CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-898/S036

Trade Name: Pravachol Tablets

Generic Name: pravastatin sodium

Sponsor: Bristol Myers Squibb

Approval Date: September 13, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-898/S036

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-898/S036

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-898/S-036

SEP 13 1999

Bristol-Myers Squibb
Attention: Warren C. Randolph
Director, US Regulatory Liaison, Worldwide Regulatory Affairs
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Mr. Randolph:

Please refer to your supplemental new drug application dated July 7, 1999, received July 13, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pravachol (pravastatin sodium) Tablets.

This supplemental new drug application provides for changes in the PRECAUTIONS, "Carcinogenesis, Mutagenisis, Impairment of Fertility" section of the Pravachol package insert.

This change includes the deletion of the second and third paragraphs to be replaced by:

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

We have completed the review of this supplemental application 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 July 7, 1999).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 19-898/S-036." 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 Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

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

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

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

Sincerely,

9/13/99

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 19-898
HFD-510/Div. Files
HFD-510/M. Simoneau
HFD-510/Reviewers and Team Leaders
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-102/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-21/ACS (with labeling) - for drug discussed at advisory committee meeting.
HFD-095/DDMS-IMT (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: Mas/August 23, 1999
Initialed by:MParks for Dorloff 8.23.99;RSteigerwalt8.23.99/SMoore8.23.99/EGalliers9.10.99
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APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-898/S035

LABELING

Bristol-Myers Squibb Company

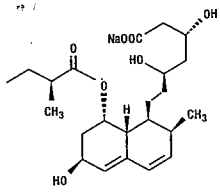
PRAVACHOL®
(pravastatin sodium) Tablets

Rx only

DESCRIPTION

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

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



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

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

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

CLINICAL PHARMACOLOGY

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

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

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

In the Pravastatin Primary Prevention Study (West of Scotland Coronary Prevention Study – WOS), the effect of improving lipoprotein levels with PRAVACHOL on fatal and nonfatal coronary heart disease (CHD) was assessed in 6595 men, without a previous myocardial infarction, and with LDL-C levels between 156–254 mg/dL (4–6.7 mmol/L). The patients were followed for a median of 4.8 years. In this randomized, double-blind, placebo-controlled study, PRAVACHOL reduced the risk of a first coronary event [either CHD death or nonfatal myocardial infarction (MI)] by 31% [7.9% vs 5.5%, placebo vs PRAVACHOL, p=0.0001: 248 events in the placebo group (CHD death=44, nonfatal MI=204) vs 174 events in the PRAVACHOL group (CHD death=31, nonfatal MI=143)]. PRAVACHOL also decreased the risk for undergoing myocardial revascularization procedures (coronary artery bypass graft surgery or coronary angioplasty) by 37% (2.5% vs 1.7%, p=0.009) and coronary angiography by 31% (4.2% vs 2.8%, p=0.007). Cardiovascular deaths were decreased by 32% (2.3% vs 1.6%, p=0.03) and there was no increase in death from non-cardiovascular causes.

Pharmacokinetics/Metabolism

PRAVACHOL (pravastatin sodium) is administered orally in the active form. In clinical pharmacology studies in man, pravastatin is rapidly absorbed, with peak plasma levels of parent compound attained 1 to 1.5 hours following ingestion. Based on urinary recovery of radiolabeled drug, the average oral absorption of pravastatin is 34% and absolute bioavailability is 17%. While the presence of food in the gastrointestinal tract reduces systemic bioavailability, the lipid-lowering effects of the drug are similar whether taken with, or 1 hour prior, to meals.

Pravastatin undergoes extensive first-pass extraction in the liver (extraction ratio 0.66), which is its primary site of action, and the primary site of cholesterol synthesis and of LDL-C clearance. *In vitro* studies demonstrated that pravastatin is transported into hepatocytes with substantially less uptake into other cells. In view of pravastatin's apparently extensive first-pass hepatic metabolism, plasma levels may not necessarily correlate perfectly with lipid-lowering efficacy. Pravastatin plasma concentrations [including: area under the concentration-time curve (AUC), peak (C_{max}), and steady-state minimum (C_{min})] are directly proportional to administered dose. Systemic bioavailability of pravastatin administered following a bedtime dose was decreased 60% compared to that following an AM dose. Despite this decrease in systemic bioavailability, the efficacy of pravastatin administered once daily in the evening, although not statistically significant, was marginally more effective than that after a morning dose. This finding of lower systemic bioavailability suggests greater hepatic extraction of the drug following the evening dose. Steady-state AUCs, C_{max} and C_{min} plasma concentrations showed no evidence of pravastatin accumulation following once or twice daily administration of PRAVACHOL (pravastatin sodium) tablets. Approximately 50% of the circulating drug is bound to plasma proteins. Following single dose administration of ^{14}C- pravastatin, the elimination half-life (t½) for total radioactivity (pravastatin plus metabolites) in humans is 77 hours.

