CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 19-898/S-031

Trade Name: Pravachol

Generic Name: pravastatin sodium

Sponsor: Bristol Meyers Squibb Pharmaceutical Research Firm

Approval Date: June 9, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-898/S-031

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-898/S-031

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 19-898/S-031

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

JUN - 9 2000

Dear Mr. Henry:

Please refer to your supplemental new drug application dated March 18, 1999, 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 April 3, 2000, received April 4, 2000, which constituted a complete response to our January 18, 2000, action letter. We also acknowledge receipt of your May 11 (fax), 2000, submission.

This supplemental new drug application provides for the additional indication of increasing HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Frederickson Types IIa and IIb). The INDICATIONS AND USAGE, "Hyperlipidemia" section of the package insert for Pravachol will state "Pravachol is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels ***and to increase HDL-C*** in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Frederickson Types IIa and IIb)." *(Italics indicate the change.)* In addition, this change is reflected in the CLINICAL PHARMACOLOGY section of the package insert by deletion of the word "variable" in the description of the HDL-raising effect of pravastatin and by inclusion of summary data on the HDL-C changes observed in the WOS and CARE trials.

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 May 11, 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-031." 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 Management Officer, 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/S-031

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 19-898/S-031

Food and Drug Administration
Rockville MD 20857

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 (S-031) dated March 18, 1999, received March 19, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pravachol (pravastatin) Tablets.

We acknowledge receipt of your submission dated April 14, 1999.

This supplemental new drug application proposes a change in the CLINICAL PHARMACOLOGY section that would, in effect, state that Pravachol increases HDL-C.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

> The current application does not include sufficient data to support the proposed change in labeling. Prior to approval of such a change in labeling, analyses of lipid-response data in patients with Type IIa and IIb hyperlipoproteinemia (HLP) treated in pravastatin controlled trials and expressed in order to convey the distribution of responses from baseline need to be submitted and reviewed.

The sections to which the changes are proposed describe the observed effects of pravastatin on HDL-C levels in normal volunteers and patients with Type IIa and IIb hyperlipoproteinemia (HLP). The data submitted apparently in support of the proposed change include a subgroup analysis from CARE among the patients with isolated hypertriglyceridemia (Type IV). From the WOSCOPS cohort, the subgroup analyzed was that with Type IIb (elevation in cholesterol and TG) or Type IV. No data from WOSCOPS in the combined Type IIa and IIb patients are shown. Finally, the other published studies cited enrolled patients with mixed dyslipidemia only (Type IIb). Assuming the WOSCOPS subgroup included mostly patients with Type IIb, these results do demonstrate a statistically significant increase in HDL-C from baseline relative to placebo in these patients. On the other hand, 4 of 5 of the published papers showed no statistically significant change in HDL-C. This is likely because, as is well documented, the effect of statins on HDL-C is variable from patient to patient.

The package inserts for certain related drugs have recently been amended to include lipid altering data conveying the distribution of effects on HDL-C levels in patients with Types IIa and IIb HLP. In the context of a developing awareness of the significance of HDL-C levels and ratios of total-C to HDL-C and of LDL-C to HDL-C, the Division has furthermore permitted labeling changes in INDICATIONS AND USAGE by adding "and to increase HDL-C" to the list of expected lipid changes in patients with Types IIa and IIb HLP. While the responses in HDL-C (and TG) to statins across individuals with hypercholesterolemia and mixed dyslipidemia are variable, such changes in the INDICATIONS AND USAGE section reflect a potential benefit of these drugs (in addition to LDL-C lowering). This statement of potential benefit is qualified in labeling not only by the enumeration of the effect as a cumulative distribution function (median, 25^{th}, 75^{th} percentiles) but also by inclusion of a disclaimer stating that the independent effect of raising HDL-C on cardiovascular morbidity and mortality in these patients is not known.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

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

Sincerely,

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/S-031

APPROVED LABELING

Current Labeling

PRAVACHOL®

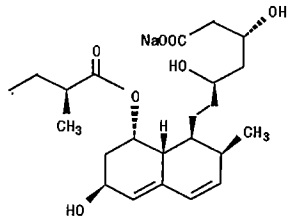
Rx only

(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 (Apo 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. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, IDL, and remnants, can also promote atherosclerosis. Elevated plasma TG are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined. In 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 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 one primary (West of Scotland Coronary Prevention Study - WOS)[1] and two secondary (Long-term Intervention with Pravastatin in Ischemic Disease - LIPID[2] and the Cholesterol and Recurrent Events - CARE[3]) prevention studies, PRAVACHOL has been shown to reduce cardiovascular morbidity and mortality across a wide range of cholesterol levels (see **Clinical Studies**).

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 ($t_{1/2}$) 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 18-fold in cirrhotic patients and 5-fold in healthy subjects. Similarly, the peak pravastatin values varied 47-fold for cirrhotic patients compared to 6-fold for healthy subjects.

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.

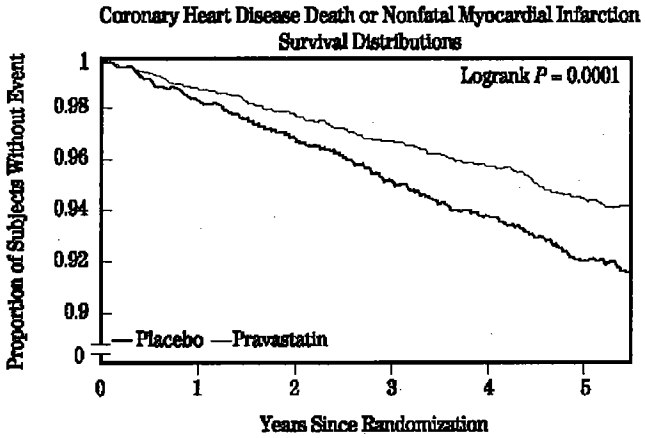
In a single oral dose study using pravastatin 20 mg, the mean AUC for pravastatin was approximately 27% greater and the mean cumulative urinary excretion (CUE) approximately 19% lower in elderly men (65 to 75 years old) compared with younger men (19 to 31 years old). In a similar study conducted in women, the mean AUC for pravastatin was approximately 46% higher and the mean CUE approximately 18% lower in elderly women (65 to 78 years old) compared with younger women (18 to 38 years old). In both studies, C_{max}, T_{max} and $t_{1/2}$ values were similar in older and younger subjects.

