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Approval Package for:

APPLICATION NUMBER:

19-898/S050

Trade Name: Pravachol Tablets

Generic Name: pravastatin sodium

Sponsor: Bristol Myers Squibb Pharmaceutical Research Institute

Approval Date: July 12, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-898/S050

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-898/S050

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-898/S-050

Bristol-Myers Squibb Pharmaceutical Research Institute
Attention: Jerry Gennaro, Ph.D.
Director, Regulatory Science
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Gennaro:

Please refer to your supplemental new drug application dated October 12, 2001, received October 15, 2001, 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 25 and June 11, 2002. Your submission of April 25, 2002 constituted a complete response to our April 11, 2002 action letter.

This supplement proposes revisions to the **ADVERSE REACTIONS, OVERDOSAGE**, and **STORAGE** sections of the Package Insert. The specific changes are as follows:

The **ADVERSE REACTIONS**; Adverse Clinical Events; Short-Term Controlled Trials, Long-Term Controlled Morbidity and Mortality Trials and Postmarketing Experience subsections were added.

To the **ADVERSE REACTIONS,** Adverse Clinical Events, Short-Term Controlled Trials, subsection, the first paragraph has been changed to read:

> All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in placebo-controlled trials of up to four months duration are identified in **Table 6**; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug:

Table 6 has been changed to read, "**Adverse Events in > 2 Percent of Patients Treated with Pravastatin 10-40 mg in Short-Term Placebo-Controlled Trials.**"

The **ADVERSE REACTIONS,** Adverse Clinical Events, Long-Term Controlled Morbidity and Mortality Trials subsection has been added to read:

> Adverse event data were pooled from seven double-blind, placebo-controlled trials (West of Scotland Coronary Prevention study [WOS]; Cholesterol and Recurrent Events study [CARE]; Long-term Intervention with Pravastatin in Ischemic Disease study [LIPID]; Pravastatin Limitation of Atherosclerosis in the Coronary Arteries study [PLAC I]; Pravastatin, Lipids and Atherosclerosis

in the Carotids study [PLAC II]; Regression Growth Evaluation Statin Study [REGRESS]; and Kuopio Atherosclerosis Prevention Study [KAPS]) involving a total of 10,764 patients treated with pravastatin 40 mg and 10,719 patients treated with placebo. The safety and tolerability profile in the pravastatin group was comparable to that of the placebo group. Patients were exposed to pravastatin for a mean of 4.0 to 5.1 years in WOS, CARE, and LIPID and 1.9 to 2.9 years in PLAC I, PLAC II, KAPS, and REGRESS. In these long-term trials, the most common reasons for discontinuation were mild, non-specific gastrointestinal complaints. Collectively, these seven trials represent 47,613 patient-years of exposure to pravastatin. Events believed to be of probable, possible, or uncertain relationship to study drug, occurring in at least 1% of patients treated with pravastatin in these studies are identified in **Table 7**.

Table 7 Adverse Events in ≥ 1 Percent of Patients Treated with Pravastatin 40 mg in Long-Term Placebo-Controlled Trials

Body System/Event	Pravastatin (N = 10,764) % of patients	Placebo (N = 10,719) % of patients
Cardiovascular		
Angina Pectoris	3.1	3.4
Dermatologic		
Rash	2.1	2.2
Gastrointestinal		
Dyspepsia/Heartburn	3.5	3.7
Abdominal Pain	2.4	2.5
Nausea/Vomiting	1.6	1.6
Flatulence	1.2	1.1
Constipation	1.2	1.3
General		
Fatigue	3.4	3.3
Chest Pain	2.6	2.6
Musculoskeletal		
Musculoskeletal Pain (includes arthralgia)	6.0	5.8
Muscle Cramp	2.0	1.8
Myalgia	1.4	1.4
Nervous System		
Dizziness	2.2	2.1
Headache	1.9	1.8
Sleep Disturbance	1.0	0.9
Depression	1.0	1.0
Anxiety/Nervousness	1.0	1.2
Renal/Genitourinary		
Urinary Abnormality (includes dysuria, frequency, nocturia)	1.0	0.8
Respiratory		
Dyspnea	1.6	1.6
Upper Respiratory Infection	1.3	1.3
Cough	1.0	1.0
Special Senses		
Vision Disturbance (includes blurred vision, diplopia)	1.6	1.3

Events of probable, possible, or uncertain relationship to study drug that occurred in < 1.0% of pravastatin-treated patients in the long-term trials included the following; frequencies were similar in placebo-treated patients:

Dermatologic: pruritus, dermatitis, dryness skin, scalp hair abnormality (including alopecia), urticaria.
Endocrine/Metabolic: sexual dysfunction, libido change.
Gastrointestinal: decreased appetite.
General: fever, flushing.
Immunologic: allergy, edema head/neck.
Musculoskeletal: muscle weakness.
Nervous System: paresthesia, vertigo, insomnia, memory impairment, tremor, neuropathy (including peripheral neuropathy).
Special Senses: lens opacity, taste disturbance.

The **ADVERSE REACTIONS,** Adverse Clinical Events, Postmarketing Experience subsection has been added to read:

In addition to the events reported above, as with other drugs in this class, the following events have been reported rarely during postmarketing experience with PRAVACHOL, regardless of causality assessment:
Musculoskeletal: myopathy, rhabdomyolysis.
Nervous System: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), peripheral nerve palsy.
Hypersensitivity: anaphylaxis, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, asthenia, photosensitivity, chills, malaise, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.
Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, cirrhosis, fulminant hepatic necrosis, hepatoma.
Dermatologic: A variety of skin changes (e.g., nodules, discoloration, dryness of mucous membranes, changes to hair/nails).
Reproductive: gynecomastia.
Laboratory Abnormalities: elevated alkaline phosphatase and bilirubin; thyroid function abnormalities.