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

Approximately 20% of a radiolabeled oral dose is excreted in urine and 70% in the feces. After intravenous administration of radiolabeled pravastatin to normal volunteers, approximately 47% of total body clearance was via renal excretion and 53% by non-renal routes (i.e., biliary excretion and biotransformation). Since there are dual routes of elimination, the potential exists both for compensatory excretion by the alternate route as well as for accumulation of drug and/or metabolites in patients with renal or hepatic insufficiency.

In a study comparing the kinetics of pravastatin in patients with biopsy confirmed cirrhosis (N=7) and normal subjects (N=7), the mean AUC varied 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.

Clinical Studies

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

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

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

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

*Mean percent change from baseline after 8 weeks

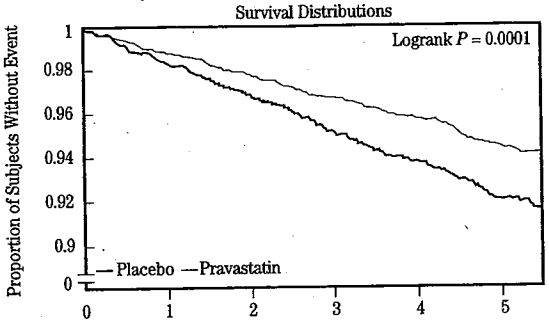
In another clinical trial, patients treated with pravastatin in combination with cholestyramine (70% of patients were taking cholestyramine 20 or 24 g per day) had reductions equal to or greater than 50% in LDL-C. Furthermore, pravastatin attenuated cholestyramine-induced increases in TG levels (which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

Prevention of Coronary Heart Disease

In the Pravastatin Primary Prevention Study (West of Scotland Coronary Prevention Study – WOS)[1], the effect of PRAVACHOL on fatal and nonfatal coronary heart disease (CHD) was assessed in 6595 men 45–64 years of age, without a previous MI, and with LDL-C levels between 156–254 mg/dL (4–6.7 mmol/L). In this randomized, double-blind, placebo-controlled study, patients were treated with standard care, including dietary advice, and either PRAVACHOL 40 mg daily (N=3302) or placebo (N=3293) and followed for a median duration of 4.8 years.

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

Coronary Heart Disease Death or Nonfatal Myocardial Infarction
Survival Distributions



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

Atherosclerosis and Myocardial Infarction

In the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I)[2] study, the effect of pravastatin therapy on coronary atherosclerosis was assessed by coronary angiography in patients with coronary disease and moderate hypercholesterolemia (baseline LDL-C range = 130-190 mg/dL). In this double-blind, 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)[3], the effect of pravastatin on coronary atherosclerosis was assessed by coronary angiography in 885 patients with angina pectoris, angiographically documented coronary artery disease and hypercholesterolemia (baseline total cholesterol range = 160-310 mg/dL). In this double-blind, multicenter, controlled clinical trial, angiograms were evaluated at baseline and at two years in 653 patients (323 treated with pravastatin). Progression of coronary atherosclerosis was significantly slowed in the pravastatin group as assessed by changes in mean segment diameter (p=0.037) and minimum obstruction diameter (p=0.001).

Analysis of pooled events from PLAC I, the Pravastatin, Lipids and Atherosclerosis in the Carotids Study (PLAC II)[4], REGRESS, and the Kuopio Atherosclerosis Prevention Study (KAPS)[5] (combined N=1891) showed that treatment with pravastatin was associated with a statistically significant reduction in the composite event rate of fatal and nonfatal myocardial infarction (46 events or 6.4% for placebo versus 21 events or 2.4% for pravastatin, p=0.001). The predominant effect of pravastatin was to reduce the rate of nonfatal myocardial infarction.