Clinical Studies

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 myocardial infarction (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. Median (25^{th}, 75^{th} percentile) percent changes from baseline after 6 months of pravastatin treatment in Total C, LDL-C, TG, and HDL were –20.3 (-26.9, -11.7), -27.7 (-36.0, -16.9), -9.1 (-27.6, 12.5), and 6.7 (-2.1, 15.6), respectively.

PRAVACHOL significantly reduced the rate of first coronary events (either coronary heart disease [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 [CABG] surgery or percutaneous transluminal coronary angioplasty [PTCA]) by 37% (80 vs 51 patients, p=0.009) and coronary angiography by 31% (128 vs 90, p=0.007). Cardiovascular deaths were decreased by 32% (73 vs 50, p=0.03) and there was no increase in death from non-cardiovascular causes.

Secondary Prevention of Cardiovascular Events

In the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID)[2] study, the effect of PRAVACHOL, 40 mg daily, was assessed in 9014 patients (7498 men; 1516 women; 3514 elderly patients [age ≥65 years]; 782 diabetic patients) who had experienced either an MI (5754 patients) or had been hospitalized for unstable angina pectoris (3260 patients) in the preceding 3-36 months. Patients in this multicenter, double-blind, placebo-controlled study participated for an average of 5.6 years (median of 5.9 years) and at randomization had total cholesterol between 114 and 563 mg/dL (mean 219 mg/dL), LDL-C between 46 and 274 mg/dL (mean 150 mg/dL), triglycerides between 35 and 2710 mg/dL (mean 160 mg/dL), and HDL-C between 1 and 103 mg/dL (mean 37 mg/dL). At baseline, 82% of patients were receiving aspirin and 76% were receiving antihypertensive medication. Treatment with PRAVACHOL significantly reduced the risk for total mortality by reducing coronary death (see **Table 1**). The risk reduction due to treatment with PRAVACHOL on CHD mortality was consistent regardless of age. PRAVACHOL significantly reduced the risk for total mortality (by reducing CHD death) and CHD events (CHD mortality or nonfatal MI) in patients who qualified with a history of either MI or hospitalization for unstable angina pectoris.

Table 1 LIPID - Primary and Secondary Endpoints				
	Number (%) of Subjects			
Event	**Pravastatin (N = 4512)**	**Placebo (N = 4502)**	**Risk Reduction**	***P*-value**
Primary Endpoint				
CHD mortality	287 (6.4)	373 (8.3)	24%	0.0004
Secondary Endpoints				
Total mortality	498 (11.0)	633 (14.1)	23%	<0.0001
CHD mortality or non-fatal MI	557 (12.3)	715 (15.9)	24%	<0.0001
Myocardial revascularization procedures (CABG or PTCA)	584 (12.9)	706 (15.7)	20%	<0.0001
Stroke				
All-cause	169 (3.7)	204 (4.5)	19%	0.0477
Non-hemorrhagic	154 (3.4)	196 (4.4)	23%	0.0154
Cardiovascular mortality	331 (7.3)	433 (9.6)	25%	<0.0001

In the Cholesterol and Recurrent Events (CARE)[3] 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 baseline, 84% of patients were receiving aspirin and 82% were taking antihypertensive medications. Median (25th, 75th percentile) percent changes from baseline after 6 months of pravastatin treatment in Total C, LDL-C, TG, and HDL were -22.0 (-28.4, -14.9), -32.4 (-39.9, -23.7), -11.0 (-26.5, 8.6), and 5.1 (-2.9, 12.7), respectively. Treatment with PRAVACHOL significantly reduced the rate of first recurrent coronary events (either CHD death or nonfatal MI), the risk of undergoing revascularization procedures (PTCA, CABG), and the risk for stroke or transient ischemic attack (TIA) (see **Table 2**).

Table 2	CARE - Primary and Secondary Endpoints			
	Number (%) of Subjects			
Event	**Pravastatin (N = 2081)**	**Placebo (N = 2078)**	**Risk Reduction**	***P*-value**
Primary Endpoint				
CHD mortality or non-fatal MI *	212 (10.2)	274 (13.2)	24%	0.003
Secondary Endpoints				
Myocardial revascularization procedures (CABG or PTCA)	294 (14.1)	391 (18.8)	27%	<0.001
Stroke or TIA	93 (4.5)	124 (6.0)	26%	0.029

* The risk reduction due to treatment with PRAVACHOL was consistent in both sexes.

In the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I)[4] study, the effect of pravastatin therapy on coronary atherosclerosis was assessed by coronary angiography in patients with coronary disease and moderate hypercholesterolemia (baseline LDL-C range = 130-190 mg/dL). In this double-blind, multicenter, controlled clinical trial angiograms were evaluated at baseline and at 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)[5], 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)[6], REGRESS, and the Kuopio Atherosclerosis Prevention Study (KAPS)[7] (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.

Primary Hypercholesterolemia (Fredrickson Type IIa and IIb)

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 is as effective as the same total daily dose given twice a day. In multicenter, double-blind, placebo-controlled studies of patients with primary hypercholesterolemia, treatment with pravastatin in daily doses ranging from 10 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).

