DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JAN 26 1998

TRANSMITTED VIA FACSIMILE

Thomas E. Costa
Vice-President & Senior Counsel
Bristol-Myers Squibb Company
U.S. Pharmaceuticals
P.O. Box 4500
Princeton, NJ 08543-4500

Re: **NDA 19-898**
Pravachol (pravastatin sodium) tablets
MACMIS ID # 5878

Dear Mr. Costa:

Reference is made to Bristol-Myers Squibb Company's (BMS) August 21, 1997, and September 22, 1997, FDA form 2253 submissions for Pravachol. These materials consist of the following:

August 21, 1997: D3-A240A Brochure

September 22, 1997: D3-A239A Brochure
D3-K033 Journal Ad

Reference is also made to communications by a BMS sales representative with a representative from the Division of Drug Marketing, Advertising and Communications (DDMAC) at the 1997 American Heart Association (AHA) meeting.

The Division of Drug Marketing, Advertising and Communications (DDMAC) has reviewed these materials and communications and has determined that they are misleading in violation of the Federal Food, Drug, and Cosmetic Act and applicable regulations for the following reasons:

AHA Meeting

During this AHA meeting, Paul Spence (BMS representative) discussed mechanisms of actions for Pravachol that are not consistent with the approved product labeling. The representative discussed the reanalysis of the WOSCOP study and stated that the reduction of first MI with Pravachol is related

to mechanisms of action other than LDL-C lowering. The BMS representative also provided promotional materials citing information supporting this claim. For example, the representative cited a passage in the reprint "Reduction in Cardiovascular Events During Pravastatin Therapy by Byington et al., (1995) that discusses alternative mechanisms of action other than LDL-lowering:

> This finding suggests that this agent (Pravastatin) may have an effect beyond simple lipid lowering. Mechanisms such as plaque stabilization, restoration of endothelial function, and a decrease in platelet activation are possible explanations for this additional benefit.

The BMS representative also referred the DDMAC representative to a BMS sponsored continuing medical education symposium on November 9 and November 11, 1997, for further discussion of this issue.

This promotion is misleading because it is not consistent with the mechanism of action provided in the clinical pharmacology section of the approved product labeling for Pravachol. The labeling states that "[I]n multicenter clinical trials, those pharmacologic and/or non-pharmacologic interventions that simultaneously lowered LDL-C and increased HDL-C reduced the rate of cardiovascular events (both fatal and nonfatal myocardial infarctions)" and "[T]he effects of pravastatin on Lp(a), fibrinogen, and certain other independent biochemical risk markers for coronary heart disease are unknown."

Risk Information

- The brochures and journal advertisement are misleading because they fail to present important risk information for Pravachol. The materials fail to provide adequate information about the bolded warning regarding myopathy and rhabdomyolysis including advising the patients to report unexplained muscle pain, tenderness or weakness to the health care provider and discontinuing Lescol if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

- The presentation of risk information in the brochures and journal ad is misleading because it is not reasonably comparable to the presentation of efficacy information. The warning information in the brochure is presented in small

type at the bottom of the page titled "Proven safety and tolerability." For example, the statements "It is recommended that liver function tests be performed prior to and at 12 weeks following initiation of therapy or an elevation in dose" are presented in small dark type at the bottom of the page. This presentation is not adequate to communicate the bolded warning. DDMAC has previously commented on this issue in our April 18, 1996, letter of comments for Pravachol. In this letter, DDMAC stated that a reprint carrier lacked fair balance because the presentation of risk information was not reasonably comparable to the presentation of efficacy information. In this letter, DDMAC also recommended that the statements of warnings and contraindications be made more prominent; e.g. enlarged and bulleted.

- The statements in the brochures "Low potential for interactions with many commonly prescribed medications. Including certain calcium channel blockers, antidepressants and antihistamines" are misleading because they fail to reveal facts material to the risk information. BMS selectively presents positive findings regarding the drug interactions while failing to present the warning regarding drug interactions with concurrent use of immunosuppressive drugs, gemfibrizol, niacin, and erythromycin. For example, the warning section of the approved product labeling states that "The risk of myopathy during treatment with another HMG-CoA reductase inhibitor is increased with concurrent therapy with either erythromycin, cyclosporine, niacin, or fibrates" and "The combined use of pravastatin and fibrates should be avoided unless the benefit ... is likely to outweigh the increased risk of this drug combination."

- The statement in the brochures, "Pravachol is not metabolized by the cytochrome P450 3A4 enzyme system to a clinically significant extent," is misleading because it is not supported by substantial evidence. The claim is based on data from an *in vitro* study and the data are not adequate to support the clinical significance of the claim.

- The statement, "May enhance acceptance of treatment and long-term compliance" is misleading because it is not supported by substantial data that demonstrates that less frequent liver function testing enhances acceptance and compliance.

Misleading Presentation of Clinical Trial Data

Reanalysis of the WOSCOP Study

- In the brochures, BMS presents a reanalysis of the WOSCOP study to evaluate if the reduction in first MI (MI event rate) was related to the amount of LDL-C reduction. In this reanalysis, patients were divided into 5 groups based on percent LDL-C reductions. The analysis and graphic presentation imply that while some LDL-C reduction is necessary to achieve benefit in terms of event reduction, patients with mean LDL-C reductions of 23% received similar benefit to those patients whose LDL-C was lowered by 41%.

