponsor published these studies in one article.

(1) Comparative Pharmacokinetic Study of Pravastatin in Healthy Elderly and Young Male Subjects (Protocol 27,201-9)

Fifteen healthy elderly (aged 65 to 75 years) and 10 healthy young (aged 19 to 31 years) men completed an open-label, single-dose study. Subjects received a single 20 mg (2 x 10 mg tablets) dose of pravastatin orally. Concentrations of pravastatin and SQ 31,906 (3α-hydroxy isomeric metabolite), and the inhibitory activity of pravastatin on HMG CoA reductase) were determined in serum, protein-free filtrate, and urine samples using G-C/NICI-MS (for serum and protein-free filtrate samples) and HPLC (for urine samples). Samples were collected for 48 hours following the dose of pravastatin. The results for pravastatin and SQ 31,906 are summarized in Table 7.1.

Table 7.1 **Mean (± SEM) Bioavailability of Pravastatin and SQ 31,906 in Healthy Elderly and Young Men**

Compound Age Group	AUC $_{0-12}$ hr ng/hr/ml	C_{max} ng/mL	T_{max} hr	$T_{1/2}$ hr	CUE % of dose
Pravastatin Elderly (N=15)	114.6 (16.7)	42.1 (5.3)	1.2 (0.1)	2.0 (0.2)	6.1 (0.8)
Pravastatin Young (N=10)	90.2 (17.1)	45.5 (8.4)	1.0 (0.1)	1.6 (0.2)	7.5 (1.2)
SQ 31,906 Elderly (N=15)	43.5 (10.2)	18.5 (4.5)	1.3[a] (0.1)	2.0 (0.3)	1.2 (0.3)
SQ 31, 906 Young (N=10)	34.0 (7.3)	18.5 (3.9)	1.0 (0.1)	1.4 (0.2)	1.1 (0.2)

Protocol 27,201-9

Source: Overall Clinical Pharmacology Summary for Pravastatin Sodium, Bristol-Myers Squibb Company; June 30, 1988.

Abbreviations: AUC $_{0-12}$ hr, area under the plasma concentration-time curve from 0-12 hours; C_{max}, maximum plasma concentration; CUE, cumulative urinary excretion over 48 hours as % of dose.

a $P \leq 0.05$ vs young.

(2) Comparative Pharmacokinetic Study of Pravastatin in Healthy Elderly and Young Female Subjects (Protocol 27,201 - 12)

Fifteen healthy elderly (aged 65 to 78 years) and 30 healthy young (aged 18 to 38 years) women completed an open-label, single-dose study. Fifteen of the young women were taking oral contraceptives and 15 had tubal ligation. Subjects received a single 20 mg (2 x 10 mg tablets) dose of pravastatin orally. Concentrations of pravastatin and SQ 31,906 were determined in serum, protein-free filtrate, and urine samples using GC/NICI-MS (for serum and protein-free filtrate samples) and HPLC (for urine samples). Samples were collected for 48 hours following the dose of pravastatin. The results for pravastatin and SQ 31,906 are summarized in Table 7.2.

Table 7.2 **Mean (± SEM) Bioavailability of Pravastatin and SQ 31,906 in Healthy Elderly and Young Women**

Compound Age Group	AUC $_{0-12}$ hr ng hr/ml	C_{max} ng/mL	T_{max} hr	$T_{1/2}$ hr	CUE % of dose
Pravastatin Elderly (N=12)	127.9[a] (19.0)	50.8 (8.6)	1.1 (0.1)	1.6 (0.2)	5.5 (1.1)
Pravastatin Young TL[b] (N=14)	82.5 (9.4)	39.8 (5.1)	1.0 (0.1)	1.6 (0.2)	5.9 (0.8)
Pravastatin Young OC[c] (N=13)	93.3 (14.6)	52.0 (10.1)	1.0 (0.1)	1.3 (0.1)	7.4 (2.0)
SQ 31,906 Elderly (N=12)	65.0 (12.8)	29.7 (5.1)	1.1 (0.1)	1.4 (0.2)	0.8 (0.2)
SQ 31, 906 Young TL (N=14)	39.8 (6.1)	23.4 (3.7)	0.8 (0.1)	1.3 (0.1)	1.2 (0.2)
SQ 31, 906 Young OC (N=13)	51.7 (9.2)	31.6 (6.3)	1.0 (0.1)	1.2 (0.1)	1.3 (0.3)

Protocol 27,201-12.