In the Cholesterol and Recurrent Events (CARE)[6] study the effect of PRAVACHOL, 40 mg daily, on coronary heart disease death and nonfatal MI was assessed in 4159 patients (3583 men and 576 women) who had experienced a myocardial infarction in the preceding 3–20 months and who had normal (below the 75th percentile of the general population) plasma total cholesterol levels. Patients in this double-blind, placebo controlled study participated for an average of 4.9 years and had a mean baseline total cholesterol of 209 mg/dL. LDL cholesterol levels in this patient population ranged from 101 mg/dL–180 mg/dL (mean = 139 mg/dL). At baseline, 84% of patients were receiving aspirin and 82% were taking antihypertensive medications. Treatment with PRAVACHOL significantly reduced the rate of first recurrent coronary events (either CHD death or nonfatal MI) by 24% [274 patients with events (13.3%) in the placebo group vs 212 patients with events (10.4%) in the PRAVACHOL group, p=0.003]. The reduction in risk was consistent in both sexes. The risk of undergoing revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) was significantly reduced by 27% (p<0.001) in the PRAVACHOL treated patients [391 (19.6%) vs 294 (14.2%) patients]. PRAVACHOL also significantly reduced the risk for stroke or transient ischemic attack (TIA) by 26% [124 (6.3%) vs 93 (4.7%) patients, p=0.029].

INDICATIONS AND USAGE

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

Primary Prevention of Coronary Events

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

- Reduce the risk of myocardial infarction
- Reduce the risk of undergoing myocardial revascularization procedures
- Reduce the risk of cardiovascular mortality with no increase in death from non-cardiovascular causes

Secondary Prevention of Cardiovascular Events

Atherosclerosis

In hypercholesterolemic patients *with* clinically evident coronary artery disease, including prior MI, PRAVACHOL (pravastatin sodium) is indicated to:

- Slow the progression of coronary atherosclerosis
- Reduce the risk of acute coronary events

Myocardial Infarction

In patients with previous myocardial infarction, and normal (below the 75th percentile of the general population) cholesterol levels, PRAVACHOL is indicated to:

- Reduce the risk of recurrent myocardial infarction
- Reduce the risk of undergoing myocardial revascularization procedures
- Reduce the risk of stroke or transient ischemic attack (TIA)

Hypercholesterolemia and Mixed Dyslipidemia

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

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

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

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

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

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

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

* Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).

** Other risk factors for coronary heart disease (CHD) include: age (males: ≥45 years; females: ≥55 years or premature menopause without estrogen replacement therapy); family history of premature CHD; current cigarette smoking; hypertension; confirmed HDL-C <35 mg/dL (<0.91 mmol/L); and diabetes mellitus. Subtract one risk factor if HDL-C is ≥60 mg/dL (≥1.6 mmol/L).

*** In CHD patients with LDL-C levels 100-129 mg/dL, the physician should exercise clinical judgement in deciding whether to initiate drug treatment.

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

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

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

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

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

Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued immediately and the patient apprised of the potential hazard to the fetus (see **PRECAUTIONS: Pregnancy**).

WARNINGS

Liver Enzymes

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

In the largest long-term placebo-controlled clinical trial with pravastatin (Pravastatin Primary Prevention Study; see **Clinical Pharmacology**), the overall incidence of AST and/or ALT elevations to greater than three times the upper limit of normal was 1.05% in the pravastatin group as compared to 0.75% in the placebo group. One (0.03%) pravastatin-treated patient and 2 (0.06%) placebo-treated patients were discontinued because of transaminase elevations. Of the patients with normal liver function at week 12, three of 2875 treated with pravastatin (0.10%) and one of the 2919 placebo patients (0.03%) had elevations of AST greater than three times the upper limit of normal on two consecutive measurements and/or discontinued due to elevations in transaminase levels during the 4.8 years (median treatment) of the study.

It is recommended that liver function tests be performed prior to and at 12 weeks following initiation of therapy or the elevation of dose. Patients who develop increased transaminase levels or signs and symptoms of liver disease should be monitored with a second liver function

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

Skeletal: myopathy, rhabdomyolysis, arthralgia.

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

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

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

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

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

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

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

Laboratory Test Abnormalities

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

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

Concomitant Therapy

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

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

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

Since the maximal effect of a given dose is seen within 4 weeks, periodic lipid determinations should be performed at this time and dosage adjusted according to the patient's response to therapy and established treatment guidelines. The recommended dosage range is generally 10 to 40 mg administered once a day at bedtime. In the elderly, maximum reductions in LDL-cholesterol may be achieved with daily doses of 20 mg or less.

In patients taking immunosuppressive drugs such as cyclosporine (see **WARNINGS: Skeletal Muscle**) concomitantly with pravastatin, therapy should begin with 10 mg of pravastatin once-a-day at bedtime and titration to higher doses should be done with caution. Most patients treated with this combination received a maximum pravastatin dose of 20 mg/day.

Concomitant Therapy

The lipid-lowering effects of PRAVACHOL on total and LDL cholesterol are enhanced when combined with a bile-acid-binding resin. When administering a bile-acid-binding resin (e.g., cholestyramine, colestipol) and pravastatin, PRAVACHOL should be given either 1 hour or more before or at least 4 hours following the resin. See also **ADVERSE REACTIONS: Concomitant Therapy**.