  This presentation is misleading because the trial was not designed to test for differences in outcome (MI events) based on the percent LDL-C reduction. Since the study was not adequately powered to detect differences between groups based on percent LDL-C reduction, the results implying similarity in outcome based on LDL-C reductions of 23% and 41% are misleading.

  Further, the presentation is misleading because it is not consistent with the National Cholesterol Education Program's (NCEP) Treatment Guidelines. The NCEP guidelines use a goal LDL-C level and not a percent reduction to assess treatment response, so that patients with any baseline LDL-C level can be treated appropriately. Thus, for some patients with a baseline LDL greater than 190 mg/dl, lowering LDL levels by 23% would not meet the NCEP treatment goal of less than 160 mg/dl. In addition, the guidelines also state the these treatment goals are a minimum, and lowering LDL-C below these goals, if possible, is desirable.

- The statements, "Early benefits for patients with Pravachol. MI risk reduction was observed within 6 months and reached statistical significance at 18 months" in conjunction with the graph with the large red arrow pointing to the 6 month time point are misleading because they imply that individual patients may achieve a benefit at 6 months. However, the data are not adequate to support this claim because the onset of benefit for individual patients cannot be extrapolated from this study. DDMAC has addressed this issue previously in our July 19, 1996, letter of comments for Pravachol. In that letter, DDMAC noted that the claim, "Impact on MI begins at 6 months" would be misleading

because it suggests that individual patients may achieve a benefit at six months. DDMAC also noted that BMS should communicate that the impact of timing on the onset of benefit for individual patients cannot be extrapolated from this study. In your July 22, 1996, letter, BMS agreed to delete the information concerning impact on MI at about six months. However, BMS has continued the violative presentation.

- In brochure D3-A240, the headline "Pravachol reduced the risk of MI by 62%" is misleading because it overstates the efficacy data and does not adequately communicate the findings from the pooled studies. The inclusion of the extremely small statement under the graph ("Event rates 7.9% placebo vs 5.5% Pravachol") in light typeface is not adequate to correct this misleading message. DDMAC has previously commented on this issue in our April 5, 1996, and April 18, 1996, letters of comment. In these letters, DDMAC stated that the headline "Pravachol...reduces the risk of heart attack by 62%" would be misleading because it does not adequately communicate the context of the findings from the pooled studies. DDMAC recommended that BMS revise the statement to indicate the event rates for placebo and Pravachol.

- The footnoted statement in the brochures, "It is not clear to what extent the findings of the Pravastatin Primary Prevention Study can be extrapolated to a similar population of women" lacks adequate prominence in comparison to the presentation of efficacy information.

Misleading Presentation of Mechanism of Action

- The brochures are misleading because they imply that Pravachol has a mechanism of action other than LDL lowering that is responsible for the reduction of first MI without adequate supporting evidence. For example, the brochures include red bolded headings, "Is the reduction of First MI with Pravachol related to the amount of LDL-C reduction?" and "While some LDL reduction was required, greater lowering of LDL-C did not lead to further reduction in MI." These headings and the presentation as a whole imply that the reduction in first MI with Pravachol is related to mechanisms other than LDL lowering.

  Further, the presentation is misleading because it is not consistent with the mechanism of action presented in the

clinical pharmacology section of the approved product labeling, as noted on page two of our letter:

> In multicenter clinical trials, those pharmacologic and/or non-pharmacologic interventions that simultaneously lowered LDL-C and increased HDL-C reduced the rate of cardiovascular events (both fatal and nonfatal myocardial infarctions) .... The effects of pravastatin on Lp(a), fibrinogen, and certain other independent biochemical risk markers for coronary heart disease are unknown.

Thus, it is misleading to imply that the reduction of first MI with Pravachol in the WOSCOP study is related to mechanisms of action other than LDL-C or lipid-lowering because the data are not adequate to support the clinical significance of this claim.

Indication Statement

The presentation of the indication statement in the brochures lacks adequate prominence because it is presented in a small type footnote that is difficult to read. Similarly, the indication statement in the journal ad is difficult to read because it is presented in small type and is positioned in block text immediately after the risk information. Pravachol is indicated as an adjunct to diet in patients whose response to diet and nonpharmacologic measures has not been adequate. Without presenting this information prominently, BMS suggests that Pravachol may be used in a broader population than indicated. DDMAC has addressed this issue previously in our July 19, 1996, letter of comments for Pravachol. In that letter, DDMAC noted that the visual aid would be misleading because it failed to adequately present the indication for Pravachol.

In order to address these violations, DDMAC requests that BMS immediately discontinue the dissemination and use of the violative pieces noted in this letter and any other promotional materials that contain similar themes. DDMAC requests that BMS submit a written response to this letter no later than February 9, 1997. This response should include the following:

- A list of all materials and a description of any misleading promotional activities that have been discontinued;

- BMS's plan to comply with DDMAC's request.

If BMS has further comments, please contact the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857. In all future correspondence regarding this launch, please refer to MACMIS ID #5878 in addition to the NDA number.

Sincerely,

Anne M. Reb, NP
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications