DEPARTMENT OF HEALTH & HUMA N SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED VIA FACSIMILE

Philomena McArthur, Esq.
Bristol-Myers Squibb Company
P.O. Box 4500
Princeton, NJ 08543-4500

RE: NDA 19-898
Pravachol (pravastatin sodium)
MACMIS ID#9544

Dear Ms. McArthur:

This letter concerns Bristol-Myers Squibb's (BMS) dissemination of promotional materials for Pravachol. The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a professional visual aid (D3-A386) for Pravachol as part of its routine monitoring and surveillance program. From its review, DDMAC has concluded that this piece is false or misleading and lacking in fair balance, in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. Specifically, the visual aid makes misleading efficacy claims, broadens the approved indication for Pravachol, and lacks fair balance.

Misleading Efficacy Presentation

In the visual aid, you present the statements "MI reduction was observed at 6 months and reached statistical significance at 15 months" from the West of Scotland (WOS) Study and "MI reduction was observed at 7 months and reached statistical significance at 10 months" from the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study. These statements imply that individual patients will achieve benefits from Pravachol therapy at approximately 6 or 7 months. However, data from retrospective analyses are not adequate to support these types of claims because the onset of clinical benefit prior to the end of the study (i.e., approximately 5 years) cannot be extrapolated from these studies. Therefore, these claims are misleading because they are not supported by substantial evidence.

We refer you to our untitled letter dated January 26, 1998, in which we outlined objections to similar violative statements and your February 9, 1998, response to our untitled letter stating that you would delete such violative statements from your promotional materials.

Furthermore, presenting the combined risk reduction in fatal/nonfatal MI from the LIPID study (29%) implies that Pravachol will significantly reduce the risk of both fatal MI and nonfatal MI. However, the number of fatal MIs in the LIPID study was very small, and the majority of the risk reduction shown in this graph is attributable to

nonfatal MIs. Therefore, this presentation is misleading because it implies that Pravachol will significantly reduce the risk of fatal MI's when such has not been demonstrated by substantial evidence.

Indications and Usage

The visual aid is misleading because it does not clearly communicate that Pravachol is indicated in patients with high cholesterol or heart disease *when the response to diet and other nonpharmacological measures alone have been inadequate*. Although this contextual information appears on the last page of the visual aid, it is presented in small font and is imbedded with other important information. In contrast, claims such as "provides effective lipid management" and "provides proven protection against cardiovascular events" are prominently presented throughout the visual aid. Such claims do not convey that Pravachol should be used in addition to diet and other nonpharmacological measures and is not indicated to reduce heart attacks and lower cholesterol when used alone. Therefore, BMS misleadingly broadens the approved product indication for Pravachol.

Misleading Comparative Claim

In the visual aid, you present the statement "Unlike most other statins, Pravachol is not metabolized by cytochrome P450 3A4 to a clinically significant extent" (underline added). The phrase "unlike most other statins" suggests that the majority of statins are metabolized by cytochrome P450 3A4 to a clinically significant extent and, therefore, implies that Pravachol is safer than most statins. However, you have not provided substantial evidence to support this implication. Therefore, this claim is misleading because it makes an implied clinical superiority claim of safety that is not supported by substantial evidence.

Lack of Fair Balance

Promotional materials are lacking in fair balance if they fail to present risk information with a prominence and readability reasonably comparable to the presentation of the claims, taking into account factors such as typography, layout, contrast, headlines, paragraphing, white space, and any other techniques apt to achieve emphasis. The visual aid lacks fair balance because claims are prominently presented with bullets, graphs, white space, and large headings. In contrast, the risk information is presented in block format, with minimal white space and without headings or other means of signaling the reader specifically to important warnings and contraindications. Furthermore, the risk information is presented at the end of the visual aid following a complex and condensed paragraph of Pravachol's indication.

BMS should immediately cease dissemination of promotional materials or activities that contain these and similar claims or presentations concerning Pravachol. In addition, BMS should respond in writing no later than April 12, 2001, describing its plan to comply. BMS should also include a list of materials being discontinued, as well as the date of discontinuation.