The **OVERDOSAGE** section was changed to read:

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

The **STORAGE** section was changed to read:

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

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

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted June 11, 2002).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no 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 18-898/S-050." Approval of this submission by FDA is not required before the labeling is used.

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

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

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

If you have any questions, call Margaret Simoneau, R.Ph., Regulatory Project Manager, at (301) 827-6411.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

David Orloff
7/12/02 08:56:09 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-898/S050

LABELING

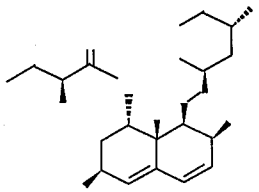
Rx only

PRAVACHOL®
(pravastatin sodium) Tablets

DESCRIPTION

PRAVACHOL® (pravastatin sodium) is one of a new class of lipid-lowering compounds, the HMG-CoA reductase inhibitors, which reduce cholesterol biosynthesis. These agents are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme catalyzing the early rate-limiting step in cholesterol biosynthesis, conversion of HMG-CoA to mevalonate.

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



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

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

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

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 ($t_{½}$) 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.

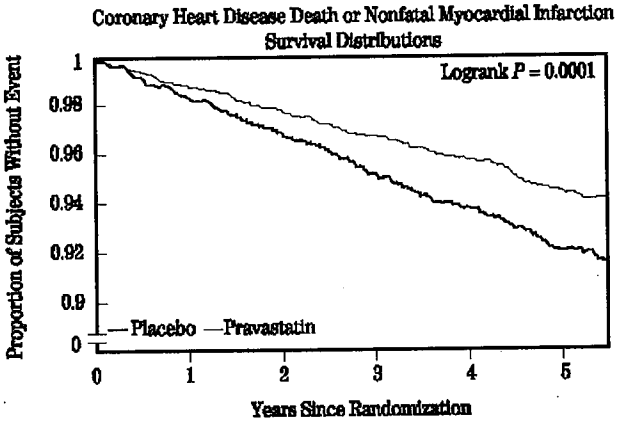
In a single oral dose study using pravastatin 20 mg, the mean AUC for pravastatin was approximately 27% greater and the mean cumulative urinary excretion (CUE) approximately 19% lower in elderly men (65 to 75 years old) compared with younger men (19 to 31 years old). In a similar study conducted in women, 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 $t_{½}$ 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 40 mg (N = 4512)**	**Placebo (N = 4502)**	**Risk Reduction**	***P*-value**
Primary Endpoint				
CHD mortality	287 (6.4)	373 (8.3)	24%	0.0004
Secondary Endpoints				
Total mortality	498 (11.0)	633 (14.1)	23%	<0.0001
CHD mortality or 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 40 mg (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 (see **Table 3**).

In a pooled analysis of two multicenter, double-blind, placebo-controlled studies of patients with primary hypercholesterolemia, treatment with pravastatin at a daily dose of 80 mg (N = 277) significantly decreased Total-C, LDL-C, and TG. The 25^{th} and 75^{th} percentile changes from baseline in LDL-C for pravastatin 80 mg were -43% and -30%. The efficacy results of the individual studies were consistent with the pooled data (see **Table 3**).

Treatment with PRAVACHOL modestly decreased VLDL-C and PRAVACHOL across all doses produced variable increases in HDL-C (see **Table 3**).

Table 3	Primary Hypercholesterolemia Studies: Dose Response of PRAVACHOL Once Daily Administration			
Dose	**Total-C**	**LDL-C**	**HDL-C**	**TG**
Mean Percent Changes From Baseline After 8 Weeks*				
Placebo (N = 36)	-3%	-4%	+1%	-4%
10 mg (N = 18)	-16%	-22%	+7%	-15%
20 mg (N = 19)	-24%	-32%	+2%	-11%
40 mg (N = 18)	-25%	-34%	+12%	-24%
Mean Percent Changes From Baseline After 6 Weeks**				
Placebo (N = 162)	0%	-1%	-1%	+1%
80 mg (N = 277)	-27%	-37%	+3%	-19%

* a multicenter, double-blind, placebo controlled study

**pooled analysis of 2 multicenter, double-blind, placebo controlled studies

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

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. (See **Table 4.**)

Table 4	Patients With Fredrickson Type IV Hyperlipidemia Median (25^{th}, 75^{th} 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 **Table 5.**

Table 5	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:

NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD[a] or CHD risk equivalents (10-year risk > 20%)	< 100	≥ 100	≥ 130 (100-129: drug optional)[b]
2+ Risk factors (10-year risk ≤ 20 %)	< 130	≥ 130	10-year risk 10%-20%: ≥ 130
			10-year risk < 10%: ≥ 160
0 -1 Risk factor[c]	< 160	≥ 160	≥ 190 (160-189: LDL-lowering drug optional)

a CHD, coronary heart disease.

b Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.

c Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still ≥ 200 mg/dL, non-HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

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. In three long-term (4.8-5.9 years), placebo-controlled clinical trials (WOS, LIPID, CARE; see **CLINICAL PHARMACOLOGY: Clinical Studies**), 19,592 subjects (19,768 randomized), were exposed to pravastatin or placebo. In an analysis of serum transaminase values (ALT, AST), incidences of marked abnormalities were compared between the pravastatin and placebo treatment groups; a marked abnormality was defined as a post-treatment test value greater than three times the upper limit of normal for subjects with pretreatment values less than or equal to the upper limit of normal, or four times the pretreatment value for subjects with pretreatment values greater than the upper limit of normal but less than 1.5 times the upper limit of normal. Marked abnormalities of ALT or AST occurred with similar low frequency (≤ 1.2%) in both treatment groups. Overall, clinical trial experience showed that liver function test abnormalities observed during pravastatin therapy were usually asymptomatic, not associated with cholestasis, and did not appear to be related to treatment duration.