HOW SUPPLIED

PRAVACHOL® (pravastatin sodium) Tablets are supplied as:

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

20 mg tablets: Yellow, rounded, rectangular-shaped, biconvex with a P embossed on one side and PRAVACHOL 20 engraved on the opposite side. They are supplied in bottles of 90 (NDC 0003-5178-05) and bottles of 1000 (NDC 0003-5178-75). Bottles contain a desiccant canister.

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

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

Storage

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

REFERENCES

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[6]Sacks FM, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med.* 1996;335:1001-9.

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Bristol-Myers Squibb
Princeton, NJ 08543

Revised October 1999

5154DIM-12 1092990A2
515432DIM-03 1109268
J4-538K 1092990A2

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p < 0.01$). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

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

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

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

Pregnancy

Pregnancy Category X.

See **CONTRAINDICATIONS**.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area ($mg/meter^2$). Rare reports of congenital anomalies have been received following intrauterine exposure to other HMG-CoA reductase inhibitors. In a review[8] of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or lovastatin, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a three-to-four-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. As safety in pregnant women has not been established and there is no apparent benefit to therapy with PRAVACHOL during pregnancy (see **CONTRAINDICATIONS**), treatment should be immediately discontinued as soon as pregnancy is recognized. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.

Nursing Mothers

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

Pediatric Use

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

ADVERSE REACTIONS

Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events

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

	All Events		Events Attributed to Study Drug	
Body System/Event	**Pravastatin (N = 900) %**	**Placebo (N = 411) %**	**Pravastatin (N = 900) %**	**Placebo (N = 411) %**
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

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

Biotransformation pathw...

evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of three times the upper limit of normal or greater persist, withdrawal of pravastatin therapy is recommended.

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

Skeletal Muscle

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

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

PRECAUTIONS

General

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

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been 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 $t_{1/2}$ was not affected by itraconazole, suggesting that the relatively small increases in C_{max} and AUC were due solely to increased bioavailability rather than a decrease in clearance, consistent with inhibition of p-glycoprotein transport by itraconazole. This drug transport system is thought to affect bioavailability and excretion of HMG-CoA reductase inhibitors, including pravastatin. The AUC and C_{max} of another HMG-CoA reductase inhibitor which is known to be metabolized by cytochrome P450 3A4 increased by factors of 19 and 17, respectively, when given with itraconazole.

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

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

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

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

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

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

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

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

Endocrine Function

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

CNS Toxicity

CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

5154DIM-12
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PRAVACHOL®
(pravastatin sodium) Tablets

5154DIM-12
1092990A2
J4-538K
1092990A2

PRAVACHOL®
(pravastatin sodium) Tablets

515432DIM-03
1109268

PRAVACHOL®
(pravastatin sodium) Tablets

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-898/S036

PHARMACOLOGY REVIEW(S)

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS:

Reviewer Name: Ronald W. Steigerwalt, Ph.D. Pharmacology Team Leader
Division Name: Division of Metabolic and Endocrine Drug Products (DMEDP)
HFD#510
Review Completion Date: August 6, 1999
Review number: 5 (for this reviewer)

IND/NDA NUMBER: NDA 19-898
Serial number/date/type of submission: This is a labeling supplement dated July 7, 1999.
Information to sponsor: Yes () No (X)
Sponsor (or agent): Bristol-Meyers Squibb Pharmaceutical Research Institute; P.O. Box 5400 Princeton, NJ 08534-5400

DRUG

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

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

Drug Class: HMG-CoA Reductase inhibitor "statin"

Indication: Cholesterol lowering drug: Primary prevention of coronary events, secondary prevention of cardiovascular events; reduction of risk of recurrent myocardial infarction.

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

Route of administration: Oral

SUMMARY:
PRAVACHOL® is an HMG-CoA Reductase inhibitor that was approved in 1991 at the doses indicated in this supplement. A mouse carcinogenicity study was reviewed under IND [redacted] (November 21, 1994 and July 26, 1995) and recommendations were made to the sponsor to change the label. This supplement contains a response to a fax sent on September 2, 1997 regarding changes to the carcinogenicity section of the label. (see attached documents).
The sponsor has made the appropriate changes. No further action is necessary from pharmacology.

RECOMMENDATIONS:

From a pharmacology standpoint, the proposed changes to the labeling supplement dated July 7, 1999 may be approved. No further action is necessary from pharmacology.