Source: Overall Clinical Pharmacology Summary for Pravastatin Sodium. Bristol-Myers Squibb Company; June 30, 1988.

Abbreviations: AUC $_{0-12}$ hr, area under the plasma concentration-time curve from 0-12 hours; C_{max}, maximum plasma concentration; CUE, cumulative urinary excretion over 48 hours as % of dose.

a $P \leq 0.05$ vs young TL.

b With tubal ligation.

c Taking oral contraceptives

In both studies urinary excretion of pravastatin and SQ 31.906 was slightly decreased in the elderly compared to the young men and women. The sponsor explained that these findings were attributed to excretory organ functional decline as a consequence of the aging process.

Reviewer's Comment:

In elderly male and female subjects, the exposure of pravastatin (AUC) was increased by 27% and 46%, respectively compared with young men and women. However, body weight may be different in elderly and young subjects. In both studies, the body weight information was not available. It is unknown whether these differences could be corrected with the body weight.

LABELING COMMENTS:

(~~Strikeout text~~ should be removed from labeling; Double underlined text should be added to labeling; ☛ indicates an explanation only and is not intended to be included in the labeling)

In Pharmacokinetics/metabolism Section:

In a single oral dose study of pravastatin 20 mg in healthy elderly men aged 65 to 75 years, —

the mean AUC value for pravastain was approximately 27% greater in elderly compared with younger men aged 19 to 31 years and mean cumulative urinary exceretion (CUE) was decreased approximatly 19% in the elderly (A1). In a similar study conducted in women, the mean AUC for pravastatin was approximatly 46% higher in elderly women (65 to 78 years old) compared with younger women (18 to 38 years old) and mean CUE decreased approximatlet 18% in the elderly [A2]. In both

studies, Cmax, Tmax, and T1/2 values were similar in older and younger subjects [A1, A2].

☛ This statement about bioavailability parameters is not appropriate and should be removed.

General Comment:

Currently FDA is attempting to standardize the content and presentation of information/data that is to be given in the Pharmacokinetics section of the Clinical Pharmacology section of a product's package insert. Therefore, the package insert's Pharmacokinetics section should present information/data, as appropriate, under the subheadings of Absorption, Distribution, Metabolism, and Excretion. Following this, there should then be a section with the heading of Special Populations and pharmacokinetic information/data, as appropriate, should be included under the subheadings of Geriatric, Pediatric, Gender, Race, Renal Insufficiency, Hepatic Insufficiency and Drug-Drug Interactions. Where relevant information/data are lacking it should be so stated. We suggest the sponsor re-format Pharmacokinetics section in subsequent submission.

RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed a supplement to NDA 19-898 for Pravachol® submitted on 08-24-1999. The labeling change and comment should be conveyed to the sponsor as appropriate.

/S/ 6-22-00

Xiaoxiong (Jim) Wei, M.D., Ph.D.

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD/initialed by Hae-Young Ahn, Ph.D., Team Leader /S/

CC: NDA 19-898 (orig., 1 copy), HFD-510(Simoneau), HFD-850(Lesko), HFD-870(Huang, Ahn, Wei), CDR.

Code: AP

Attachment: Study Summary

1 page(s) has been removed because it contains trade secret and/or confidential information that is not disclosable.