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

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

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.

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 ($t_{1/2}$) 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: Concomitant administration of 40 mg 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 20 mg pravastatin and 0.2 mg 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 (up to 20 mg), 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. (See **WARNINGS: Skeletal Muscle.)**

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. These effects in dogs were observed at approximately 59 times the human dose of 80 mg/day, based on AUC. Similar CNS vascular lesions have been observed with several other drugs in this class.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

In a 2-year study in mice fed pravastatin at doses of 250 and 500 mg/kg/day, there was an increased incidence of hepatocellular carcinomas in males and females at both 250 and 500 mg/kg/day ($p<0.0001$). At these doses, lung adenomas in females were increased ($p=0.013$). These effects in mice were observed at approximately 15 times (250 mg/kg/day) and 23 times (500 mg/kg/day) the human dose of 80 mg, based on AUC. In

another 2-year study in mice with doses up to 100 mg/kg/day (producing drug exposures approximately 2 times the human dose of 80 mg, based on AUC), there were no drug-induced tumors.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; a forward mutation assay in L5178Y TK +/- mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a 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 10X (rabbit) or 120X (rat) the human exposure based on surface area ($mg/meter^2$). Rare reports of congenital anomalies have been received following intrauterine exposure to other HMG-CoA reductase inhibitors. In a review[9] of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or lovastatin, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a three-to-four-fold increase in congenital

anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. As safety in pregnant women has not been established and there is no apparent benefit to therapy with PRAVACHOL during pregnancy (see **CONTRAINDICATIONS**), treatment should be immediately discontinued as soon as pregnancy is recognized. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.

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

Adverse Clinical Events

Short-Term Controlled Trials

All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in placebo-controlled trials of up to four months duration are identified in **Table 6**; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug:

Table 6	Adverse Events in > 2 Percent of Patients Treated with Pravastatin 10-40 mg in Short-Term Placebo-Controlled Trials			
	All Events		Events Attributed to Study Drug	
Body System/Event	**Pravastatin (N = 900) % of patients**	**Placebo (N = 411) % of patients**	**Pravastatin (N = 900) % of patients**	**Placebo (N = 411) % of patients**
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.

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

Long-Term Controlled Morbidity and Mortality Trials

Adverse event data were pooled from seven double-blind, placebo-controlled trials (West of Scotland Coronary Prevention study [WOS]; Cholesterol and Recurrent Events study [CARE]; Long-term Intervention with Pravastatin in Ischemic Disease study [LIPID]; Pravastatin Limitation of Atherosclerosis in the Coronary Arteries study [PLAC I]; Pravastatin, Lipids and Atherosclerosis in the Carotids study [PLAC II]; Regression Growth Evaluation Statin Study [REGRESS]; and Kuopio Atherosclerosis Prevention Study [KAPS]) involving a total of 10,764 patients treated with pravastatin 40 mg and 10,719 patients treated with placebo. The safety and tolerability profile in the pravastatin group was comparable to that of the placebo group. Patients were exposed to pravastatin for a mean of 4.0 to 5.1 years in WOS, CARE, and LIPID and 1.9 to 2.9 years in PLAC I, PLAC II, KAPS, and REGRESS. In these long-term trials, the most common reasons for discontinuation were mild, non-specific gastrointestinal complaints. Collectively, these seven trials represent 47,613 patient-years of exposure to pravastatin. Events believed to be of probable, possible, or uncertain relationship to study drug, occurring in at least 1% of patients treated with pravastatin in these studies are identified in **Table 7**.

Table 7 Adverse Events in ≥ 1 Percent of Patients Treated with Pravastatin 40 mg in Long-Term Placebo-Controlled Trials

Body System/Event	Pravastatin (N = 10,764) % of patients	Placebo (N = 10,719) % of patients
Cardiovascular		
Angina Pectoris	3.1	3.4
Dermatologic		
Rash	2.1	2.2
Gastrointestinal		
Dyspepsia/Heartburn	3.5	3.7
Abdominal Pain	2.4	2.5
Nausea/Vomiting	1.6	1.6
Flatulence	1.2	1.1
Constipation	1.2	1.3
General		
Fatigue	3.4	3.3
Chest Pain	2.6	2.6
Musculoskeletal		
Musculoskeletal Pain (includes arthralgia)	6.0	5.8
Muscle Cramp	2.0	1.8
Myalgia	1.4	1.4
Nervous System		
Dizziness	2.2	2.1
Headache	1.9	1.8
Sleep Disturbance	1.0	0.9
Depression	1.0	1.0
Anxiety/Nervousness	1.0	1.2
Renal/Genitourinary		
Urinary Abnormality (includes dysuria, frequency, nocturia)	1.0	0.8
Respiratory		
Dyspnea	1.6	1.6
Upper Respiratory Infection	1.3	1.3
Cough	1.0	1.0
Special Senses		
Vision Disturbance (includes blurred vision, diplopia)	1.6	1.3

Events of probable, possible, or uncertain relationship to study drug that occurred in < 1.0% of pravastatin-treated patients in the long-term trials included the following; frequencies were similar in placebo-treated patients:

Dermatologic: pruritus, dermatitis, dryness skin, scalp hair abnormality (including alopecia), urticaria.

Endocrine/Metabolic: sexual dysfunction, libido change.

Gastrointestinal: decreased appetite.

General: fever, flushing.

Immunologic: allergy, edema head/neck.

Musculoskeletal: muscle weakness.

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

Special Senses: lens opacity, taste disturbance.

Postmarketing Experience

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

Musculoskeletal: myopathy, rhabdomyolysis.

Nervous System: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), peripheral nerve palsy.

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

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

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

Reproductive: gynecomastia.

Laboratory Abnormalities: elevated 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 has been limited experience with overdosage of pravastatin. If an overdose occurs, it should be treated symptomatically with laboratory monitoring and supportive measures should be instituted as required. (See **WARNINGS.**)

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 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. If a daily dose of 40 mg does not achieve desired cholesterol levels, 80 mg once daily is recommended.

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.

80 mg tablets: Yellow, oval-shaped, biconvex with BMS embossed on one side and 80 engraved on the opposite side. They are supplied in bottles of 90 (NDC 0003-5195-10) and bottles of 500 (NDC 0003-5195-12). 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

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

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[1] Shepherd J, et al. Prevention of Coronary Heart Disease with Pravastatin in Men with Hypercholesterolemia (WOS). *N Engl J Med* 1995; 333:1301–7.

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Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

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~~N2004-02~~

Revised May 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-898/S050

MEDICAL REVIEW(S)

MEDICAL TEAM LEADER'S MEMO TO LABELING SUPPLEMENT

NDA # 19-898/Supplement 050
Sponsor: Bristol-Myers Squibb
Proposal: Changes to Adverse Reactions Section of Label

Background
The sponsor has submitted a labeling supplement which proposes to change the ADVERSE REACTION section of the label to include pooled safety data from 7 controlled trials: WOSCOP, CARE, LIPID, PLAC I AND II, REGRESS, and KAPS. These trials have been submitted to the Agency and reviewed for separate indications in the past. Based on a reanalysis of all the safety data from these trials, the sponsor proposes to re-organize the label to include Short-Term Trials and Long-Term Morbidity and Mortality Trials subsections. Under the latter subsection, the sponsor has inserted a table summarizing the AEs occurring in ≥ 1% of patients treated with pravastatin. Under the Postmarketing Experience subsection, the sponsor proposes to delete events that have already been reported under the clinical trials section.

Comments on Proposed Labeling Changes
The pooling of safety data from the 7 controlled trials is acceptable and is in accordance with the draft guidance to industry entitled "*Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics*" which allows for pooled data presentation of AEs. The primary objections to the data presentation include:

- / WOSCOPS, CARE, and LIPID were designed as clinical outcome studies
- actual number of patients exposed to pravastatin and placebo be used. In addition, the shorter mean duration of drug exposure for the REGRESS, PLAC I and II, and KAPS studies should be distinguished from the other 3 studies of longer duration.

The ADVERSE REACTIONS section of the label should be changed to the following:

Adverse Clinical Events

Short-Term Controlled Trials

All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in ~~the~~ placebo-controlled trials of up to four months duration are identified in **Table 6**; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug:

Table 6	Adverse Events in > 2 Percent of Patients Treated with Pravastatin 10-40 mg in Short-Term Placebo-Controlled Trials			
	All Events		Events Attributed to Study Drug	
Body System/Event	**Pravastatin (N = 900) % of patients**	**Placebo (N = 411) % of patients**	**Pravastatin (N = 900) % of patients**	**Placebo (N = 411) % of patients**
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.

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

Long-Term Morbidity and Mortality Controlled Trials

Adverse event data were pooled from seven double-blind, 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]); Pravastatin Limitation of Atherosclerosis in the Coronary Arteries study [PLAC I]; Pravastatin, Lipids and Atherosclerosis in the Carotids study [PLAC II]; Regression Growth Evaluation Statin Study [REGRESS]; and Kuopio Atherosclerosis Prevention Study [KAPS]) involving a total of 10 patients treated with pravastatin 40 mg and 10,719 patients treated with placebo. The safety and tolerability profile in the pravastatin group was comparable to that of the placebo group. Patients were exposed to pravastatin for a mean of 4.10 to 5.11 years in WOS, CARE, and LIPID amd 1.9 to 2.8 years in PLAC I, PLAC II, KAPS, and REGRESS. In these long-term trials, the most common reasons for discontinuation were mild, non-specific gastrointestinal complaints. Collectively, these seven trials represent 47,613 patient-years of exposure to pravastatin. Events believed to be of probable, possible, or uncertain relationship to study drug, occurring in at least 1% of patients treated with pravastatin in these studies are identified in **Table 7.**

Table 7 Adverse Events in ≥ 1 Percent of Patients Treated with Pravastatin 40 mg in Long-Term Placebo-Controlled Trials

Body System/Event	Pravastatin (N = 10,764) % of patients	Placebo (N = 10,719) % of patients
Cardiovascular		
Angina Pectoris	3.1	3.4
Dermatologic		
Rash	2.1	2.2
Gastrointestinal		
Dyspepsia/Heartburn	3.5	3.7
Abdominal Pain	2.4	2.5
Nausea/Vomiting	1.6	1.6
Flatulence	1.2	1.1
Constipation	1.2	1.3
General		
Fatigue	3.4	3.3
Chest Pain	2.6	2.6
Musculoskeletal		
Musculoskeletal Pain (includes arthralgia)	6.0	5.8
Muscle Cramp	2.0	1.8
Myalgia	1.4	1.4
Nervous System		
Dizziness	2.2	2.1
Headache	1.9	1.8
Sleep Disturbance	1.0	0.9
Depression	1.0	1.0
Anxiety/Nervousness	1.0	1.2
Renal/Genitourinary		
Urinary Abnormality (includes dysuria, frequency, nocturia)	1.0	0.8
Respiratory		
Dyspnea	1.6	1.6
Upper Respiratory Infection	1.3	1.3
Cough	1.0	1.0
Special Senses		
Vision Disturbance (includes blurred vision, diplopia)	1.6	1.3

Events of probable, possible, or uncertain relationship to study drug that occurred in < 1.0% of pravastatin-treated patients in the long-term trials included the following; frequencies were similar in placebo-treated patients:

Dermatologic: pruritus, dermatitis, dryness skin, scalp hair abnormality (including alopecia), urticaria.