Ronald W. Steigerwalt

Ronald W. Steigerwalt, Ph.D.
Pharmacology Team Leader

8/6/99

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

Attachments:
1. Fax from September 7, 1997 requesting label change
2. Text of proposed label from sponsor (July 7, 1999)

IND 27,201
Pravachol (pravastatin) tablets
Bristol-Myers Squibb
Submissions: November 21, 1994 and July 26, 1995
(Phase IV study)
Pharmacology Review Comments

RECOMMENDATION: The sponsor stated that pravastatin "produced increased incidences of hepatocellular tumors in males and females and lung adenomas in females". The label for pravastatin should be amended to include this new data.

Carcinogenecis, Mutagenesis, Impairment of Fertility
First paragraph on rat data would remain unchanged.
Second paragraph on mouse carcinogenicity data obtained with pravastatin would be deleted.
Third paragraph with mouse data from simvastatin would be deleted.

In place of the current second paragraph would be the new data:

"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 ($p<0.0001$).

Cleared for faxing Ronald W Steigerwalt

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p < 0.01$). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

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

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

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

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

Pregnancy

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

DELETE Paragraph

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-898/S036 `

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Labeling Review

Application Number: NDA 19-898/S-036

Name of Drug: Pravachol (pravastatin) tablets

Sponsor: Bristol-Myers Squibb Company

Materials Reviewed: August 17, 1998 (S-021) last approved labeling and July 7, 1999 revised draft labeling for supplement-036.

The changes to the PRECAUTIONS, Carcinogenesis, Mutagenisis, Impairment of Fertility section of the Pravachol package insert are listed in the approval letter. These were Agency requested changes in a September 2, 1997 fax to the sponsor.

Requested changes for supplement-036 were accepted by the reviewing team. This is BMS submission CARC99.QXD (January 29, 1999), revision to page 7 of 9.

Medical Team Leader Mary H. Parks for David Orloff 8/23/99

Chemistry Team Leader Stephen L. Moore 8/23/99

Pharmacology Team Leader Ronald W. Steigerwalt 8/23/99

Chief, Project Manager Ellis Gallo Ellis 9/10/99

Project Manager Margaret Simoneau 8/23/99

cc: NDA 19-898/S-036
Div File

PROPOSED REVISIONS

Bristol-Myers Squibb Company

~~5154DIM-11 51-000876-09~~
~~5154J2DIM-02 51-007960-01~~
~~J4-538J 51-006141-04~~

Rx only

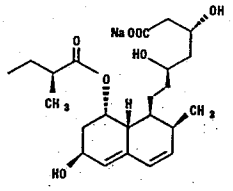
PRAVACHOL®

(pravastatin sodium) Tablets

DESCRIPTION

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

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



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

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

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

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CLINICAL PHARMACOLOGY

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

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

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

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

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

Pharmacokinetics/Metabolism

PRAVACHOL (pravastatin sodium) is administered orally in the active form. In clinical pharmacology studies in man, pravastatin is rapidly absorbed, with peak plasma levels of parent compound attained 1 to 1.5 hours following ingestion. Based on urinary recovery of radiolabeled drug, the average oral absorption of pravastatin is 34% and absolute bioavailability is 17%. While the presence of food in the gastrointestinal tract reduces systemic bioavailability, the lipid-lowering effects of the drug are similar whether taken with, or 1 hour prior, to meals.

Pravastatin undergoes extensive first-pass extraction in the liver (extraction ratio 0.66), which is its primary site of action, and the primary site of cholesterol synthesis and of LDL-C clearance. *In vitro* studies demonstrated that pravastatin is transported into hepatocytes with substantially less uptake into other cells. In view of pravastatin's apparently extensive first-pass hepatic metabolism, plasma levels may not necessarily correlate perfectly with lipid-lowering efficacy. Pravastatin plasma concentrations [including: area under the concentration-time curve (AUC), peak (C_{max}), and steady-state minimum (C_{min})] are directly proportional to administered dose. Systemic bioavailability of pravastatin administered following a bedtime dose was decreased 60% compared to that following an AM dose. Despite this decrease in systemic bioavailability, the efficacy of pravastatin administered once daily in the evening, although not statistically significant, was marginally more effective than that after a morning dose. This finding of lower systemic bioavailability suggests greater hepatic extraction of the drug following the evening dose. Steady-state AUCs, C_{max} and C_{min} plasma concentrations showed no evidence of pravastatin accumulation following once or twice daily administration of PRAVACHOL (pravastatin sodium) tablets. Approximately 50% of the circulating drug is bound to plasma proteins. Following single dose administration of ^{14}C- pravastatin, the elimination half-life (t½) for total radioactivity (pravastatin plus metabolites) in humans is 77 hours.