2 page(s) of revised draft labeling has been redacted from this portion of the review.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 19-898/S037

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: Geriatric labeling

Reviewer Name: Ronald W. Steigerwalt, Ph.D. Pharmacology Team Leader
Division Name: Division of Metabolic and Endocrine Drug Products (DMEDP)
HFD#510
Review Completion Date: June 19, 2000
Review number: 6 (for this reviewer)

IND/NDA NUMBER: NDA 19-898 SE8-037
Serial number/date/type of submission: This is a labeling supplement dated August 24, 1999.
Information to sponsor: Yes () No (X)
Sponsor (or agent): Bristol-Meyers Squibb Pharmaceutical Research Institute; P.O. Box 5400 Princeton, NJ 08534-5400

DRUG
Trade Name: PRAVACHOL®
Chemical Name: 1-Naphthalene-hepatnoic acid, 1,2,6,7,8,8a-hexahydro-(β)],6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-,monosodium salt, [1S-[1(α)(β)S*,[δ]S*)2α,6(α),8(β)(R*),8a(α)]]-

Relevant INDs/NDAs/DMFs: NDA 19-898 approved in 1991

Drug Class: HMG-CoA Reductase inhibitor "statin"

Indication: Cholesterol lowering drug: Proposal for geriatric labeling

Clinical formulation: Currently, 10, 20, 40 mg tablets with inactive ingredients of croscarmellose sodium, lactose, magnesium oxide, magnesium stearate, microcrystalline cellulose, and povidone. Each tablet size also contains approved dyes.

Route of administration: Oral

SUMMARY:
PRAVACHOL® is an HMG-CoA Reductase inhibitor that was approved in 1991 at the doses indicated in this supplement. Label was updated in a supplement submitted July 7, 1999. The current supplement provided for the inclusion of geriatric labeling. No changes have been made to the preclinical information in the label. No additional preclinical studies were needed to support this supplement.

RECOMMENDATIONS:

From a pharmacology standpoint, the proposed changes to the labeling supplement dated August 24, 1999 may be approved. No further action is necessary from pharmacology.

Ronald W. Steigerwalt, Ph.D.
Supervisory Pharmacologist, DMEDP

6/19/00

cc: IND Arch
HFD510
HFD510/Steigerwalt/Simoneau/
Review Code: AP
Filename: 19898.lbl037.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 19-898/S037

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

PATENT INFORMATION CERTIFICATION

In accordance with the provisions of 21 CFR §314.53, Bristol-Myers Squibb Company, submits the following patent information:

Patent Number:	**4,346,227**
Date of Patent Expiration:	**October 20, 2005**
Type of Patent:	**Composition**
Name of Patent Owner:	**Sankyo Company, Limited**
Patent Number:	**5,030,447**
Date of Patent Expiration:	**July 9, 2008**
Type of Patent:	**Formulation**
Name of Patent Owner:	**E. R. Squibb & Sons, Inc.**
Patent Number:	**5,180,589**
Date of Patent Expiration:	**July 9, 2008**
Type of Patent:	**Formulation**
Name of Patent Owner:	**E. R. Squibb & Sons, Inc.**

The undersigned declares that the currently listed patents, Patent No. 4,346,227, Patent No. 5,030,447 and Patent No. 5,180,589, cover the formulation, composition, and/or method of use of Pravachol® (pravastatin) for geriatric patients. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

John M. Kilcoyne

John M. Kilcoyne
Associate Counsel – Patents
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000

Dated: June 5, 2000

GERIATRIC LABELING

EXCLUSIVITY SUMMARY FOR NDA # 19-898 SUPPL # 37

Trade Name Pravachol Generic Name Pravastatin

Applicant Name Bristol Myers Squibb HFD # 516

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA?

YES /___/ NO /✓/

b) Is it an effectiveness supplement?

YES /✓/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE8

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

YES /✓/ NO /___/

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

_____

_____

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

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /✓/

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

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

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /✓/ NO /___/

If yes, NDA # 19-848. Drug Name Prandial (Transdermal).

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved.

Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

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

YES /___/ NO /___/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

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

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

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

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

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

YES /___/ NO /___/

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

_____

_____

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain: _____

_____

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

YES /___/ NO /___/

If yes, explain: _____

_____

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

_____

_____

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

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

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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

_____ _____

_____ _____

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

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

Investigation #1

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

! _____

Investigation #2

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

_____

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

Investigation #1

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

_____ ! _____

_____ ! _____

Investigation #2

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

_____ ! _____

_____ ! _____

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

YES /___/ NO /___/

If yes, explain: _____

_____

/S/ 6-23-00
Signature
Title: Mary Ann Holovac

6/19/00
Date

/S/
Signature of Office/
Division Director

6/23/00
Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA # 19-898 Supplement # 37 Circle one: SE1 SE2 SE3 SE4 SE5 SE6 SE8

#510 Trade and generic names/dosage form: Pravachol (pravastatin) Action: (AP) AE NA

Applicant Bristol-Myers Squibb Therapeutic Class Lipid Altering Group

Indication(s) previously approved Prim Prev of Coron events; Secondary Prev of CV events; hyper cholesterolemia & mixed dyslipid

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Proposed indication in this application geriatric labeling

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ___No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

___Neonates (Birth-1month) ___Infants (1month-2yrs) ___Children (2-12yrs) ___Adolecents(12-16yrs)

___ **1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ **2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

✓ **3. PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

✓ c. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing.

✓ (2) Protocols were submitted and approved. Written request issued August 4, 1997

___ (3) Protocols were submitted and are under review.

___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ **4. PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ **5. If none of the above apply, attach an explanation, as necessary.**

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___Yes ___No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Medical Team Leader (e.g., medical review, medical officer, team leader)

/S/ 6-20-00

Signature of Preparer and Title Date

Orig NDA/BLA #_____

HF_____/Div File

NDA/BLA Action Package

HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT KHYATI ROBERTS, HFD-6 ROBERTSK

PRAVACHOL® (Pravastatin Sodium) Tablets

DEBARMENT CERTIFICATION UNDER THE GENERIC DRUG ENFORCEMENT ACT OF 1992

Bristol-Myers Squibb Company certifies that it did not and will not use, in any capacity, the services of any person debarred under subsections (a) or (b) [Section 306(a) or (b)], in connection with this supplemental application.

APPEARS THIS WAY
ON ORIGINAL

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

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

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

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

Please mark the applicable checkbox.

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

Clinical Investigators		
	SEE ATTACHED LISTS	

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

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

NAME	TITLE
HUBERT POULEUR, M.D., Ph.D.	VP CARDIOVASCULAR R&D
FIRM/ORGANIZATION: BRISTOL MYERS SQUIBB COMPANY	
SIGNATURE	DATE: June 4, 00

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Bristol-Myers Squibb Company	June 19, 2000
TELEPHONE NO. *(Include Area Code)* 609-252-4000	**FACSIMILE (FAX) Number** *(Include Area Code)* 609-252-6000

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:

P.O. Box 4000
Princeton, NJ 08543-4000

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 19-898/S-037

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY	
Pravastatin Sodium	Pravachol	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* [1S-[1a(betaS*,thetaS*)2a,6a,8beta(R*),8alpha]]-1, 2, 6, 7, 8a-hexahydro-beta,theta,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-1-naphthaleneheptanoic acid, monosodium salt		CODE NAME *(If any)* SQ 31,000
DOSAGE FORM: Tablet	STRENGTHS: 10, 20, 40mg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:
Lipid-lowering agent

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☑ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☑ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☑ OTHER

REASON FOR SUBMISSION: Clarification of Financial Disclosure Information

PROPOSED MARKETING STATUS (check one) ☑ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☑ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) Draft Labeling Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Fred Henry, Director, Metabolic/Endocrine Products	June 19, 2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
P.O. Box 4000, Princeton, NJ 08543-4000	(609) 252-6610

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.