Your response should be directed to me by facsimile at 301-594-6771 or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857.

We remind you that only written communications are considered official. In all future correspondence regarding this particular matter please refer to MACMIS ID #9544 in addition to the NDA number.

Sincerely,

(see accompanying page for electronic signature)

Andrew S.T. Haffer, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

/s/

Andrew Haffer
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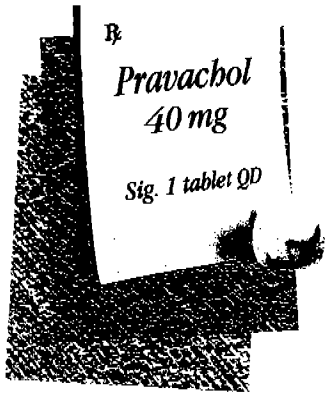
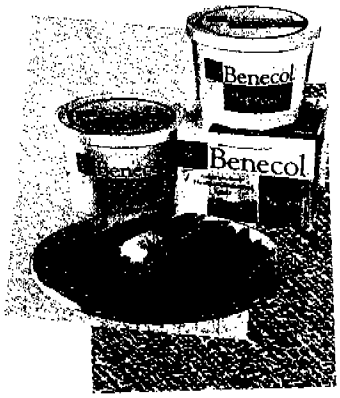
TeamUp for Health

TeamUp for Health



Prescribe **Pravachol** *to help reduce the risk of cardiovascular events*

- Provides effective lipid management[1]
- Provides proven protection against cardiovascular events[1]
- Unlike most other statins, *Pravachol* is not metabolized by cytochrome P450 3A4 to a clinically significant extent[1]



Recommend **Benecol® Spread** *to refocus your* **Pravachol** *patients' attention on dietary management of cholesterol*

- Helps promote healthy cholesterol levels as part of a healthy lifestyle
- Plant stanol ester, the dietary ingredient in *Benecol Spread*, works to block the absorption of cholesterol in the intestine[2,3]
- *Benecol Spread* starts to work in 2 weeks when used three times per day in place of similar spreads[4]
- Supported by double-blind, placebo-controlled clinical studies[3,4,5]

Please see Pravachol INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS (including Skeletal Muscle), PRECAUTIONS, and ADVERSE REACTIONS in the accompanying full prescribing information.

Two different approaches to lipid management

Pravachol *inhibits synthesis of cholesterol in the liver*[1]

In addition, *Pravachol*...

- Is not metabolized by CYP450 3A4 to a clinically significant extent[1]
- Offers reduced potential for CYP450 3A4-mediated drug interactions[1]

Plant stanol ester (in **Benecol Spread***) works to block the absorption of cholesterol in the intestine*[2]

In addition, *Benecol Spread*...

- The ingredient in *Benecol Spread*, plant stanol ester, is virtually unabsorbed[2]
- In a controlled clinical study of *Benecol Spread*, there was no significant difference in the incidence of adverse events for any body system, including the digestive system, between *Benecol Spread* and placebo[3]

Benecol®

PRAVACHOL®
pravastatin sodium 40 mg tablets

Pravachol effectively improves the lipid profile of your patients at risk of MI[1]