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

Approximately 20% of a radiolabeled oral dose is excreted in urine and 70% in the feces. After intravenous administration of radiolabeled pravastatin to normal volunteers, approximately 47% of total body clearance was via renal excretion and 53% by non-renal routes (i.e., biliary excretion and biotransformation). Since there are dual routes of elimination, the potential exists both for compensatory excretion by the alternate route as well as for accumulation of drug and/or metabolites in patients with renal or hepatic insufficiency.

In a study comparing the kinetics of pravastatin in patients with biopsy confirmed cirrhosis (N=7) and normal subjects (N=7), the mean AUC varied 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.

Clinical Studies

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

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

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Primary Hypercholesterolemia Study Dose Response of PRAVACHOL* Once Daily Administration At Bedtime				
Dose	Total-C	LDL-C	HDL-C	TG
10 mg	-16%	-22%	+ 7%	-15%
20 mg	-24%	-32%	+ 2%	-11%
40 mg	-25%	-34%	+12%	-24%

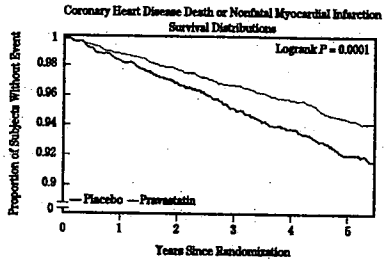
*Mean percent change from baseline after 8 weeks

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

Prevention of Coronary Heart Disease

In the Pravastatin Primary Prevention Study (West of Scotland Coronary Prevention Study – WOS)[1], the effect of PRAVACHOL on fatal and nonfatal coronary heart disease (CHD) was assessed in 6595 men 45–64 years of age, without a previous MI, and with LDL-C levels between 156–254 mg/dL (4–6.7 mmol/L). In this randomized, double-blind, placebo-controlled study, patients were treated with standard care, including dietary advice, and either PRAVACHOL 40 mg daily (N=3302) or placebo (N=3293) and followed for a median duration of 4.8 years.

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



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

Atherosclerosis and Myocardial Infarction

In the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I)[2] study, the effect of pravastatin therapy on coronary atherosclerosis was assessed by coronary angiography in patients with coronary disease and moderate hypercholesterolemia (baseline LDL-C range = 130-190 mg/dL). In this double-blind, 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)[3], the effect of pravastatin on coronary atherosclerosis was assessed by coronary angiography in 885 patients with angina pectoris, angiographically documented coronary artery disease and hypercholesterolemia (baseline total cholesterol range = 160-310 mg/dL). In this double-blind, multicenter, controlled clinical trial, angiograms were evaluated at baseline and at two years in 653 patients (323 treated with pravastatin). Progression of coronary atherosclerosis was significantly slowed in the pravastatin group as assessed by changes in mean segment diameter (p=0.037) and minimum obstruction diameter (p=0.001).

Analysis of pooled events from PLAC I, the Pravastatin, Lipids and Atherosclerosis in the Carotids Study (PLAC II)[4], REGRESS, and the Kuopio Atherosclerosis Prevention Study (KAPS)[5] (combined N=1891) showed that treatment with pravastatin was associated with a statistically significant reduction in the composite event rate of fatal and nonfatal myocardial infarction (46 events or 6.4% for placebo versus 21 events or 2.4% for pravastatin, p=0.001). The predominant effect of pravastatin was to reduce the rate of nonfatal myocardial infarction.

In the Cholesterol and Recurrent Events (CARE)[6] study the effect of PRAVACHOL, 40 mg daily, on coronary heart disease death and nonfatal MI was assessed in 4159 patients (3583 men and 576 women) who had experienced a myocardial infarction in the preceding 3–20 months and who had normal (below the 75th percentile of the general population) plasma total cholesterol levels. Patients in this double-blind, placebo controlled study participated for an average of 4.9 years and had a mean baseline total cholesterol of 209 mg/dL. LDL cholesterol levels in this patient population ranged from 101 mg/dL–180 mg/dL (mean = 139 mg/dL). At

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CONTRAINDICATIONS
Hypersensitivity to any component of this medication.

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

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

ucts of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued immediately and the patient apprised of the potential hazard to the fetus (see **PRECAUTIONS: Pregnancy**).

WARNINGS

Liver Enzymes

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

In the largest long-term placebo-controlled clinical trial with pravastatin (Pravastatin Primary Prevention Study; see **Clinical Pharmacology**), the overall incidence of AST and/or ALT elevations to greater than three times the upper limit of normal was 1.05% in the pravastatin group as compared to 0.75% in the placebo group. One (0.03%) pravastatin-treated patient and 2 (0.06%) placebo-treated patients were discontinued because of transaminase elevations. Of the patients with normal liver function at week 12, three of 2875 treated with pravastatin (0.10%) and one of the 2919 placebo patients (0.03%) had elevations of AST greater than three times the upper limit of normal on two consecutive measurements and/or discontinued due to elevations in transaminase levels during the 4.8 years (median treatment) of the study.