Endocrine/Metabolic: sexual dysfunction, libido change.

Gastrointestinal: decreased appetite.

General: fever, flushing.

Immunologic: allergy, edema head/neck.

Musculoskeletal: muscle weakness.

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

Special Senses: lens opacity, taste disturbance.

The remaining portion of the ADVERSE REACTION section is acceptable.

In addition, with the recently submitted proposed label, this reviewer noted a change under the STORAGE section that will need to be reviewed by Chemistry.

Recommendations
This labeling supplement is approvable pending the recommended changes to the label.

Mary H. Parks, MD
Deputy Director
HFD-510

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/s/

Mary Parks
4/8/02 04:45:39 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-898/S050

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Division of Metabolic & Endocrine Drug Products

Labeling Review

Application Number: 19-898/S-050

Name of Drug: Pravachol (pravastatin) Tablets

Sponsor: Bristol-Myers Squibb

Submission Date: October 12, 2001. Label review from April 3, 2002 submission.

Background and Summary:

This supplement proposes revisions to the **ADVERSE REACTIONS, OVERDOSAGE,** and **STORAGE** sections of the package insert.

The last approved labeling, Supplement-046, was approved on December 18, 2001, with accepted draft labeling of December 17, 2001. The FPL (Package Insert Identifier # 5154DIM-17) was compared to the proposed draft labeling and accepted in an Agency Acknowledge and Retain letter dated March 22, 2002.

Review:

ADVERSE REACTIONS section has included information from a collective database of seven long-term morbidity and mortality trials. The *Adverse Clinical Events* subsection was arranged into three further subsections: *Short-Term Controlled Trials, Long-Term Controlled Trials, and Postmarketing Experience.*

OVERDOSAGE section has been updated.

STORAGE section changes were recommended by the Agency.

The attached enclosure, pages 24 through 33 of the package insert from the April 3, 2002 submission, show the proposed changes that the Agency has agreed to in addition to further recommendations.

Conclusion:

Clinical review of the proposed labeling changes were unacceptable. Agency will issue an approvable letter with the requested changes noted.

Reviewed by: M.A. Simoneau, R.Ph., Regulatory Project Manager/E.Galliers 4/10/02
(See appended electronic signature page)

ENCLOSURE

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

Adverse Clinical Events

Short-Term Controlled Trials

All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in ~~the~~ placebo-controlled trials of up to four months duration are identified in **Table 6**; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug:

Table 6	Adverse Events in > 2 Percent of Patients Treated with Pravastatin 10-40 mg in Short-Term Placebo-Controlled Trials			
	All Events		Events Attributed to Study Drug	
Body System/Event	**Pravastatin (N = 900) % of patients**	**Placebo (N = 411) % of patients**	**Pravastatin (N = 900) % of patients**	**Placebo (N = 411) % of patients**
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.

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

Long-Term Controlled Trials

Adverse event data were pooled from seven double-blind, 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]); Pravastatin Limitation of Atherosclerosis in the Coronary Arteries study [PLAC I]; Pravastatin, Lipids and Atherosclerosis in the Carotids study [PLAC II]; Regression Growth Evaluation Statin Study [REGRESS]; and Kuopio Atherosclerosis Prevention Study [KAPS]) involving a total of 10 patients treated with pravastatin 40 mg and 10,719 patients treated with placebo. The safety and tolerability profile in the pravastatin group was comparable to that of the placebo group. Patients were exposed to pravastatin for a mean of 4.0 to 5.1 years in WOS, CARE, and LIPID amd 1.9 to 2.8 years in PLAC I, PLAC II, KAPS, and REGRESS. In these long-term trials, the most common reasons for discontinuation were mild, non-specific gastrointestinal complaints. Events believed to be of probable, possible, or uncertain relationship to study drug, occurring in at least 1% of patients treated with pravastatin in these studies are identified in **Table 7.**

Table 7 Adverse Events in ≥ 1 Percent of Patients Treated with Pravastatin 40 mg in Long-Term Placebo-Controlled Trials

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Dermatologic		
Rash	2.1	2.2
Gastrointestinal		
Dyspepsia/Heartburn	3.5	3.7
Abdominal Pain	2.4	2.5
Nausea/Vomiting	1.6	1.6
Flatulence	1.2	1.1
Constipation	1.2	1.3
General		
Fatigue	3.4	3.3
Chest Pain	2.6	2.6
Musculoskeletal		
Musculoskeletal Pain (includes arthralgia)	6.0	5.8
Muscle Cramp	2.0	1.8
Myalgia	1.4	1.4
Nervous System		
Dizziness	2.2	2.1
Headache	1.9	1.8
Sleep Disturbance	1.0	0.9
Depression	1.0	1.0
Anxiety/Nervousness	1.0	1.2
Renal/Genitourinary		
Urinary Abnormality (includes dysuria, frequency, nocturia)	1.0	0.8
Respiratory		
Dyspnea	1.6	1.6
Upper Respiratory Infection	1.3	1.3
Cough	1.0	1.0
Special Senses		
Vision Disturbance (includes blurred vision, diplopia)	1.6	1.3

Events of probable, possible, or uncertain relationship to study drug that occurred in < 1.0% of pravastatin-treated patients in the long-term trials included the following; frequencies were similar in placebo-treated patients:

Dermatologic: pruritus, dermatitis, dryness skin, scalp hair abnormality (including alopecia), urticaria.

Endocrine/Metabolic: sexual dysfunction, libido change.

Gastrointestinal: decreased appetite.

General: fever, flushing.

Immunologic: allergy, edema head/neck.

Musculoskeletal: muscle weakness.

