DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Peter R. Dolan
Chairman and Chief Executive Officer
Bristol-Myers Squibb Company
345 Park Avenue
New York, NY 10154-0037

RE: NDA 19-898
Pravachol (pravastatin sodium) Tablets
MACMIS ID #11419

WARNING LETTER

Dear Mr. Dolan:

This Warning Letter details the dissemination of promotional materials for Pravachol® (pravastatin sodium) Tablets by Bristol-Myers Squibb Company (BMS). These promotional materials are false or misleading in that they claim that Pravachol has been approved by the Food and Drug Administration (FDA) for conditions and patients for which it has not been approved. Specifically, you disseminated these claims in advertisements (ads) and labeling pieces directed to consumers, and in labeling pieces directed to healthcare professionals. The direct-to-consumer (DTC) ads appear in periodicals such as *Time*, *Good Housekeeping*, *Smithsonian*, *Southern Living*, *US News & World Report*, *Reader's Digest*, *Prevention*, and *Diabetes Forecast*, in daily newspapers including *The Washington Post* and *The New York Times*, and in the *Better Homes and Gardens Eating for Life Cookbook*.[1] The labeling pieces include a DTC fulfillment letter[2] and a professional formulary switch sales aid.[3] The Division of Drug Marketing, Advertising, and Communications (DDMAC), in consultation with the Division of Metabolic and Endocrine Drug Products (DMEDP), reviewed these pieces and concluded that they violate the Federal Food, Drug, and Cosmetic Act (Act). Your advertisements are violative of Section 502(n) of the Act and your promotional labeling is false or misleading in violation of Section 502(a) of the Act. 21 U.S.C. § 352(a) and (n). Moreover, promotional claims recommending or suggesting Pravachol for a use other than that for which FDA has reviewed safety and effectiveness data create a new "intended use" for which adequate directions must be provided in product labeling. 21 U.S.C. § 352(f)(1); 21 CFR 201.5, 201.100, 201.128. Absent such directions, your product is misbranded under Section 502(f)(1) of the Act. 21 U.S.C. § 352(f)(1).

[1] ID numbers D3-K0125, D3-K0118, D3-K0122, D3-K0127, and D3-K0128
[2] ID numbers D3-D0259
[3] ID number D3-X0062

Your DTC and professional-directed promotional materials broaden the conditions and patient populations for which Pravachol is indicated. The multifaceted DTC campaign is directed to a diverse consumer audience through ads in various newspapers and magazines with both national and local distribution. The messages in the DTC ads also appear in Pravachol promotional labeling pieces that are given or sent to consumers ("fulfillment materials") and in materials disseminated to healthcare professionals. DDMAC views this as evidence of an orchestrated campaign to disseminate violative messages.

Moreover, DDMAC had previously objected, in untitled letters dated March 29, 2001, and December 3, 2001, to your dissemination of Pravachol professional and DTC promotional materials that broadened the product's approved indication, overstated its efficacy, and made unsubstantiated efficacy claims. We are concerned that you are continuing to promote Pravachol in a similarly violative manner.

Background

The Indications and Usage section of the Pravachol approved product labeling (PI) states that Pravachol is indicated for, among other things, "…prevention of coronary events…in hypercholesterolemic patients without clinically evident coronary heart disease," that is, to prevent heart-related events in those patients who have high cholesterol, but who do **not** have clinically evident coronary heart disease (CHD). The "coronary events" sought to be prevented are nonfatal myocardial infarction (MI) ("heart attack") or death from cardiovascular causes. Pravachol is indicated for patients with high cholesterol to reduce the risk of having these coronary events, as well as to reduce the risk that the patient will require myocardial revascularization surgery. Pravachol is **not** indicated to reduce the risk of **stroke** in this patient population, that is, those who do not have clinically evident CHD.

Pravachol is also indicated for "…prevention of cardiovascular events…in patients with clinically evident coronary heart disease," that is, to prevent events in the entire cardiovascular system (including the brain) in those patients who have diagnosed CHD. This indication includes reducing the risk of "**stroke and stroke/transient ischemic attack (TIA)**."

Broadening of Indication--Stroke/TIA Prevention

Your promotional materials imply that Pravachol is approved for prevention of stroke in patients who do not have clinically evident CHD. Pravachol is only approved to reduce the risk of stroke in patients with clinically evident CHD.