Hypertriglyceridemia (Fredrickson Type IV)

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

Patients With Fredrickson Type IV Hyperlipidemia Median (25th, 75th percentile) Percent Change From Baseline		
	Pravastatin 40 mg (N=429)	**Placebo (N=430)**
Triglycerides	-21.1 (-34.8, 1.3)	-6.3 (-23.1, 18.3)
Total-C	-22.1 (-27.1, -14.8)	0.2 (-6.9, 6.8)
LDL-C	-31.7 (-39.6, -21.5)	0.7 (-9.0, 10.0)
HDL-C	7.4 (-1.2, 17.7)	2.8 (-5.7, 11.7)
Non-HDL-C	-27.2 (-34.0, -18.5)	-0.8 (-8.2, 7.0)

Dysbetalipoproteinemia (Fredrickson Type III)

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

Patients With Fredrickson Type III Dysbetalipoproteinemia Median (min, max) Percent Change From Baseline		
	Median (min, max) at Baseline (mg/dL)	**Median % Change (min, max) Pravastatin 40 mg (N=20)**
Study 1		
Total-C	386.5 (245.0, 672.0)	-32.7 (-58.5, 4.6)
Triglycerides	443.0 (275.0, 1299.0)	-23.7 (-68.5, 44.7)
VLDL-C *	206.5 (110.0, 379.0)	-43.8 (-73.1, -14.3)
LDL-C *	117.5 (80.0, 170.0)	-40.8 (-63.7, 4.6)
HDL-C	30.0 (18.0, 88.0)	6.4 (-45.0, 105.6)
Non-HDL-C * N=14	344.5 (215.0, 646.0)	-36.7 (-66.3, 5.8)
	Median (min, max) at Baseline (mg/dL)	**Median % Change (min, max) Pravastatin 40 mg (N=26)**
Study 2		
Total-C	340.3 (230.1, 448.6)	-31.4 (-54.5, -13.0)
Triglycerides	343.2 (212.6, 845.9)	-11.9 (-56.5, 44.8)
VLDL-C	145.0 (71.5, 309.4)	-35.7 (-74.7, 19.1)
LDL-C	128.6 (63.8, 177.9)	-30.3 (-52.2, 13.5)
HDL-C	38.7 (27.1, 58.0)	5.0 (-17.7, 66.7)
Non-HDL-C	295.8 (195.3, 421.5)	-35.5 (-81.0, -13.5)

INDICATIONS AND USAGE

Therapy with PRAVACHOL (pravastatin sodium) 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.

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

In patients with clinically evident coronary heart disease, PRAVACHOL (pravastatin sodium) is indicated to:

- Reduce the risk of total mortality by reducing coronary death
- Reduce the risk of myocardial infarction
- Reduce the risk of undergoing myocardial revascularization procedures
- Reduce the risk of stroke and stroke/transient ischemic attack (TIA)
- Slow the progression of coronary atherosclerosis

Hyperlipidemia

PRAVACHOL is indicated as an adjunct to diet to reduce elevated Total-C, LDL-C, Apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia (Frederickson Type IIa and IIb)[8].

PRAVACHOL is indicated as adjunctive therapy to diet for the treatment of patients with elevated serum triglyceride levels (Fredrickson Type IV).

PRAVACHOL is indicated for the treatment of patients with primary dysbetalipoproteinemia (Fredrickson Type III) who do not respond adequately to diet.

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).

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:

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

For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In many hypertriglyceridemic patients, LDL-C may be low or normal despite elevated Total-C. In such cases, 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).

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 products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they 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 2875 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

PRAVACHOL (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 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 ($t_{½}$) 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 $t_{½}$ 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 $AUC_{0\text{-}12hr}$ 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 $\geq$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 several other drugs in this class.

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

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.

In a 2-year study in mice fed pravastatin at doses of 250 and 500 mg/kg/day, there was an increased incidence of hepatocellular carcinomas in males and females at both 250 and 500 mg/kg/day ($p<0.0001$). At these doses, lung adenomas in females were increased ($p=0.013$). Serum drug levels were 30 to 40 times (250 mg/kg/day) and 50 times (500 mg/kg/day) that of humans given 40 mg pravastatin, as measured by AUC. In another 2-year study in mice with doses at up to 100 mg/kg/day (producing plasma drug levels up to 5 times human drug levels at 40 mg, there were no drug-induced tumors.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; a forward mutation assay in L5178Y TK +/- mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene

conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a 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[9] of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or lovastatin, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a three-to-four-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. As safety in pregnant women has not been established and there is no apparent benefit to therapy with PRAVACHOL during pregnancy (see **CONTRAINDICATIONS**), treatment should be immediately discontinued as soon as pregnancy is recognized. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only

when such patients are highly unlikely to conceive and have been informed of the potential hazards.

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.

Geriatric Use

Two secondary prevention trials with pravastatin (CARE and LIPID) included a total of 6593 subjects treated with pravastatin 40 mg for periods ranging up to 6 years. Across these 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 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**)..

ADVERSE REACTIONS

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

asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. (See also **PRECAUTIONS: Geriatric Use** section).

Adverse Clinical Events

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

	All Events		Events Attributed to Study Drug	
Body System/Event	**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	1.3	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	1.9	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	6.2	3.9	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.

In three large, placebo-controlled trials (West of Scotland Coronary Prevention study [WOS], Cholesterol and Recurrent Events study [CARE], and Long-term Intervention with Pravastatin in Ischemic Disease study [LIPID]) involving a total of 19,768 patients treated with PRAVACHOL (N = 9895) or placebo (N = 9873), the safety and tolerability profile in the pravastatin group was comparable to that of the placebo group over the median 4.8 to 5.9 years of follow-up.

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 over dosage 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, 20 or 40 mg once daily. PRAVACHOL can be administered as a single dose at any time of the day, with or without food. In patients

with a history of significant renal or hepatic dysfunction, a starting dose of 10 mg daily is recommended.

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.

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 **20 mg** (NDC 0003-5178-06) potency.