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

Special Senses: lens opacity, taste disturbance.

Postmarketing Experience

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

REVIEWER'S NOTE: Certain events below are deleted from the Postmarketing subsection because they now are included above in the Clinical Trials subsections.

Musculoskeletal: myopathy, rhabdomyolysis.

~~*Neurological*~~*Nervous System:* dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), peripheral nerve palsy~~, anxiety, insomnia, depression~~.

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

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

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

Reproductive: gynecomastia

Laboratory Abnormalities: elevated 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 has been limited experience with overdosage of pravastatin. If an overdose occurs, it should be treated symptomatically and supportive measures should be instituted as required. Measurement of liver enzymes and monitoring for signs and symptoms of myopathy are recommended.

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 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. If a daily dose of 40 mg does not achieve desired cholesterol levels, 80 mg once daily is recommended.

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.

80 mg tablets: Yellow, oval-shaped, biconvex with BMS embossed on one side and 80 engraved on the opposite side. They are supplied in bottles of 90 (NDC 0003-5195-10) and bottles of 500 (NDC 0003-5195-12). 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

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

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/s/

Margaret Simoneau
4/10/02 12:11:15 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-898/S-050

Bristol-Myers Squibb Pharmaceutical Research
Attention: Jerry Gennaro, Ph.D.
Director, Regulatory Science
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Gennaro:

Please refer to your October 12, 2001, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pravachol (pravastatin) Tablets.

We also refer to your submission dated September 9, 2002, containing final printed labeling (FPL) for this supplemental application which was approved on July 12, 2002.

This supplement provides for changes to the **ADVERSE REACTIONS, OVERDOSAGE**, and **STORAGE** sections of the Package Insert.

We note that this submission has been superseded by supplement 0-052 (which was approved on October 29, 2002). The FPL [Package Insert Identifier # 5154DIM-19 (1092990A9)] for S-050 will be retained in our files.

If you have any questions, call Margaret Simoneau, Regulatory Project Manager, at (301) 827-6411.

Sincerely,

{See appended electronic signature page}

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

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

/s/

Margaret Simoneau
11/14/02 09:00:16 AM

N-000 (MR)

ORIG AMENDMENT

ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
Tel: 609 252-4345 Fax: 609 252-6000
gerald.gennaro@bms.com

Jerry Gennaro, Ph.D.
Director
Metabolic/Endocrine Products
FDA Liaison & Global Regulatory Strategy

NDA 19-898/S-050
PRAVACHOL (pravastatin sodium) Tablets

April 25, 2002

David Orloff, MD
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. Orloff:

Reference is made to our labeling supplement (S-050) to NDA 19-898, submitted October 12, 2001; to our reformatted labeling proposal submitted on April 3, 2002; and to the approvable letter of April 11, 2002 that contained FDA's recommended changes to the April 3 proposed text.

Bristol-Myers Squibb wishes to request a teleconference to review and discuss the four areas cited in the approvable letter in which FDA has requested changes. The objective of this teleconference would be to reach agreement on the final labeling. Attached are copies of text in three versions:

1. Current Approved Label Text (version February 2002; No annotations; Same as submitted on April 3)

2. Current Label Text overlayed (strike-through format) with Sponsor's Proposed Text (Same as submitted on April 3).

3. Label Text as proposed by FDA in its approvable letter with highlighting limited to the four areas covered in FDA's approvable letter and the sponsor's current counter-proposals for discussion.

To facilitate review, we list below our comments on the four areas highlighted by FDA in its April 11 approvable letter.

Under **ADVERSE REACTIONS: Adverse Clinical Events: Short-Term Controlled Trials**

The agency's April 11 proposed text has been incorporated in the sponsor's current proposal.

Under **ADVERSE REACTIONS; Adverse Clinical Events; Long-Term Controlled Trials**

The sponsor proposes a paragraph heading of "Long-Term Controlled Morbidity and Mortality Trials," which incorporates the term proposed by the agency (*i.e.*, 'controlled') while retaining a description (i.e., "morbidity and mortality") that the sponsor believes is medically relevant to interpretation of the adverse event data in the cited trials.

Under **ADVERSE REACTIONS; Adverse Clinical Events; Long-Term Controlled Trials**

The majority of the agency's proposed text has been incorporated with the following exceptions.

The sponsor wishes to retain the estimate of patient-years exposure in these seven trials as relevant to the clinical interpretation of the overall safety profile. If removed, the cumulative exposure for these seven trials could not be correctly estimated from the remaining data. For example, if one were to assume a nominal value of 3.4 years as an average exposure for all cited trials, not knowing that over 90% of patients were enrolled in the longer-term trials, the patient-years exposure would be underestimated by over 20%.

We also note that there may have been two mistranscriptions of numbers in the agency's proposed text. The agency proposed the overall number of patients treated with pravastatin as 10,864 rather than as 10,764 and the range for PLAC I, PLAC II, KAPS, and REGRESS as 1.9 to 2.8 years rather than as 1.9 to 2.9 years. Our proposal restores the latter set of numbers that we believe to be correct. However, the differences are extremely minor and the sponsor is prepared to adopt whichever set is accepted by the agency as correct.

Under **OVERDOSAGE**

We wish to use the requested teleconference to explore appropriate labelling for this section and have, accordingly, not offered a specific counter-proposal to the agency's recommended text. Though the agency's OVERDOSAGE proposal

in current class labelling for statins, adoption of the agency's proposed text would mark

pravastatin as the only currently approved statin with such an overdosage statement. The sponsor believes that the extensive clinical experience with pravastatin, and specifically the overdosage experience documented in the referenced supplement, does not support such a distinction.