FORM FDA 356h (7/97)

DSI

NOT NEEDED

SAFETY UPDATE REVIEW
NOT REQUIRED

EER

NOT NEEDED

MICROBIOLOGY REVIEW
NOT REQUIRED

NO ADVISORY COMMITTEE MEETING

NO FEDERAL REGISTER NOTICES;
OTC OR DESI DOCUMENTS

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-5610 Fax: 609 252-6000

Fred Henry
Director
Metabolic/Endocrine Products
FDA Liaison and Global Strategy Unit
Regulatory Science

NDA 19-898/S-037
PRAVACHOL® (pravastatin sodium) Tablets

June 19, 2000

John K. Jenkins
Acting Director, Division of Metabolism and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health & Human Services
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Jenkins:

Reference is made to our approved New Drug Application for Pravachol® (pravastatin sodium) Tablets, NDA 19-898. Additional reference is made to Supplemental New Drug Application S-037, which included proposed changes to the label regarding the effect of Pravachol in geriatric patients. Further reference is made to my conversation with Dr. William Lubas regarding the financial disclosure documentation submitted on June 5, 2000.

Page 5 of the June 5 submission, preceding the list of investigators and describing the inability of the sponsor to obtain certification of 21CFR54.2(b) regarding financial disclosure of equity interest, was included inadvertently. The studies included in Supplement S-037 were completed prior to February 2, 1999, and thus as sponsor we are not obligated to identify any equity interest in Bristol-Myers Squibb which any investigators had at the time of the study per Section II.2.D of the Draft Guidance for Industry on Financial Disclosure by Clinical Investigators. This information was sought at the time of an earlier submission prior to release of the current draft guidance. No inappropriate compensation or proprietary interest as per Section II.2.A and II.2.B of the above guidance is assured for all studies and investigators in Supplement S-037.

If you have any questions regarding this submission, please contact me at (609) 252-5610.

Sincerely,

Fred Henry
Director
Metabolic/Endocrine Products
FDA Liaison and Global Strategy Unit
Regulatory Science

Desk Copies: Ms. Margaret Simoneau
Dr. William Lubas

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-5610 Fax: 609 252-6000

Fred Henry
Director
Metabolic/Endocrine Products
FDA Liaison and Global Strategy Unit
Regulatory Science

NDA 19-898/S-037
PRAVACHOL® (pravastatin sodium) Tablets

June 14, 2000

John Jenkins, M.D.
Acting Director, Division of Metabolic and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Jenkins:

Reference is made to our approved New Drug Application for Pravachol® (pravastatin sodium) Tablets, NDA 19-898. Additional reference is made to Supplemental New Drug Application S-037, which included proposed changes to the label regarding the effect of Pravachol in geriatric patients. Further reference is made to the Agency's facsimile transmission dated June 8, 2000 and my discussion with Ms. Margaret Simoneau regarding labeling changes proposed by the FDA medical team. As a result, the draft labeling was revised to address these recommended changes.

At this time we are providing a hard copy of the revised labeling which was sent to Ms. Simoneau via fax on June 13. If you have any questions regarding this submission, please contact me at (609) 252-5610.

Sincerely,

Fred Henry
Director, Metabolic/Endocrine Products
FDA Liaison and Global Strategy Unit
Regulatory Science

FH/JBS/dk
Attachments

Desk Copy: Ms. Margaret Simoneau (HFD-510, 14B04)

10 page(s) of revised draft labeling has been redacted from this portion of the review.

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-5610 Fax: 609 252-6000

Fred Henry
Director
Metabolic/Endocrine Products
FDA Liaison and Global Strategy Unit
Regulatory Science

RESPONSE TO FDA REQUEST FOR INFORMATION/S-037

NDA 19-898/S-037
PRAVACHOL® (pravastatin sodium) Tablets

June 5, 2000

John Jenkins, M.D.
Acting Director, Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Jenkins:

Reference is made to our approved New Drug Application for Pravachol® (pravastatin sodium) Tablets, NDA 19-898. Further reference is made to our Supplemental Application S-037, dated August 24, 1999 which included proposed text for the "Geriatric Use" subsection under PRECAUTIONS in the Pravachol® package insert, as well as changes to the CLINICAL PHARMACOLOGY and ADVERSE EVENTS sections. Final reference is made to my phone conversation with Ms. Margaret Simoneau on May 12, 2000 in which she requested submission of patent information/certification and financial disclosure information for this supplement.