DTC Materials

The following claims appear in the DTC print ads (bolded emphasis added):

- "WORRIED ABOUT HAVING A HEART ATTACK? WORRIED ABOUT HAVING A **STROKE**?" (headline, *Time*, *Good Housekeeping*, *Smithsonian*, *Southern Living*)

- "PRAVACHOL IS THE ONLY CHOLESTEROL LOWERING DRUG PROVEN TO HELP PROTECT AGAINST 1ST AND 2ND HEART ATTACK **AND STROKE**." (subheadline, *Time*, *Good Housekeeping*, *Smithsonian*, *Southern Living*, *US News & World Report,* Washington *Post*, New York *Times*, *Diabetes Forecast*)

- "Landmark clinical studies, involving 19,592 people, show that Pravachol…is the only cholesterol lowering drug proven to help prevent both 1st and 2nd heart attack **and stroke** in people with high cholesterol **or** heart disease." (within body of ad, *Time*, *Good Housekeeping*, *Smithsonian*, *Southern Living*, Washington *Post*, New York *Times*)

- "In 4 large clinical studies, involving over 25,000 people, Pravachol was proven to significantly reduce the risk of heart attack **and stroke**." (*US News & World Report*)

- "Pravachol doesn't just lower your cholesterol numbers--it's the only cholesterol lowering drug proven to reduce your risk of 1st or 2nd heart attack **or stroke**, to help you live a longer, healthier life." (*Diabetes Forecast)*

These claims imply that Pravachol is approved for prevention of stroke in all patients worried about having a stroke, whether or not they have clinically evident CHD. This implication is false. The PI specifically states that Pravachol is indicated to "reduce the risk of stroke" "in patients **with clinically evident coronary heart disease**" (emphasis added) only. The "landmark clinical studies" referenced in the ads were designed to determine the effect of Pravachol on reducing the risk of coronary events (that is, fatal and nonfatal CHD) in men who had elevated cholesterol, but had not had an MI (WOSCOPS), reducing coronary events in patients who had already experienced an MI or had been hospitalized for unstable angina (LIPID), and reducing the risk of both coronary and cardiovascular events (including stroke) in patients who had already experienced an MI and had normal cholesterol levels (CARE). None of the studies were designed to determine the effect of Pravachol on reducing the risk of stroke in any population other than those who already had CHD.

The repetitive nature of the claims in the body of the ads reinforces the message in the headlines and subheadlines. Indeed, because of the misleading communication of the indication for Pravachol, the DTC ads suggest that Pravachol is the "drug of choice" if consumers are "worried about having a stroke." FDA is unaware of substantial evidence or substantial clinical experience that supports this claim.

Your assertion that "Pravachol is the **only** cholesterol lowering drug proven to help prevent 1st and 2nd heart attack and stroke in people with high cholesterol or heart disease" (emphasis added) is false. Pravachol is only approved to reduce the risk of stroke in people with clinically evident CHD. Moreover, another HMG-CoA reductase inhibitor, Zocor (simvastatin), has been approved to reduce the risk of CHD death, MI, stroke, and revascularization in patients with CHD, or without CHD but at

high risk of coronary events because of diabetes, peripheral vessel disease, or history of stroke or other cerebrovascular disease, based on data from the Heart Protection Study.[4]

Professional Materials

The following claim appears in the professional piece (bolded emphasis added):

- "In addition to diet, when diet and exercise are not enough, in patients with elevated cholesterol **or** CHD, PRAVACHOL 40 mg—THE ONLY STATIN PROVEN TO: Help prevent both first/recurrent MI **and stroke**…"

As stated above, this claim falsely implies that Pravachol is approved for prevention of stroke in all patients, regardless of whether or not they have clinically evident CHD. Again, the claim that Pravachol is "the only statin proven to help prevent both first/recurrent MI and stroke" is false because Zocor, another statin, has been shown through the Heart Protection Study to provide this level of protection against stroke in patients without CHD (but at high risk of coronary events due to diabetes, peripheral vessel disease, history or stroke or other cerebrovascular disease) for which Pravachol is not approved.

Broadening of Indication--Diabetes Patient Population

Your promotional materials broaden the indication to include the diabetes patient population.

DTC Materials

The following claims appear in the DTC print ad in *Diabetes Forecast*, a publication directed to consumers with diabetes:

- "Worried that having diabetes puts you at greater risk of a heart attack?"
- "Worried that having diabetes puts you at greater risk of stroke?"
- "DIABETES MEANS GREATER WORRIES ABOUT CHOLESTEROL."
- "Plain and simple, when you have diabetes, it's not enough to keep an eye on your blood sugar. You've got to watch your cholesterol too. Levels that may be acceptable for others can be too high for you. Fortunately, **landmark clinical studies involving people with diabetes** show: If you have high cholesterol or heart disease, and a healthy diet and exercise aren't enough, adding Pravachol can make a difference." (emphasis added)

[4] The Indications and Usage section of the Zocor PI states, "In patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, ZOCOR is indicated to:

- Reduce the risk of total mortality by reducing CHD deaths.
- Reduce the risk of non-fatal myocardial infarction and stroke.
- Reduce the need for coronary and non-coronary revascularization procedures."

These claims imply that Pravachol has been shown to be effective to reduce cholesterol and the risk of cardiovascular outcomes specifically in patients with diabetes. This implication is false. FDA is not aware of substantial evidence or substantial clinical experience, let alone "landmark clinical studies" measuring cardiovascular outcomes with the use of Pravachol in a diabetes patient population that support the above claims. The ad appears to rely on the National Cholesterol Education Program's Adult Treatment Panel III Guidelines ("NCEP Guidelines"). Although the NCEP Guidelines list diabetes as a CHD "risk equivalent" (that is, patients with diabetes should be treated as if they already have established CHD), they do not provide substantial evidence for the claim that Pravachol has demonstrated a clinical benefit in patients with diabetes.