STORAGE

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

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Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

5154DIM-15 1092990A5 Revised July 2000
515432DIM-06 1109268A3
J4-538N 1092990A5

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-898/S-031

MEDICAL REVIEW(s)

NDA 19-898/S-031
Response to approvable letter of 1-18-00
Pravachol (pravastatin sodium) tablets
Bristol-Myers Squibb
Category: Lipid altering
Proposed labeling change: Additions to Clinical Pharmacology of information on HDL-raising effects of pravastatin; additions to Indications and Usage of language reflecting expected effects on pravastatin on HDL-C levels in patients with Types IIa and IIb
Date of submission: April 3, 2000
Date of review: May 26, 2000

Medical Team Leader review

Administrative background
The date of the original submission of S-031 was March 18, 1999. The sponsor initially proposed changes to Clinical Pharmacology consisting of deletion of the word "variable" as a descriptor of the HDL-raising effects of pravastatin. No data were submitted. The "approvable" letter dated 1-18-00 required that the sponsor provide the following in order to support the proposed changes in labeling and to support additional changes in Indications and Usage:

> "...analyses of lipid-response data in patients with Type IIa and IIb hyperlipoproteinemia (HLP) treated in pravastatin controlled trials and expressed in order to convey the distribution of responses from baseline..."

In the current submission, the sponsor has provided the required analyses. The submission contains subgroup analyses from two studies previously completed and submitted to FDA in support of labeling changes, and so approved. No new clinical trials have been conducted. These analyses have not previously been reviewed.

Rationale
The package inserts for simvastatin and atorvastatin have recently been amended to include lipid altering data conveying the distribution of effects on HDL-C levels in patients with Types IIa and IIb HLP. In the context of a developing awareness of the significance of HDL-C levels and ratios of total-C to HDL-C and of LDL-C to HDL-C, the Division has furthermore permitted labeling changes in Indications and Usage by adding "and to increase HDL-C" to the list of expected lipid changes in patients with Types IIa and IIb HLP. While the responses in HDL-C (and TG) to statins across individuals with hypercholesterolemia and mixed dyslipidemia are variable, the change in the Indications and Usage section reflects a potential benefit of these drugs (in addition to LDL-C lowering). This statement of potential benefit is further qualified in labeling not only by the enumeration of the effect as a cumulative distribution function (median, 25^{th}, 75^{th} percentiles) but also by inclusion of a disclaimer stating that the independent effect of raising HDL-C on CV morbidity and mortality in these patients is not known.

Comments on the submission

Clinical data analyses

The current submission contains analyses of lipid-response data from the West of Scotland Coronary Prevention Study (WOSCOPS) and from Cholesterol and Recurrent Events (CARE), two large, multicenter, double-blind, randomized, placebo-controlled studies in coronary prevention. The results of these studies have been submitted previously to the Agency, reviewed by DMEDP, and support labeling for pravastatin.

This supplement was submitted also in electronic format.

The data supporting the changes in labeling are contained in two tables, one from WOSCOPS and the other from CARE, that summarize the lipid-response data in the subgroups of both studies with Fredrickson Types IIa and IIb HLP at baseline. These are patients with either isolated elevations in LDL-C or with combined elevations in LDL-C and TG. These subgroups included 5830 patients from WOSCOPS (total enrolled 6595), evenly distributed across placebo and pravastatin groups, and 3270 patients from CARE (total enrolled 4159), also evenly distributed across treatment groups. At the request of the Division, the sponsor has included data on mean, median, 25th, and 75th percentile change from baseline for total-C, HDL-C, LDL-C and TG.

With regard to changes from baseline in HDL-C, the effects appear modest in both trials. The mean percent changes from baselines in WOSCOPS were 3.32 and 7.26, respectively, for placebo and pravastatin. In CARE, the corresponding mean percent changes were 1.47 and 5.51, respectively. The responses in HDL-C are variable, as reflected in the distribution of changes from baseline, which will be included in labeling. As stated above, while the independent effect of raising HDL-C with this drug in these patients is not known, there is ample evidence to support the effect as potentially salutary, and therefore worth enumerating in labeling. Finally, though no formal biometrics review was requested, Dr. Sahlroot's analyses confirm that the between-group differences in mean change from baseline in HDL-C are highly statistically significant for both studies.

Labeling comments

The original proposed labeling (in the April 3, 2000 submission) addressed the requested analyses in a separate paragraph in Clinical Pharmacology that did not name the two studies from which the analyses derived. At my request by telephone and consistent with the labeling for other similarly labeling statins, the median (25th, 75th percentile) percent changes from baseline in the major lipid parameters were integrated separately into the test discussions of WOSCOPS and CARE. The labeling is thus acceptable.

Summary

The sponsor has responded adequately to the requirements for approval of S-031 as described in the letter of 1-18-00. The data analyses submitted support the proposed changes in labeling. The labeling is accepted.

Recommendation
This supplemental NDA may be approved.

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

D. Orloff
5-26-00

CC:
NDA 19-898 Arch
HFD-510

6/9/00

NDA 19-898/S-031 resubmission
Pravachol (pravastatin sodium) Tablets
Bristol-Myers Squibb Company
Category: Lipid altering
Date of submission: April 3, 2000
Date of review: May 9, 2000

Medical Officer Review

This present submission is in response to the letter from FDA, dated January 18, 2000, which found S-031 to be approvable. However, before the application could be approved, FDA required "sufficient data to support the proposed change in labeling" in the section Clinical Pharmacology and to add the same to the section Indications; this latter "would . . . state that Pravachol increases HDL-C." The FDA letter requested analyses of lipid-response data in patients with Types IIa and IIb hyperlipoproteinemia who had been treated in pravastatin controlled trials and in whom such data were expressed "in order to convey the distribution of responses from baseline."

The company has replied in this resubmission with analyses of assessments of effect of pravastatin in subjects with Fredrickson Type IIa and Type IIb hyperlipoproteinemia (HLP) who were contained in two placebo-controlled morbidity and mortality studies conducted earlier.

(1) In the West of Scotland Coronary Prevention Study (WOSCOPS, study 1) a total of 6595 men who originally had no evidence of a previous myocardial infarction (MI) and who had LDL-C > or = 4.0 mmol/L (155 mg/dL) were randomized to regimen of either pravastatin 40 mg or placebo given once daily for a median of 4.8 years. Baseline and 6-month on-treatment HDL-C measurements were available for 2921 pravastatin-treated subjects and 2905 of those given placebo. Median (25^{th}, 75^{th} percentile) per cent change from baseline in HDL-C after six months treatment are summarized by the sponsor. Mean per cent change from baseline mean in placebo-treated subjects was 3.32 and in pravastatin-treated patients was 7.26.