At this time, we are supplying the Division with Financial Disclosure documentation on investigators who were involved in studies used to support these changes, and patent information/certification to support this submission.

If you have any questions, please feel free to contact me at (609) 252-5610.

Sincerely,

Fred Henry
Director
Metabolic/Endocrine Products
FDA Liaison and Global Strategy Unit
Regulatory Science

FH/JBS/ls/dk

Desk Copies: Ms. Margaret Simoneau (HFD 510, Rm. 14B04)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-898/S-037

Bristol-Myers Squibb
P.O Box 4000 -
Princeton, NJ 08543-4000

Attention: Warren C. Randolph
Director, U.S. Regulatory Liaison

Dear Mr. Randolph:

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	Pravachol® (pravastatin sodium) Tablets
NDA Number:	19-898
Supplement Number:	S-037
Date of Supplement:	August 24, 1999
Date of Receipt:	August 26, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on October 25, 1999, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

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

S

/S/

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Electronic Mail Message

Date: 5/8/00 4:40:52 PM
From: David Orloff (ORLOFFD)
To: Margaret Simoneau (SIMONEAUM)
To: Mary Parks (PARKSM)
To: William Lubas (LUBASW)
Subject: 19-898/S-037

Peggy,
Dr. Lubas will be the medical officer for this supplement that provides for geriatric labeling for pravastatin.

Thanks

DGO

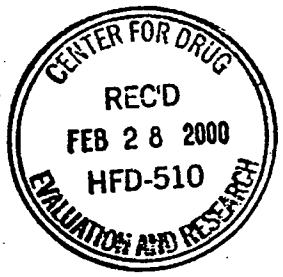
Peggy,
The clinical studies submitted for NDA 19-898/S-037 are not ongoing but have already been completed. Therefore, there are no safety updates to be submitted with this supplement.

William Lubas

/S/
6/19/00

Bristol-Myers Squibb
Pharmaceutical Research Institute
P.O. Box 4000 Princeton, NJ 08543-4000

Worldwide Regulatory Affairs



NDA 19-898/S-037
PRAVACHOL (pravastatin sodium) Tablets

February 25, 2000

John K. Jenkins, M.D.
Acting Director, Division of Metabolism and Endocrine
Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health & Human Services
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Jenkins:

Reference is made to our approved New Drug Application for Pravachol® (pravastatin sodium) Tablets, NDA 19-898 and to our supplemental application dated August 2, 1999 (S-037). This supplement provided for revisions to the Pravachol® package insert concerning treatment of geriatric patients.

Additional reference is made teleconference between myself and Mr. Bill Koch and Dr. Sue Jane Wang, in which Dr. Wang requested datasets used in the cholesterol and recurrent events (CARE, S-026) analyses.

At this time we are providing the requested datasets on CD-ROM (in Ms. Simoneau's desk copy only) as a review aid, together with the explanatory notes as previously provided in the CARE submission.

Please contact me at (609) 252-5610 with any questions.

Sincerely,

Fred Henry
Director
Metabolic/Endocrine Products
FDA Liaison and Global Strategy Unit
Regulatory Science

FH/ls/dk
Attachment

Desk Copy: Dr. Sue Jane Wang (HFD-715, Room 9B04)
Ms. Margaret Simoneau (HFD-510, Room 14B04) (w/ CD-ROM)

The CARE data sets are located in the following directories:

CD-1

ANALYSIS - This directory contains a SAS transport file called **ANALYSIS.XPT**, which contains all of the SAS data sets used for the analysis.