Proposed BMS participants for the labelling teleconference would be:

Rene Belder	Executive Director, Clinical
Fred Fiedorek	Vice President, Development
Kate Gelperin	Director, Regulatory Affairs
Jerry Gennaro	Director, Regulatory Science
Peter Hoehn	Director, Marketing
Judy Kinaszczuk	Associate Director, Regulatory Affairs
Porter Layne	Group Director, Regulatory Sciences
Kannan Natarajan	Director, Clinical Biostatistics

Please feel free to contact me by phone (609-252-4345) or FAX (609-252-6000) if I can assist in scheduling the requested teleconference.

Sincerely,

Jerry Gennaro, PhD
Director, Regulatory Sciences
FDA Liaison and Global Strategy Unit
Regulatory Science

JG/dk
Attachments

Desk Copy: Margaret Simoneau (HFD-510, Room 14B04) (w/ diskette)

SLR-050 (NC)

SUPPL NEW CORRESP

ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
Tel: 609 252-4345 Fax: 609 252-6000
gerald.gennaro@bms.com

Jerry Gennaro, Ph.D.
Director
Metabolic/Endocrine Products
FDA Liaison & Global Regulatory Strategy

NDA 19-898/S-050
PRAVACHOL® (pravastatin sodium) Tablets

April 17, 2002

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

Dear Dr. Orloff:

Reference is made to our approved New Drug Application for Pravachol® (pravastatin sodium) Tablets, NDA 19-898. Additional reference is made to our Supplemental Application S-050 (dated October 12, 2001) in which we proposed changes in the ADVERSE REACTIONS and OVERDOSAGE sections of the Pravachol package insert.

In response to the approvable letter dated April 11, 2002, as an action from the Agency on this submission, we wish to inform the Division of our intention to file an amendment to this application as per 21CFR 314.120 (a)(1).

Please contact me at (609) 252-4345 if you have any questions regarding this submission.

Sincerely,

5-1-02

Jerry Gennaro, Ph.D.
Director, Metabolic/Endocrine Products
FDA Liaison and Global Regulatory Strategy Unit
Regulatory Science

JG/JBS/jo

Bristol-Myers Squibb
Pharmaceutical Research Institute ORIGINAL

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-4345 Fax: 609 252-6000

Jerry Gennaro, Ph.D.
Director
Life Style Products
FDA Liaison and Global Strategy Unit
Regulatory Science

NDA 19-898/S-050
PRAVACHOL® (pravastatin sodium) Tablets

SLR 050 B2
NDA SUPP AMEND

April 3, 2002

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

SX
4/08/02
Acceptable
Cmc -

Dear Dr. Orloff:

Reference is made to our approved New Drug Application for Pravachol® (pravastatin sodium) Tablets, NDA 19-898. Additional reference is made our Supplemental Application S-050 (dated October 12, 2001) in which we proposed changes in the ADVERSE REACTIONS and OVERDOSAGE sections of the Pravachol package insert. Final reference is made to my telephone conversation on March 28, 2002 with Ms. Margaret Simoneau of the Agency, in which she requested that the proposed changes in this supplement be incorporated into the most current approved labeling.

Enclosed, following this letter, is (1) the current approved label text for pravastatin (version date February 2002) and (2) a strikethrough version of that same text showing the changes, in the **ADVERSE REACTIONS** and **OVERDOSAGE** sections, proposed in the October 12, 2001 sNDA, as requested by Ms. Simoneau.

In presenting these proposed changes relative to the current approved label text, it was necessary to make the following adjustments:

1. The proposed table for "Adverse Events ~~in ≥1% of Patients Treated with Pravastatin 40 mg in Long-Term Placebo-Controlled Trials~~" is now designated as **Table 7** and given a title to make it consistent with the table numbering and formatting convention used elsewhere in the current label.

2. The title for the existing **Table 6** is expanded to include "Short-Term" in order to more clearly distinguish it from **Table 7** (Long-Term).

3. The paragraph on safety and tolerability of the 80 mg dose, ~~[redacted]~~ the description of long-term trials in the current label, is now is moved to a position preceding long-term trials so that it can more appropriately be grouped with short-term trials.

4. The label text now includes wording on **STORAGE** that was suggested by the FDA (11-Dec-01), though not yet submitted as Final Printed Labeling.

With the exception of these format adjustments, the proposed changes are identical to those submitted on October 12, 2001.

If I can be of any further assistance, please do not hesitate to contact me at (609) 252-4353.

Sincerely,

Jerry Gennaro, Ph.D.
Director
FDA Liaison and Global Regulatory Strategy Unit
Regulatory Science

JG/JBS/jo
Attachments

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

ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
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gerald.gennaro@bms.com

Jerry Gennaro, Ph.D.
Director
Metabolic/Endocrine Products
FDA Liaison & Global Regulatory Strategy

SLR 050 BL
NDA SUPP AMEND

AMENDMENT TO NDA LABELING SUPPLEMENT

NDA 19-898/S-050
PRAVACHOL® (pravastatin sodium) Tablets

June 11, 2002

RECEIVED
JUN 17 2002
HFD-510 / CDER

Dr. David Orloff, M.D.
Director, Division of Metabolism and Endocrine
Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Orloff:

Reference is made to our approved New Drug Application for PRAVACHOL® (pravastatin sodium) Tablets, NDA 19-898 and to our Supplemental Application S-050 (dated October 12, 2001 and received by the agency on October 15, 2001). Additional reference is made to the FDA's approvable letter for this supplement issued on April 11, 2002.

We now wish to amend this sNDA with labeling that reflects changes proposed by the agency in its approvable letter of April 11, 2002, as further modified and agreed upon during our teleconference of May 30, 2002.