(2) In the Cholesterol and Recurrent Events (CARE, study 2) trial a total of 4159 men and women with a previous MI and with total cholesterol < 240 mg/dL and TG < 350 mg/dL were randomized to pravastatin 40 mg or placebo given once a day for a median of 4.9 years. In order to assess effect of pravastatin on HDL-C in those subjects with Fredrickson Type IIa and Type IIb HLP, lipid data from CARE subjects with Fredrickson Type IV HLP (TG > 200 mg/dL and LDL-C < 160 mg) were removed from the lipid analyses data sets. Baseline and 6-month on-treatment HDL-C measurements then remained available for 1642 pravastatin-treated and for 1628 placebo-treated subjects with Type IIa and IIb HLP. The sponsor has tabulated and summarized median (25^{th}, 75^{th} percentile) per cent change from baseline in HDL-C after 6 months of treatment. Mean per cent change from baseline mean in placebo-treated subjects was 1.47 and in pravastatin-treated patients was 5.51.

Recommendations:

(1) The cited data and tabulations appear to respond to the additional calculations and presentation asked in the FDA letter of Jan 18, 2000. To my non-statistically trained eye the results and tables appear as if responses are of a significant nature, chiefly because of the large n involved in both Tables 1 and 2, and that therefore this resubmission may be approved.

(2) However, because of the character of clinical response and dependence upon numerical values and because the company has not provided any measures or discussion of significance of lab results in either the printed or electronic submissions, I asked Dr Todd Sahlroot of Biostatistics on May 9 to study these Tables and provide some report of statistical interpretation of HDL results. He has reported in the copies of the two tables that are attached to this review that these results are highly significant with p values < .0001.

(3) The labeling has already been critiqued in the review dated Jan 3, 2000, and has been reviewed once again for this present MOR; it is satisfactory from a medical standpoint in both Clinical Pharmacology and in Indications.

Elton Herman

Elton Herman

See Team Leader memo 5-26-00 for labeling review.

D. Owen 5-26-00

cc: Orig NDA 19-898/S-031
HFD-510
HFD-510/EHerman/05-10-2000

PROTOCOL 27201 66

Table 1
Type IIa and IIb Hyperlipoproteinemia

WOSCOPS

Baseline, On-Therapy, and Percent Change From Baseline

6 Month Lab Data
Randomized Subjects

Lab Test	Treatment Group	n	Baseline Mean	Baseline (sd)	On Therapy Mean	On-Therapy (sd)	Percent Change from Baseline Mean	Percent Change from Baseline (sd)	Percent Change 25th Pctl	Percent Change Median	Percent Change 75th Pctl
CHOL	PLACEBO	2908	271.73	22.45	271.17	29.86	-0.04	9.31	-6.10	-0.39	5.71
	PRAVASTATIN	2922	271.59	22.76	221.29	16.90	-18.43	12.28	-26.86	-20.30	-11.66
HDLC	PLACEBO	2905	43.92	9.44	45.17	11.30	3.32	16.02	-5.69	2.14	11.17
	PRAVASTATIN	2921	44.13	9.37	47.08	11.03	7.26	15.00	2.12	6.66	15.63
LDLC	PLACEBO	2900	191.85	17.33	189.14	26.07	-1.25	11.76	-8.72	-1.54	5.69
	PRAVASTATIN	2920	191.79	17.48	143.36	31.04	-25.17	15.07	-35.99	-27.67	-16.86
TRIGF	PLACEBO	2908	163.91	69.40	170.51	87.12	7.17	38.30	-17.08	1.42	23.11
	PRAVASTATIN	2922	161.36	69.02	149.20	74.27	-4.04	33.89	-27.57	-9.10	12.48
VLDL	PLACEBO	2900	33.48	15.02	35.38	18.86	12.51	52.37	-18.51	4.71	31.09
	PRAVASTATIN	2920	33.14	15.21	29.37	15.14	-4.53	44.86	-33.32	-11.11	15.54

$$Z = \frac{(7.26 - 3.32)}{\sqrt{\frac{(16.02)^2}{2905} + \frac{(15.00)^2}{2921}}} = \frac{3.94}{\sqrt{.0883 + .0770}} = 9.69$$

$$P < .0001$$

Program Source: E@.LVDM.BMCS896.PPP(LIPDWOS)

RUN DATE: 27JAN00

PROTOCOL 27201-67

Table 2
Type IIa and IIb Hyperlipoproteinemia

CARE

Baseline, On-Therapy, and Percent Change From Baseline

6 Month Lab Data
Randomized Subjects

Lab Test	Treatment Group	n	Baseline Mean	Baseline (sd)	On Therapy Mean	On Therapy (sd)	Percent Change from Baseline Mean	Percent Change from Baseline (sd)	Percent Change 25th Pctl	Percent Change Median	Percent Change 75th Pctl
CHOL	PLACEBO	1628	206.25	17.55	206.62	24.99	0.31	10.00	-5.78	0.00	6.46
	PRAVASTATIN	1642	206.41	17.36	161.63	25.76	-20.65	11.05	-28.35	-22.01	-14.92
HDLC	PLACEBO	1628	40.50	9.30	40.86	9.73	1.47	12.79	-6.80	0.98	8.24
	PRAVASTATIN	1642	40.09	8.96	42.06	10.10	5.51	14.06	-2.86	5.11	12.73
LDLC	PLACEBO	1628	139.69	15.09	137.94	21.90	-1.08	12.99	-9.12	-1.22	7.07
	PRAVASTATIN	1642	140.07	14.96	97.22	21.61	-30.50	14.10	-39.91	-32.43	-23.68
TRIG	PLACEBO	1628	130.49	36.93	139.33	56.18	8.43	36.19	-15.79	3.76	24.54
	PRAVASTATIN	1642	131.31	37.32	121.57	50.19	-5.85	31.30	-26.53	-10.95	8.60

$$Z = \frac{5.51 - 1.47}{\sqrt{\frac{(12.79)^2}{1628} + \frac{(14.06)^2}{1642}}} = \frac{4.04}{\sqrt{.1005 + .1204}} = 8.60$$

$$P < .0001$$

007

Program Source: E#:LVDM.BHC5896.PPP(LIPDCARE)

RUN DATE: 27JAN00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-898/S-031

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

& CLINPHARM PHOLAC.