RAW - This directory contains all of the raw data sets in SAS transport format. The screening data for the study are located in **SCR.XPT**, the post randomization or study data are in **RNDO1.XPT, RND02.XPT, RND03.XPT, RND04.XPT**, and the formats used in the data sets are in **FORMAT.XPT**. Using a SAS PROC COPY command on each of the transport file will create a data set per CRF form. These raw data sets were used to create all of the other data sets.

CD-2

SUPPLEMT - This directory contains SAS transport files of laboratory and adverse event data sets that were used in the study. The laboratory data sets have been organized into one data set per lab test.

CD 2 of 2
AES.XPT
LAB01.XPT
LAB02.XPT
LAB03.XPT
LAB04.XPT
LAB05.XPT
LAB06.XPT
LAB07.XPT
LAB08.XPT
LAB09.XPT
LAB10.XPT
LAB11.XPT
MASUB.XPT

The media for this electronic submission has been prepared as follows:

The total size of the electronic submission is 892 MG. There are 20 files and 3 folders. The electronic submission has been provided on 2 CD-ROM disks.

The files have been checked for viruses on February 25, 2000, with Norton Antivirus Software (Version 5.01.01 for Windows NT 4.0) and no viruses were detected.

RECORD OF TELEPHONE CONVERSATION OR MEETING	DATE: 01/18/00 1240 to 1255
Geriatric Labeling: FDA does not have KAPS, REGRESS, PLAC I, and PLACII studies, (BMS will supply today) FDA requires stratification of data by age And trial. FDA requires analysis of individual statistical end points in Section 11. FDA needs SAS program files JAZ disk rec'd from BMS broken please William C. Koch, R.Ph. 01/20/00 Regulatory Project Manager	**NDA: 19-898/S-037** **Telecon/Meeting initiated by:** sponsor FDA: Sue Jane Wang (9B07) **Product name: Pravachol(pravastatin)** **Firm name: BMS** **Name and title of person with whom conversation was held: Fred Henry BMS** **Telephone: (609) 252-5610**

Cc: Original NDA 19-898/S-037
Division File

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-5228 Fax: 609 252-6000

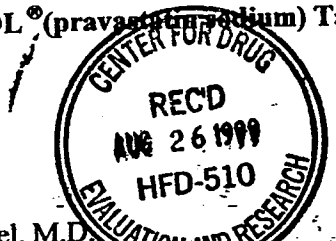
NDA NO. 19-898 REF. NO. 037
NDA SUPPL FOR SE8

ORIGINAL

Warren C. Randolph
Director
U.S. Regulatory Liaison
Worldwide Regulatory Affairs

GERIATRIC LABELING SUPPLEMENT

NDA 19-898
PRAVACHOL® (pravastatin sodium) Tablets



August 24, 1999

Solomon Sobel, M.D.
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health & Human Services
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

Dear Dr. Sobel:

Reference is made to our approved New Drug Application for Pravachol® (pravastatin sodium) Tablets, NDA19-898. At this time, in accordance with 21CFR201.57(f)(10), we are submitting four copies of draft labeling in which we are proposing text for the "Geriatric Use" subsection under PRECAUTIONS in the Pravachol® package insert. Additionally, pharmacokinetic data for pravastatin in elderly subjects is proposed for the CLINICAL PHARMACOLOGY section. A statement concerning the elderly under ADVERSE EVENTS is deleted in the draft and is replaced by a reference to the more detailed discussion under Geriatric Use. The fourth copy of the draft labeling is provided in an envelope attached to the archival copy of the submission.

A summary document is provided in support of the draft labeling. The primary support is from our extensive clinical trial experience (over 2,000 subjects over the age of 65 years who received pravastatin), but the pertinent literature and post-marketing safety experience are also included in the summary. Review of this large body of data has led to the conclusion that the effects of pravastatin in the elderly are not different from those in younger subjects, with respect to either safety or efficacy. Annotations in the draft labeling provide references to appropriate data in the summary to support each change.