This submission contains paper and electronic (review aid) copies, in WORD format, of the Pravastatin labeling discussed during our teleconference of May 30, 2002. The files represent (1) only the changes agreed upon during the teleconference, (2) a 'clean' final copy ("promerg"), and (3) a tracking copy ("pro"). Furthermore, I verify that these versions are identical to those provided to the agency by confidential e-mail to Ms. Margaret Simoneau on May 30, 2002.

Additionally, as requested by Ms. Simoneau, we are including a PDF version of the final 'clean' text. The diskette provided with Ms. Simoneau's copy of this submission was checked for viruses on June 11, 2002 with Norton Antivirus Software (Version 5.01.01 for Windows NT 4.0) and no viruses were detected.

If you have any questions concerning this submission or require additional information, please feel free to contact me by phone (609-252-4345) or FAX (609-252-6000).

Sincerely,

Jerry Gennaro, Ph.D.
Director, Metabolic/Endocrine Products
FDA Liaison and Global Regulatory Strategy

JG/HMK/jo
Attachments

Desk Copy: Ms. Margaret Simoneau (with diskette) (HDF-510, Room 14B04)

ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

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RECEIVED
SEP 13 2002
FDR/CDER

Jerry Gennaro, Ph.D.
Director
Metabolic/Endocrine Products
FDA Liaison & Global Regulatory Strategy

FPL FOR APPROVED SUPPLEMENT NDA 19-898 / S-050

SLR050 FA
NDA SUPPL AMENDMENT

NDA 19-898 / S-050
PRAVACHOL (pravastatin sodium) Tablets

September 9, 2002

David Orloff, MD
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
Attention: Division Document Room (8B-45)
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Orloff:

Reference in made to our labelling supplement (S-050) to NDA 19-898, submitted October 12, 2001, and to FDA's Approval Letter dated July 12, 2002.

Enclosed are 20 copies of the final printed Pravachol® package insert, code 5154DIM-19. One copy of the labeling is mounted on heavyweight paper and attached to the archival copy; nine copies are mounted and attached to the Reviewer's copy. Ten unmounted copies are enclosed in an envelope.

If I can provide any further information or assistance on this submission, please feel free to contact me by phone (609-252-4345) or FAX (609-252-6000).

Sincerely,

Jerry Gennaro, Ph.D.
Director, Metabolic/Endocrine Products
FDA Liaison & Global Regulatory Strategy

JG/dk
Attachment

Copy (Cover Letter): Margaret Simoneau (HFD-510, Room 14B-04)

ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-4722 Fax: 609 252-6000

Porter P. Layne, Ph.D.
Group Director
Metabolic/Endrocrine Products
FDA Liaison and Global Strategy Unit
Regulatory Science

NDA NO. 19898 REF NO. 050
NDA SUPPL FOR SUPP

NDA 19-898
PRAVACHOL® (pravastatin sodium) Tablets

October 12, 2001

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

Dear Dr. Orloff:

Reference is made to our approved New Drug Application for Pravachol® (pravastatin sodium) Tablets, NDA 19-898. Pursuant to 21 CFR 314.70, we are now submitting a Supplemental Application which updates the ADVERSE REACTIONS section of the Pravachol® Package Insert to include adverse reaction information from a collective database of seven of our long term morbidity and mortality trials, PLAC I, PLAC II, REGRESS, KAPS, WOS, CARE, and LIPID. Please refer to the Review Guide which follows this letter for a description of the studies. Collectively, these seven trials represent 47,613 patient years of exposure to pravastatin. The *Adverse Clinical Events* subsection of the ADVERSE REACTIONS section of the insert has now been arranged into 3 further subsections: *Short-Term Trials, Long Term Morbidity and Mortality Trials, and Postmarketing Experience.*

To support these modifications, we have provided two incidence tables which summarize Adverse Drug Experience (ADE) information for the combined studies, Table A provides all ADEs in the combined studies with an incidence in pravastatin-treated subjects of greater than or equal to ✕ %, Table B provides ADEs with an incidence in pravastatin-treated subjects of greater than or equal to ✕ % in ——— of the trials, ——— % when the trials ——— ——— / Please refer to the enclosed Review Guide for further description of the submission contents.

Additionally, we wish to update the OVERDOSAGE section of the insert to more accurately reflect a recent survey of overdose information conducted to support supplement S-046 (submitted March 1, 2001), which provided information to support marketing of an 80 mg Pravachol® tablet. The Pravastatin Sodium Summary of Overdose Information that was originally included in supplement S-046 has been included in this submission to support the labeling modification.

This supplement is provided as a fully electronic Archival submission. It has been prepared per The Guidance for Industry: Providing Regulatory Submissions in Electronic Format - General and NDAs, January 1999. The total size of the enclosed CD-ROM is approximately 1.20MB and there are 38 files and 13 folders. These files were checked for viruses on October 11, 2001 with Norton Antivirus Software (Version 5.01.01 for Windows NT 4.0) and no viruses were detected. The electronic submission has been provided to the Central Document Room.

If you have any questions regarding this submission, please feel free to call me at (609) 252-4722.

Sincerely,

Porter P. Layne

Porter P. Layne, Ph.D
Group Director
Metabolic/Endocrine Products
FDA Liaison and Global Strategy Unit
Regulatory Science

PPL/JBS/jo
Desk copy : Ms. Margaret Simoneau (HFD-510, Room 14B04)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

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

2. TELEPHONE NUMBER *(Include Area Code)*

(609) 252-4000

3. PRODUCT NAME

Pravachol (Pravastatin Sodium) Tablets

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? No
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

6. LICENSE NUMBER / NDA NUMBER

19-898

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☐ NO
(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes 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 (0910-0297)
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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Porter P. Layne	Porter P. Layne Group Director, Metabolic/Endocrine Products	October 12, 2001

FORM FDA 3397 (5/98)

Created by Electronic Document Services/USDHHS: (301) 443-2454 EF