EXCLUSIVITY SUMMARY FOR NDA # 19-898 SUPPL # 031

Trade Name Pravachol Generic Name pravastatin

Applicant Name Bristol Myers Squibb HFD # 510

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 #_____. Drug Name _____.

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# 19-898 Ravacho l

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:

27,201-66

27,201-67

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"):

27,201-66 _____

27,201-67 _____

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 # 27201 YES /✓/ ! NO /___/ Explain: _____

! _____

Investigation #2

IND # 27201 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: _____

_____

Signature
Title: Project Manager

1/13/00
Date

Signature of Office/
Division Director

1/18/00
Date

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

PATENT INFORMATION

The Pravachol® (pravastatin) products described in Bristol-Myers Squibb Company's SNDA No. 19-898/S-0__ are covered by the following patents:

(1) U.S. Patent No. 4,346,227 (assigned to Sankyo Co. Ltd.) expires October 20, 2005, and its claims cover pravastatin as a new chemical entity or composition;

(2) U.S. Patent No. 5,030,447 (assigned to E.R. Squibb & Sons, Inc.) expires July 9, 2008, and its claims cover a formulation containing pravastatin;

(3) U.S. Patent No. 5,180,589 (assigned to E.R. Squibb & Sons, Inc.) expires July 9, 2008, and its claims cover a formulation containing pravastatin;

Patents (1), (2) and (3) are now listed in the Orange Book.

The pravastatin composition patent is owned by Sankyo Co. Ltd. E.R. Squibb & Sons, Inc., a wholly owned subsidiary of Bristol-Myers Squibb Company, is a licensee under this patent, has a place of business at Province Line Road and Route 206, P.O. Box 4000, Princeton, NJ 08543 and is authorized to receive notice of patent certification under §505(b)(3) and (j)(2)(B) of the Act and §§314.52 and 314.95.

The two pravastatin formulation patents are owned by E.R. Squibb & Sons, Inc., a wholly owned subsidiary of Bristol-Myers Squibb Company.

In accordance with 21 CFR §§314.53(c) and 314.53(d)(2), certification of the above-listed patents, which cover Pravachol® described in this SNDA is made on the attached sheet.

CERTIFICATION OF PATENT INFORMATION

As the undersigned, I hereby make the following declaration under 21 CFR §§314.53(c) and 314.53(d)(2) concerning the following composition and formulation patents that cover the Pravachol® products currently approved under Section 505 of the Federal Food, Drug and Cosmetic Act.

The undersigned declares that

U.S. Patent No. 4,346,227 (assigned to Sankyo Co. Ltd.) expiring October 20, 2005, U.S. Patent No. 5,030,447 (assigned to E.R. Squibb & Sons, Inc.) expiring July 9, 2008, and U.S. Patent No. 5,180,589 (assigned to E.R. Squibb & Sons, Inc.) expiring July 9, 2008, are patents that have been previously submitted to the FDA and identified as covering the product Pravachol® (pravastatin) covered by NDA No. 19-898. In accordance with 21 C.F.R. 314.53(d)(2) the undersigned certifies that these patents cover the product that is the subject of the accompanying SNDA 19-898/S-0__. The use of the Pravachol® composition and formulations for the following indications is the subject of this SNDA.

Modification of lipoprotein levels as follows:

a. Lowering triglycerides (TG) and non-HDL-C in Frederickson Type IV patients and patients with combined hyperlipidemia

b. Lowering TG and various lipoproteins in Frederickson Type III patients

c. Lowering TG as well as total cholesterol and LDL-C in patients with combined hyperlipidemia.

As the undersigned, I hereby make the following declaration under 21 CFR §§ 314.53(d)(2)(D)(iii):

In the opinion and to the best knowledge of Bristol-Myers Squibb Company, there are no patents that claim the specific use of pravastatin for the indications sought in the subject SNDA.

Burton Rodney
Senior Associate Counsel - Patents
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000

Dated: March 18, 1999

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.

LA # 19-898 Supplement # 031 Circle one: SE1 SE2 SE3 SE4 SE5 SE6 (SE8)

S10 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 Coronary events; secondary prevention of CV events; hypercholesterolemia and MIXED dyslipidemia

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

Proposed indication in this application addition of language indicating its treatment of Type IIa + IIb: "and to increase HDL-c"

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 Aug 4, 1999

___ (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 Med. Team Leader (e.g., medical review, medical officer, team leader)

D. Mahl

Signature of Preparer and Title

6-1-00

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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT: Bristol-Myers Squibb Company

DATE OF SUBMISSION: June 9, 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-031

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*: Pravastatin Sodium

PROPRIETARY NAME *(trade name)* IF ANY: Pravachol

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*:

CODE NAME *(If any)*:

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

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 9, 2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
P.O. Box 4000, Princeton, NJ 08543-4000	(609) 252-5610

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)

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-031
PRAVACHOL® (pravastatin sodium) Tablets

June 9, 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-031, which included proposed changes to the label regarding the effect of Pravachol on HDL-cholesterol levels. Further reference is made to our submission of April 3, 2000, which provided additional analyses and revised draft labeling for this supplement. Final reference is made to my phone conversation on May 10 with Dr. David Orloff in which he suggested some editorial changes be made on the labeling text for this supplement. As a result of that conversation, the draft labeling was revised to address his comments, and a copy of the revised draft labeling was faxed to the Agency on May 11, 2000.