LDL-C

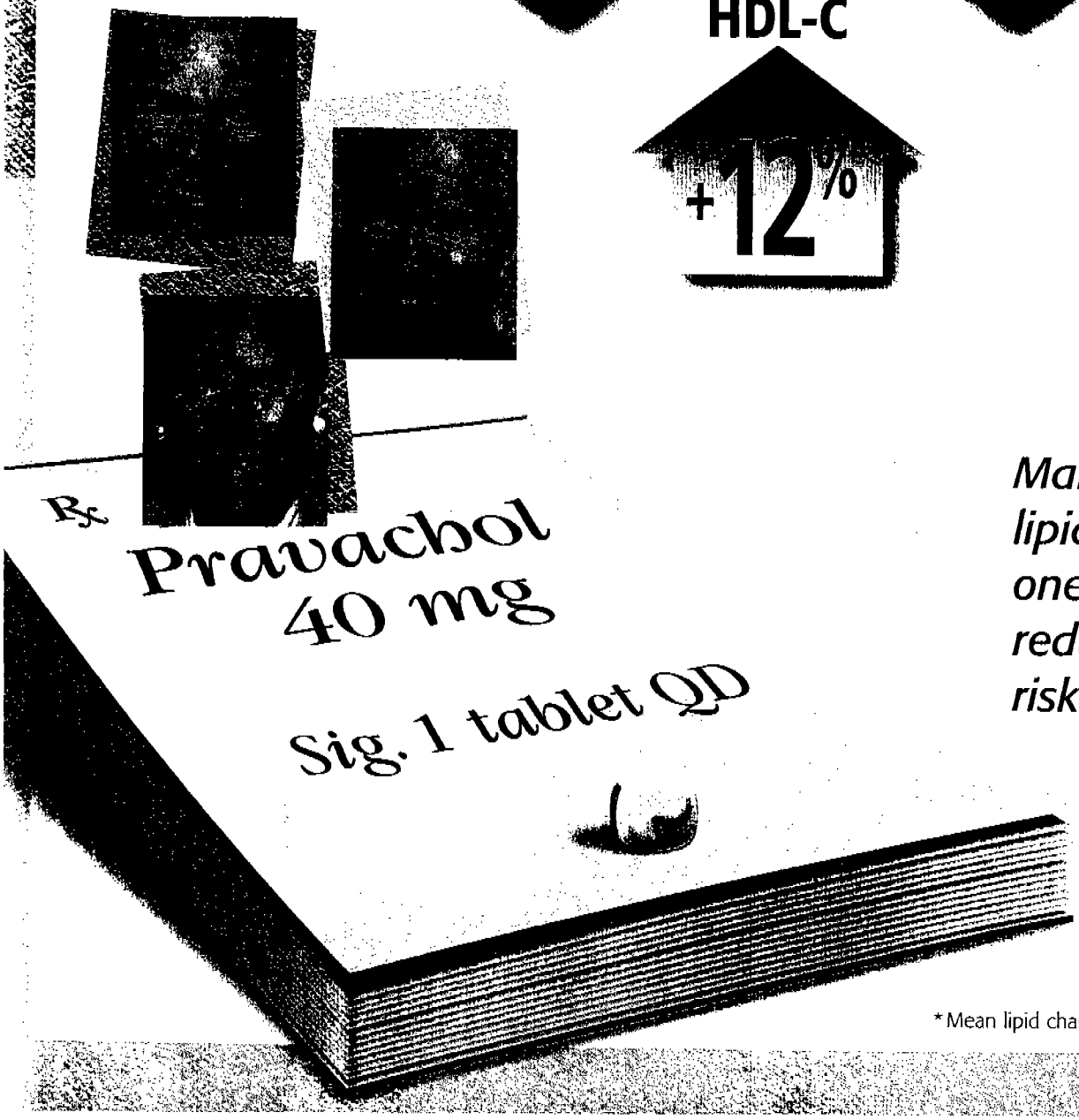
-34%*

Triglycerides

-24%*

HDL-C

+12%



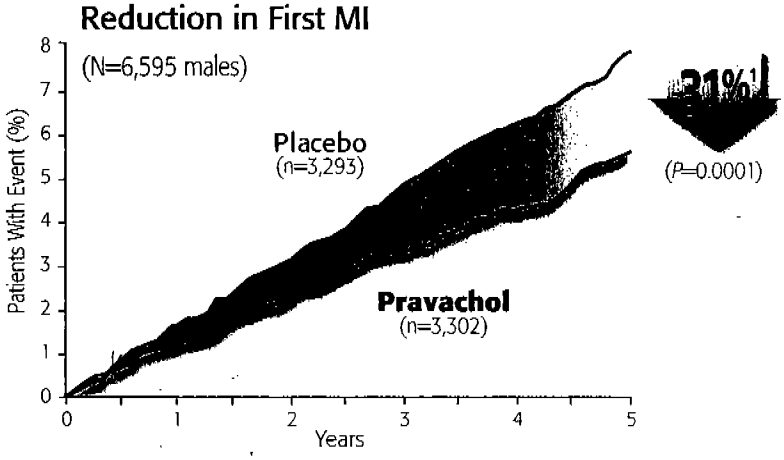
Managing the lipid profile is one part of reducing the risk of MI

*Mean lipid changes with Pravachol 40 mg.