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

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

Skeletal Muscle

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

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

PRECAUTIONS

General

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

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

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

Renal Insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life (t½) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients

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

Drug Interactions

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

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

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

Itraconazole – The mean AUC and C_{max} for pravastatin were increased by factors of 1.7 and 2.5, respectively, when given with itraconazole (a potent P450 3A4 inhibitor which also inhibits p-glycoprotein transport) as compared to placebo. The mean $t^{1}/_{2}$ was not affected by itraconazole, suggesting that the relatively small increases in C_{max} and AUC were due solely to increased bioavailability rather than a decrease in clearance, consistent with inhibition of p-glycoprotein transport by itraconazole. This drug transport system is thought to affect bioavailability and excretion of HMG-CoA reductase inhibitors, including pravastatin. The AUC and C_{max} of another HMG-CoA reductase inhibitor which is known to be metabolized by cytochrome P450 3A4 increased by factors of 19 and 17, respectively, when given with itraconazole.

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

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

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

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

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

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

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

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

Endocrine Function

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

CNS Toxicity

CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with

NO REVISIONS

PROPOSED REVISIONS

several other drugs in this class.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p < 0.01$). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

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

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

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

DELETE Paragraph

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

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

Pregnancy

Pregnancy Category X.

See **CONTRAINDICATIONS.**

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area ($mg/meter^2$). Rare reports of congenital anomalies have been received following intrauterine exposure to other HMG-CoA reductase inhibitors. In a review[8] of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or lovastatin, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a three-to-four-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. As safety in pregnant women has not been established and there is no apparent benefit to therapy with PRAVACHOL during pregnancy (see **CONTRAINDICATIONS**), treatment should be immediately discontinued as soon as pregnancy is recognized. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.

Nursing Mothers

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

Pediatric Use

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

ADVERSE REACTIONS

Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events

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

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

Body System/Event	All Events		Events Attributed to Study Drug	
	Pravastatin (N = 900) %	Placebo (N = 411) %	Pravastatin (N = 900) %	Placebo (N = 411) %
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic Rash	4.0*	1.1	1.3	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.

NO REVISIONS

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

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

Skeletal: myopathy, rhabdomyolysis, arthralgia.

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

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

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

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

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

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

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

Laboratory Test Abnormalities

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

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

Concomitant Therapy

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

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

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

Since the maximal effect of a given dose is seen within 4 weeks, periodic lipid determinations should be performed at this time and dosage adjusted according to the patient's response to therapy and established treatment guidelines. The recommended dosage range is generally 10 to 40 mg administered once a day at bedtime. In the elderly, maximum reductions in LDL-cholesterol may be achieved with daily doses of 20 mg or less.

PROPOSED REVISIONS

In patients taking immunosuppressive drugs such as cyclosporine (see **WARNINGS: Skeletal Muscle**) concomitantly with pravastatin, therapy should begin with 10 mg of pravastatin once-a-day at bedtime and titration to higher doses should be done with caution. Most patients treated with this combination received a maximum pravastatin dose of 20 mg/day.

Concomitant Therapy
The lipid-lowering effects of PRAVACHOL on total and LDL cholesterol are enhanced when combined with a bile-acid-binding resin. When administering a bile-acid-binding resin (e.g., cholestyramine, colestipol) and pravastatin, PRAVACHOL should be given either 1 hour or more before or at least 4 hours following the resin. See also **ADVERSE REACTIONS: Concomitant Therapy**.

HOW SUPPLIED
PRAVACHOL® (pravastatin sodium) Tablets are supplied as:

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

20 mg tablets: Yellow, rounded, rectangular-shaped, biconvex with a P embossed on one side and PRAVACHOL 20 engraved on the opposite side. They are supplied in bottles of 90 (NDC 0003-5178-05) and bottles of 1000 (NDC 0003-5178-75). Bottles contain a desiccant canister.