Professional Materials

The following claims appear in the professional piece:

- "**Deliver Powerful CV Protection**" [call-out headline, original emphasis]
  Patients with Diabetes and borderline-high LDL-C
  Proven efficacy to:
  Reduce the relative risk of CV events in CARE by 25%
  PRAVACHOL, n = 81/282; placebo, n = 112/304"

These claims imply that Pravachol has been approved to decrease the risk of cardiovascular (CV) events and "deliver powerful CV protection" to "patients with diabetes and borderline-high LDL-C." This implication is false. Pravachol has not been approved for CV risk reduction in patients with diabetes.

Broadening of Indication—Patients with Borderline-High Cholesterol

Professional Materials

Your promotional materials imply that Pravachol is approved for **all** patients with borderline-high cholesterol. Pravachol has only been approved for those borderline-high cholesterol patients with clinically evident CHD. The following claims appear in the professional labeling piece:

"**Meet NCEP[1] Goal[2]** [call-out headline, original emphasis]
Borderline-high Cholesterol (LDL-C 130-159 mg/dL[3])
Proven efficacy to lower LDL-C by 34%[4]
>90% of these patients only require ≤30% LDL-C reduction for goal"

"Footnotes:
1. National Cholesterol Education Program.
2. 159 mg/dL x 34%=54.1 mg/dL; 159 mg/dL-54.1 mg/dL=104.9 mg/dL;104.9 mg/dL<130 mg/dL (NCEP goal for borderline-high patients)
3. Plus ≥2 risk factors and a 10% to 20% ten-year risk for major CHD events.
4. Mean lipid change with PRAVACHOL 40 mg. >90 of these patients only require an LDL-C reduction of ≤30% to reach goal."

These claims imply that >90% of patients with borderline-high cholesterol will "meet NCEP goal" if they take Pravachol, because it is proven to decrease LDL by 34%. The totality of this presentation suggests that Pravachol is approved for **all** patients with borderline-high cholesterol. In fact, Pravachol has only been approved for those borderline-high cholesterol patients with clinically evident CHD.

Moreover, according to the NCEP Guidelines, borderline-high patients with 0 to 1 risk factors are not candidates for drug therapy. In addition, the claims do not contain qualifying context that individual results may vary. The decision to treat a patient must take into consideration the presence of CHD or CHD risk equivalents (such as diabetes). Although the results of CARE and LIPID showed a clinical benefit for Pravachol in patients with borderline-high cholesterol, the patients enrolled in these studies already had CHD.

Furthermore, the claims above are misleading because they are not accompanied by sufficient context stating that these claims only apply to patients with CHD or risk equivalents for CHD. Only one of the footnotes (which lack prominence and are not sufficient for readability) in the piece, "Plus $\geq$2 risk factors and a 10% to 20% ten-year risk for major CHD events" provides any information. However, this footnote does not identify what these "risk factors" are, and the presentation of the footnotes is inadequate to overcome the overall misleading presentation. Therefore, the overwhelming message is that **anyone** with borderline-high cholesterol can "meet NCEP goal" if they take Pravachol.

Conclusions and Requested Actions

You have engaged in a multifaceted promotional campaign that includes widely disseminated DTC and professional materials that suggest that Pravachol is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience. Your materials suggest that Pravachol is approved to reduce the risk of stroke in patients, whether or not they have clinically evident CHD. This suggestion is false because Pravachol has not been approved to reduce the risk of stroke in patients without clinically evident CHD. Claims that Pravachol is the only cholesterol lowering drug approved for stroke prevention in people without clinically evident CHD are also false. This suggestion is particularly troubling considering that another treatment has been shown to reduce such risks. Your materials also suggest that Pravachol has been approved to reduce the risk of CV events in diabetes patients, and to lower cholesterol in all borderline-high patients.

DDMAC requests that you provide a detailed response to the issues raised in this Warning Letter. Your response should contain an action plan that includes two items:

1) Immediate cessation of the dissemination of these and similar promotional materials for Pravachol that contain the same or similar claims or presentations.

2) Prompt dissemination of accurate and complete information to the audiences that received the misleading messages.

Please respond to DDMAC by August 21, 2003, with your action plan and a statement of your intent to implement "1" and "2" above. If you have any questions or comments, please contact Mark Askine or Christine Smith by facsimile at (301) 594-6759, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, Maryland 20857.

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of your promotional campaign for Pravachol, and may determine that additional measures will be necessary to fully correct the false or misleading messages resulting from your violative conduct.

We remind you that we consider only written communications official. In future correspondence regarding this particular matter, please refer to MACMIS ID #11419 as well as the NDA number. Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Mark Askine
8/7/03 11:25:48 AM
Signed for Thomas W. Abrams