Because MI is complex and unpredictable...

Rely on **Pravachol** for clinical proof of cardiovascular protection

Primary prevention—*Landmark West of Scotland Study**[6]



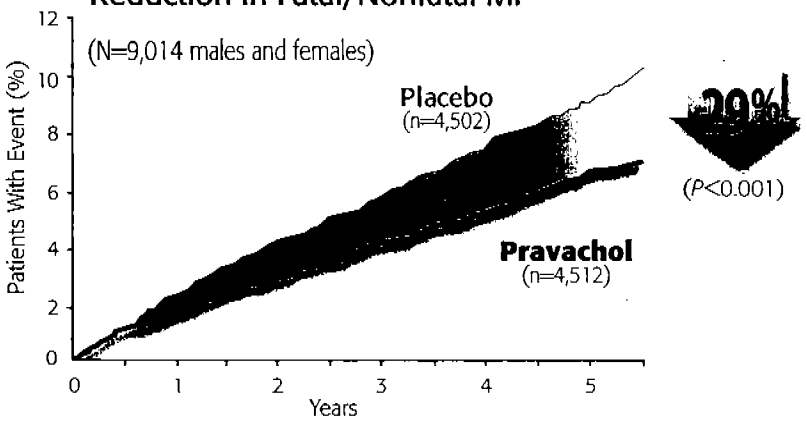
—Adapted from *N Engl J Med*
Event rates = 7.9% placebo vs 5.5% Pravachol

► MI reduction was observed at 6 months and reached statistical significance at 15 months[6,7]

* Asymptomatic; no clinically significant CAD; total cholesterol ≥ 252 mg/dL; mean baseline LDL-C=192 mg/dL.[6]

It is not clear to what extent the findings of the West of Scotland Study can be extrapolated to a similar population of women.

Secondary prevention—*Landmark LIPID Study*†[8]



—Adapted from *N Engl J Med* and Bristol-Myers Squibb Company
Event rates = 10.3% placebo vs 7.4% Pravachol

► MI reduction was observed at 7 months and reached statistical significance at 10 months[7]

† Prior MI or unstable angina; total cholesterol =155–271 mg/dL; median baseline LDL-C =150 mg/dL.[8]

Please see Pravachol INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS (including Skeletal Muscle), PRECAUTIONS, and ADVERSE REACTIONS in the accompanying full prescribing information.

PRAVACHOL®
pravastatin sodium 40 mg tablets

Introducing...

TeamUp for Health—
A program for your patients

Start your patients with the **TeamUp for Health** *program kit*

The *TeamUp for Health* program kit includes:

- ▶ One-week supply of *Pravachol*
- ▶ Coupon for a **free** tub of *Benecol Spread*
- ▶ Rebate of up to **$20** on your eligible patients' first *Pravachol* prescription
- ▶ Additional discount coupons for *Benecol Spread*
- ▶ Booklet containing important information about *Pravachol, Benecol Spread*, and the *TeamUp for Health* program

Free *membership in the* **TeamUp for Health** *program includes:*

- ▶ Rebate of up to **$20** on your eligible patients' fifth *Pravachol* prescription
- ▶ **Free** dietary evaluation from a *TeamUp for Health* dietitian
- ▶ **Free** information on healthier eating and living
- ▶ Recipes for delicious foods made with *Benecol Spread*

Make **TeamUp for Health** *an integral part of your* Pravachol *patients' healthy lifestyle*

Benecol

Please see Pravachol INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS (including Skeletal Muscle), PRECAUTIONS, and ADVERSE REACTIONS in the accompanying full prescribing information.

Important Pravachol Information

In addition to diet, when diet and other nonpharmacologic measures have been inadequate:

In patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIa and IIb), Pravachol is indicated to reduce elevated total cholesterol, LDL-C, Apo B, and triglycerides.