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

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

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

REFERENCES
[1]Shepherd J, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301–7.
[2]Pitt B, et al. Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I): Reduction in Atherosclerosis Progression and Clinical Events. *J Am Coll Cardiol* 1995;26:1133-9.
[3]Jukema JW, et al. Effects of Lipid Lowering by Pravastatin on Progression and Regression of Coronary Artery Disease in Symptomatic Man With Normal to Moderately Elevated Serum Cholesterol Levels. The Regression Growth Evaluation Statin Study (REGRESS). *Circulation* 1995;91:2528–2540.
[4]Crouse JR, et al. Pravastatin, lipids, and atherosclerosis in the carotid arteries: design features of a clinical trial with carotid atherosclerosis outcome, *Controlled Clinical Trials* 13:495, 1992.
[5]Salonen R, et al. Kuopio Atherosclerosis Prevention Study (KAPS). A population-based primary preventive trial of the effect of LDL lowering on atherosclerotic progression in carotid and femoral arteries. Research Institute of Public Health, University of Kuopio, Finland. *Circulation* 92:1758, 1995.
[6]Sacks FM, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med.* 1996;335:1001-9.
[7]Frederickson classification: Type IIa-elevation of LDL; Type IIb-elevation of LDL and VLDL. Type III (familial dysbetalipoproteinemia)–elevation of IDL. Frederickson, DS, Fat transport in lipoproteins–an integrated approach to mechanism and disorders, *N Engl J Med* 276:34, 1967.
[8]Manson JM, Freyssinges C, Ducrocq MB, Stephenson WP. Postmarketing Surveillance of Lovastatin and Simvastatin Exposure During Pregnancy. *Reproductive Toxicology* 10(6):439-446, 1996.

NO REVISIONS

Bristol-Myers Squibb
Princeton, NJ 08543

~~5154DIM-11 51-000876-00~~
~~5154328IM-02 51-007860-01~~
~~J4-538J 51-006111-04 Printed in USA Revised November 1998~~

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-898/S-036

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

JUL 20 1999

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

Dear Mr. Randolph:

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	Pravachol (pravastatin sodium) Tablet
NDA Number:	19-898
Supplement Number:	S-036
Date of Supplement:	July 07, 1999
Date of Receipt:	July 13, 1999

MB 8/12/99

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on September 11, 1999, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

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

Sincerely,

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

Bristol-Myers Squibb
Pharmaceutical Research Institute

ORIGINAL

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

NDA NO. 19-898 REF. NO. 036
NDA SUPPL FOR SLR

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

NDA 19-898
PRAVACHOL (pravastatin sodium) Tablets

July 7, 1999

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

AP
Reviewed and acceptable - see attached Review
RW Steigerwalt
8/12/99

Dear Dr. Sobel:

Reference is made to our approved New Drug Application for Pravachol® (pravastatin sodium) Tablets, NDA 19-898, and to our Investigational New Drug Application for SQ31,000 (pravastatin), IND ——— Additional reference is made to our submissions of November 21,1994 (Serial No. 259) and July 26, 1995 (Serial No. 269) to IND ——— These submissions provided the following toxicology reports:

- "SQ31,000: Dietary Exposure Study in Mice, " Study No. 93010
- "SQ31,000: Dietary Carcinogenicity Study in Mice", Study No. 92001

A facsimile transmission from FDA, dated September 2, 1997 (copy attached) provided recommendations from Dr. Ronald Steigerwalt for changes to the Carcinogenesis, Mutagenesis, and impairment of Fertility subsection of the Pravachol® package insert, based on the above submissions.

At this time we are providing proposed draft labeling which incorporates the results of the mouse carcinogenicity study submitted July 26, 1995. The proposed text is consistent with that recommended by Dr. Steigerwalt, but has been modified to include the doses which produced the serum drug level multiples of 30 to 40 times and 50 times that of humans receiving the 40mg pravastatin. A sentence referring to the lack of drug-induced tumors in another, lower-dose study in mice has been added to the text recommended by Dr. Steigerwalt.

The proposed, draft labeling is provided in a side-by-side format, with the revised text in the right-hand column.

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

Sincerely,

Warren C. Randolph

Warren C. Randolph
Director
US Regulatory Liaison
Worldwide Regulatory Affairs

WCR/jsb/ds/pak
Desk Copies: Dr . Ronald Steigerwalt
Ms. Margaret Simoneau

REVIEWS COMPLETED
AP Ltr 9/13/99
CSO ACTION:
☑ LETTER ☐ N.A.I. ☐ MEMO
Mas 9-14-99
CSO INITIALS DATE

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

APPLICANT'S NAME AND ADDRESS

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

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).

2. TELEPHONE NUMBER *(Include Area Code)*
(609) 252-4000

5. USER FEE I.D. NUMBER

6. LICENSE NUMBER / NDA NUMBER
N019-898

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.)*

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JUL 13 1999
HFD-510

☐ 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:

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Washington, DC 20201

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Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Warren C. Randolph	Warren C. Randolph Director, U.S. Regulatory Liaison	July 7, 1999

FORM FDA 3397 (5/98)

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