At this time we are providing a hard copy of the revised labeling which is identical to the revised labeling sent via fax on May 11. 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 Copies: Ms. Margaret Simoneau (HFD-510, 14B04)
Dr. David Orloff (HFD-510, 14B04)

20 Page(s) Withheld

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

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 19-898
S-031

Electronic Mail Message

Date: 6/7/00 15:00
From: Margaret Simoneau
To: Lonnie Smith* (SMITHLO)
Cc: Enid Galliers (GALLIERS)
Cc: Michael Jones (JONESM)
Subject: Re: NDA 19-898/S-031 Pravachol

Lonnie,

Please change efficacy supplement(S-031) from a SE8 to an SE1. As an additional note, there is no change in UF. This efficacy supplement will be signed off soon.

Thanks,
Peggy Simoneau

BRISTOL-MYERS SQUIBB

WORLDWIDE REGULATORY AFFAIRS

Telefax Transmission Cover Sheet

DATE: May 11, 2000

TO: Margaret Simoneau

FROM: Fred Henry

NO. OF PAGES: 21 (including cover page)

SUBJECT: Pravachol – NDA 19-898 Supplement S-031

MESSAGE:

Dear Margaret,

As per my discussion with Dr. Orloff yesterday afternoon, attached is revised Pravachol draft labeling supported by data presented in submission S-031 (HDL indication). Changes to the originally submitted draft label are found on pages 4, 5 and 7.

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

Sincerely,

Fred Henry

If not properly received, please notify promptly
Phone: (609) 252-5610
Fax: (609) 252-6000

Dr. Orloff

APPROVED

JUN - 9 2000

BRISTOL-MYERS SQUIBB

WORLDWIDE REGULATORY AFFAIRS

Telefax Transmission Cover Sheet

DATE: May 11, 2000

TO: Margaret Simoneau

FROM: Fred Henry

NO. OF PAGES: 21 (including cover page)

SUBJECT: Pravachol – NDA 19-898 Supplement S-031

MESSAGE:

Labeling adopted D. Orloff 5-26-00

Dear Margaret,

As per my discussion with Dr. Orloff yesterday afternoon, attached is revised Pravachol draft labeling supported by data presented in submission S-031 (HDL indication). Changes to the originally submitted draft label are found on pages 4, 5 and 7.

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

Sincerely,

Fred Henry

If not properly received, please notify promptly
Phone: (609) 252-5610
Fax: (609) 252-6000

20 Page(s) Withheld

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

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 19-898
S-031

Electronic Mail Message

Date: 4/10/00 12:01:40 PM
From: Jega Nathan* (NATHANJ)
To: Margaret Simoneau (SIMONEAUM)
To: Mary Parks (PARKSM)
To: Mary Guilderson (GUILDERSON)
To: Enid Galliers (GALLIERS)
To: Deborah Lorentz (LORENTZD)
To: Lonnie Smith* (SMITHLO)
To: Brenda Allen * (ALLENB)
Cc: Randy Levin (LEVINR)
Cc: Paul Henig (HENIGP)
Cc: Thomas Selnekovic (SELNEKOVIC)
Cc: Gary Anderson (ANDERSONG)
Cc: Michael Jeffries (JEFFRIESM)
Cc: Thomas Tokoli * (TOKOLI)
Cc: Barry Wheeler * (WHEELERB)
Subject: NDA 19898 S-031 "Pravachol" from Bristol-Myers Squibb. Letter Dt. 4/3

Hi

Please note we have moved all data for NDA 19898 electronic submissions
to the new server \\CDSESUB1\N19898

If you have mapped the old server (CDS021) please disconnect and remap
the new location.

EDR received a CD-ROM for NDA 19898 "Pravachol" from Bristol-Myers
Squibb,
Letter date April 03, 2000 HFD 510

Incoming-Doc-Type: SE8

Doc-Type-Seq-No: 31

Modification-Type: BL

It has item 2, 8, 10

It is copied to \\CDSESUB1\N19898\S_031\2000-04-03

It is available on network

You can find the data by entering EDR in your browser

Nathan

Bristol-Myers Squibb
Pharmaceutical Research Institute
P.O. Box 4000 Princeton, NJ 08543-4000
609 252-5610 Fax: 609 252-6000

ORIGINAL
NDA SUPP AMEND
S-031-BL

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

NDA 19-898/S-031
PRAVACHOL® (pravastatin sodium) Tablets

April 3, 2000

John 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 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-031) which included proposed changes to the CLINICAL PHARMACOLOGY section of the label regarding the effect of Pravachol on HDL-cholesterol levels. Final reference is made to the Agency's approvable letter (a copy is included in this submission) for this supplement dated January 18, 2000.

We are now providing additional analyses from the WOSCOPS (S-022) and CARE (S-026) datasets relating to the effects of pravastatin on HDL-cholesterol levels in subjects with Fredrickson Type IIa and IIb hyperlipoproteinemia which address the issues identified in the above referenced action letter. Revised labeling, which includes changes to the CLINICAL PHARMACOLOGY and INDICATIONS sections pertaining to the effects of pravastatin on HDL-cholesterol is included in this submission. Additionally, one editorial change in the CLINICAL PHARMACOLOGY section has been made to reflect the recently approved supplement S-030, which provided for dosing of Pravachol® at any time of day.

The components mentioned above are provided in electronic format. The cover letter, Form 356h and Table of Contents are provided in both paper and electronic format. The electronic portion of the submission consists of 34 files and 13 folders on one CD-ROM disk which is being sent to the Central Document Room. The total size of the electronic submission is less than 1.2 Mb. The files were screened for known viruses on March 31, 2000, with Norton

Antivirus Software, Version 5.01.1 for Windows NT 4.0 (Symantec) and no viruses were detected.

For the convenience of the Reviewer, those documents in the submission that are in electronic form contain hypertext links to other documents referenced within the text and tables. These hyperlinks for file names appear in blue type in the electronic document. Document names used in these tables conform to the scheme outlined in the FDA guidance. The proposed package insert is provided in both Word97 (".doc") and Adobe Acrobat ("pdf") formats. Additionally, the review copy and desk copies of this submission contain a paper copy of the proposed package insert for ease of review.