Pravachol is indicated for the treatment of patients with elevated serum triglyceride levels (Fredrickson Type IV).

Pravachol is indicated for the treatment of patients with primary dysbetalipoproteinemia (Fredrickson Type III).

In hypercholesterolemic patients without clinically evident coronary heart disease, Pravachol 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 noncardiovascular causes.

In patients with clinically evident coronary heart disease, Pravachol is indicated to reduce the risk of total mortality by reducing coronary death, myocardial infarction, undergoing myocardial revascularization procedures, stroke and stroke/transient ischemic attack (TIA), and to slow the progression of coronary atherosclerosis.

Pravachol is contraindicated for patients who are pregnant or nursing and in the presence of active liver disease or unexplained persistent transaminase elevations.

The risk of myopathy during treatment with another HMG-CoA reductase inhibitor is increased with concurrent therapy with erythromycin, cyclosporine, niacin, or fibrates.

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.

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. Discontinue pravastatin if myopathy is diagnosed or suspected.

It is recommended that liver function tests be performed prior to and at 12 weeks following initiation of therapy or an elevation in dose. If a patient develops increased transaminase levels, or signs and symptoms of liver disease, more frequent monitoring may be required.

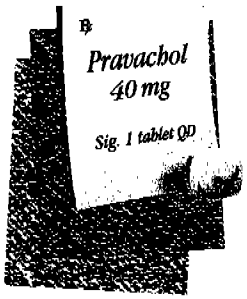
Pravachol is well tolerated. The most common adverse events are rash, fatigue, headache, and dizziness.

REFERENCES:

1. Pravachol product labeling. Bristol-Myers Squibb Company. **2.** von Bergmann K, Lütjohann D. Review of the absorption and safety of plant sterols. *Postgraduate Medicine Special Report: New developments in the management of high cholesterol.* 1998: 54-59. **3.** Nguyen TT, Dale LC, von Bergmann K, Croghan IT. Cholesterol-lowering effect of stanol ester in a US population of mildly hypercholesterolemic men and women: A randomized controlled trial. *Mayo Clin Proc.* 1999;74:1198-1206. **4.** Blair SN, et al. Incremental reduction of serum total cholesterol and low density lipoprotein cholesterol with the addition of plant stanol ester-containing spread to statin therapy. *Am J Cardiol.* In press. **5.** Miettinen TA, Puska P, Gylling H, Vanhanen H, Vartiainen E. Reduction of serum cholesterol with sitostanol-ester margarine in a mildly hypercholesterolemic population. *N Engl J Med.* 1995;333:1308-1312. **6.** Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med.* 1995;333:1301-1307. **7.** Data on file, Bristol-Myers Squibb Company. **8.** The long-term intervention with pravastatin in ischaemic disease (LIPID) study group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med.* 1998;339:1349-1357.

PRAVACHOL®
pravastatin sodium 40 mg tablets

TeamUp for Health



Prescribe **Pravachol** *40 mg once daily**

- ▶ Provides effective lipid management
- ▶ Provides proven protection against first and recurrent MI
- ▶ Offers reduced potential for CYP450 3A4 drug interactions

Recommend adding **Benecol Spread**– *three servings a day–in place of similar spreads to your* **Pravachol** *patients' healthy diet*

- ▶ Helps promote healthy cholesterol levels as part of a healthy lifestyle
- ▶ Refocuses your *Pravachol* patients' attention on the importance of diet in managing cholesterol

Be sure to provide your **Pravachol** *patients with the* **TeamUp for Health** *program kit*

*Also available as 10-mg and 20-mg starting doses.

Please see Pravachol INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS (including Skeletal Muscle), PRECAUTIONS, and ADVERSE REACTIONS in the accompanying full prescribing information.

Benecol.

McNeil CONSUMER HEALTHCARE
DIVISION OF McNEIL - PPC, INC.
FORT WASHINGTON, PA 19034 USA

PRAVACHOL®
pravastatin sodium 40 mg tablets

Bristol-Myers Squibb Company

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