The clinical data supporting the proposed labeling changes have been submitted previously in other applications to NDA 19-898. Since no new clinical data are submitted herein, we believe that no user fee is required.

If you have any questions, please feel free to contact me at (609) 252-5228.

Sincerely,

Warren C. Randolph

Warren C. Randolph
Director
US Regulatory Liaison
Worldwide Regulatory Affairs

WCR/JBS/dk
Desk Copies: Ms. Margaret Simoneau

Bristol-Myers Squibb
Pharmaceutical Research Institute
P.O. Box 4000 Princeton, NJ 08543-4000 609 921-4000

REQUEST FOR WAIVER OF ENVIRONMENTAL ASSESSMENT

NDA 19-898
Pravachol® (pravastatin sodium) Tablets

November 3, 1999

Solomon Sobel, M.D.
Director, Division of Metabolism and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Sobel:

Reference is made to our approved New Drug Application for Pravachol® (pravastatin sodium) Tablets, NDA 19-898. Additional reference is made to our approved supplemental application, S-037. Final reference is made to my telephone conversation on November 2, 1999 with Ms. Margaret Simonaeu (FDA), concerning the submission of revisions to the Pravachol® package insert regarding Geriatric use. We now wish to provide a request for waiver of environmental assessment.

Categorical exclusion of the requirement for an environmental assessment is requested under the provisions of 21 CFR 25.31 (a). The subject of the proposed action will not have a significant effect on the environment and meets the requirements for a categorical exclusion from submitting an environmental assessment, 21 CFR 25.31 (a). This change affects only the Pharmacokinetics/Metabolism and Precautions sections of the package insert. The active moiety will not be administered at higher dosage levels or for longer duration than for which it is currently approved and this change will not significantly increase the use of the active moiety.

To our knowledge, no extraordinary circumstances exist.

Please note, effective immediately, I will be assuming responsibility for the above referenced NDA.

In the future, please direct all correspondence and inquiries for the referenced NDA to:

Fred J. Henry
Director
Regulatory Science
Bristol-Myers Squibb, D22-04
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-5610

We look forward to your favorable action on this waiver request.

If there are any questions concerning this submission, please contact me at (609) 252-5610.

Sincerely,

Fred J. Henry
Director
Regulatory Science

FJH/DJG/dk
Desk Copy: Ms. Margaret Simoneau (HFD-510, Room 14B04)

Meeting Minutes

Division of Metabolic and Endocrine Drug Products
NDA 19-898/S-037

Date: Wednesday, October 20, 1999
Location: Parklawn 1456
Time: 12:30-1:00PM

FDA Attendees:
Dr. Orloff
Dr. Parks
H.Y. Ahn
R. Steigerwalt
Jim Wei
S. Wang
M. Simoneau

This was a **Filing meeting** for an efficacy supplement, (SE8), received August 24, 1999, for Pravachol (pravastatin). This is a geriatric labeling supplement.

Discussion:

- Clinical- Dr. Parks said there were no filing issues.
- Pharmacology- Ron Steigerwalt said that there were no filing issues.
- Chemistry- S. Kelly is the chemistry reviewer. Request will be made for an EA waiver or categorical exclusion from the sponsor by M. Simoneau.
- Biopharm-filable according to Jim Wei.
- Biostatistics-there were no filing issues.
- DSI- none needed.
- Submission will be a standard review.
- Clinical audits- none needed.
- Advisory Committee- not needed.
- Review Goal Date with labeling-
  UFGD for 10 months is June 26, 2000. Final reviews are due by June 1, 2000.

File date for this supplement is October 25, 1999.

Minutes preparer: M. Simoneau /S/ 11/2/99

Concurrence Chairman: Dr. Orloff /S/ 11/2/99

cc:Original NDA 19-898/S-037
DivFile

10 page(s) of revised draft labeling has been redacted from this portion of the review.