Please refer to the Reviewer's Guide which follows this letter for additional details concerning this electronic submission. 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/ls/dk
Attachments

Desk Copies: Ms. Margaret Simoneau (HFD-510, 14B04)
Dr. David Orloff (HFD-510, 14B04)

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

Effect of Pravastatin on HDL-C in Subjects with Fredrickson Type IIa and IIb Hyperlipoproteinemia

The effect of pravastatin on HDL-C levels in subjects with Fredrickson Type IIa and IIb hyperlipoproteinemia (HLP) was assessed in two placebo-controlled morbidity and mortality studies. In the West of Scotland Coronary Prevention Study (WOSCOPS, study 1), 6595 men without evidence of a previous myocardial infarction (MI) and with LDL-C $\geq$ 4.0 mmol/L (155mg/dL) were randomized to pravastatin 40 mg or placebo once daily for a median of 4.8 years. Baseline and 6-month on-treatment HDL-C measurements were available for 2921 pravastatin-treated and 2905 placebo subjects. Median (25^{th}, 75^{th} percentile) percent change from baseline in total cholesterol, HDL-C, LDL-C, triglycerides (TG), and VLDL-C after 6 months of treatment are summarized in attached Table 1.

In the Cholesterol and Recurrent Events (CARE, study 2) study, 4159 men and women with a previous MI and with total cholesterol < 240 mg/dL and TG < 350 mg/dL were randomized to pravastatin 40 mg or placebo once daily for a median of 4.9 years. For an assessment of the effect of pravastatin on HDL-C in subjects with Fredrickson Type IIa and IIb HLP, lipid data from CARE subjects with Fredrickson Type IV HLP (TG > 200 mg/dL and LDL-C < 160 mg) were removed from the lipid analyses data sets. Baseline and 6-month on-treatment HDL-C measurements were available for 1642 pravastatin-treated and 1628 placebo subjects with Type IIa and IIb HLP. Median (25^{th}, 75^{th} percentile) percent change from baseline in total cholesterol, HDL-C, LDL-C, and TG after 6 months of treatment are summarized in attached Table 2.

PROTOCOL 27201-66

Table 1
Type IIa and IIb Hyperlipoproteinemia

WOSCOPS

Baseline, On-Therapy, and Percent Change From Baseline

6 Month Lab Data
Randomized Subjects

Lab Test	Treatment Group	n	Baseline Mean	Baseline (sd)	On-Therapy Mean	On-Therapy (sd)	Percent Change from Baseline Mean	Percent Change from Baseline (sd)	Percent Change 25th Pctl	Percent Change Median	Percent Change 75th Pctl
CHOL	PLACEBO	2908	271.73	22.46	271.17	29.86	-0.04	9.31	-6.10	-0.39	5.71
	PRAVASTATIN	2922	271.59	22.76	221.29	16.90	-18.43	12.28	-26.86	-20.30	-11.66
HDLC	PLACEBO	2905	43.92	9.44	45.17	11.30	3.32	16.02	-5.69	2.14	11.17
	PRAVASTATIN	2921	44.13	9.37	47.08	11.03	7.26	15.00	-2.12	6.66	15.63
LDLC	PLACEBO	2900	191.85	17.33	189.14	26.07	-1.25	11.76	-8.72	-1.54	5.69
	PRAVASTATIN	2920	191.79	17.48	143.36	31.04	-25.17	15.07	-35.99	-27.67	-16.86
TRIGF	PLACEBO	2908	163.91	69.40	170.51	87.12	7.17	38.30	-17.08	1.42	23.11
	PRAVASTATIN	2922	161.36	69.02	149.20	74.27	-4.04	33.89	-27.57	-9.10	12.48
VLDL	PLACEBO	2900	33.48	15.02	35.38	18.86	12.51	52.37	-18.51	4.71	31.09
	PRAVASTATIN	2920	33.14	15.21	29.37	15.14	-4.53	44.86	-33.32	-11.11	15.54

Program Source: E9.LVDM.BMCS896.PPP(LIPDWOS)

RUN DATE: 27JAN00

PROTOCOL 27201-67

Table 2
Type IIa and IIb Hyperlipoproteinemia

CARE

Baseline, On-Therapy, and Percent Change From Baseline

6 Month Lab Data
Randomized Subjects

Lab Test	Treatment Group	n	Baseline Mean	Baseline (sd)	On-Therapy Mean	On-Therapy (sd)	Percent Change from Baseline Mean	Percent Change from Baseline (sd)	Percent Change 25th Pctl	Percent Change Median	Percent Change 75th Pctl
CHOL	PLACEBO	1628	206.25	17.55	206.62	24.99	0.31	10.00	-5.78	0.00	6.46
	PRAVASTATIN	1642	206.41	17.36	163.63	25.76	-20.65	11.05	-28.35	-22.01	-14.92
HDLC	PLACEBO	1628	40.50	9.30	40.86	9.73	1.47	12.79	-6.80	0.98	8.24
	PRAVASTATIN	1642	40.09	8.96	42.06	10.10	5.51	14.06	-2.86	5.11	12.73
LDLC	PLACEBO	1628	139.69	15.09	137.94	21.90	-1.08	12.99	-9.12	-1.22	7.07
	PRAVASTATIN	1642	140.07	14.96	97.22	21.61	-30.50	14.10	-39.91	-32.43	-23.68
TRIG	PLACEBO	1628	130.49	36.93	139.33	56.18	8.43	36.19	-15.79	3.76	24.54
	PRAVASTATIN	1642	131.31	37.32	121.57	50.19	-5.85	31.30	-26.53	-10.95	8.60

Program Source: E0.LVDM.BMCS896.PPP(LIPDCARE)

RUN DATE: 27JAN00

20 Page(s) Withheld

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

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 19-898
S-031

4 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

✓ § 552(b)(5) Deliberative Process

Withheld Track Number: Administrative- 19-898
S-031