DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

OCT 25 1999

TRANSMITTED VIA FACSIMILE

Ms. Carol Sever
Deputy Director
Regulatory Affairs
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516

RE: NDA 20-740
Baycol (cerivastatin sodium)
MACMIS ID# 8238

Dear Ms. Sever:

As part of its routine monitoring program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has become aware of promotional material for Baycol (cerivastatin sodium) that is false, lacking in fair balance, or otherwise misleading. Reference is made to a Sales Aid (QO 1068), submitted under cover of Form FDA 2253. The dissemination of this material by Bayer Corporation (Bayer) and/or their agents, violates the Federal Food, Drug, and Cosmetic Act and its implementing regulations. DDMAC requests that the use of the above referenced material and those containing the same or similar violations cease immediately. Specifically, DDMAC has the following objections:

Sales Aid

Baycol –the science for success

The presentation under this header is misleading because it implies, without substantial evidence, that Baycol is superior to other HMG CoA reductase inhibitors ("HMGs") because of its synthetic properties. More specifically, the statement, "Baycol is a fully

synthetic inhibitor of the HMG CoA reductase enzyme" in juxtaposition with a chart comparing the "Synthetic Pure Enantiomers" (Baycol and Lipitor) versus "Other Statins" (Pravachol, Zocor, Mevacor, and Lescol) that are "fungally derived" implies a clinical advantage for Baycol versus "other statins" that is unsubstantiated. The disclaimer, "comparisons do not imply clinical significance" that is presented in small type does not adequately correct the misleading implication.

Powerful enzyme inhibition

Again, the presentation under this header is misleading because it implies that Baycol is superior to other HMGs based on non-clinical (*in vitro*) data about the enzymatic properties of the HMGs. More specifically, the statement, "Baycol inhibits cholesterol-producing enzymes *in vitro* more completely at lower concentrations than any other statin" in juxtaposition with a graph titled, "Statin inhibition of membrane-bound HMG CoA reductase in animal hepatic tissue" uses non-clinical data to imply clinical significance and the superiority of Baycol versus the other HMGs. The disclaimer, "in vitro data do not imply clinical significance" that is presented in smaller type underneath the graph does not adequately correct the misleading implication.

Dramatic results across key lipid parameters

The presentation of HDL-C efficacy information under this header is misleading because it overstates the efficacy of Baycol. More specifically, the statement, "Baycol delivers outstanding mean increases of 10% in HDL-C" in conjunction with the statement, "Epidemiological research has shown that each 1 mg/dl increase in HDL-C is associated with a 4.4% decrease in the risk of coronary heart disease" suggests an effect of Baycol that is unsubstantiated. This presentation suggests that drug intervention with Baycol and corresponding increase in HDL-C levels will have a positive effect on cardiovascular morbidity and mortality. This effect on morbidity and mortality has not been demonstrated, however, as described in Baycol's approved product labeling which states, "The independent effect of raising HDL-C or lowering triglycerides on the risk of coronary and cardiovascular morbidity and mortality has not been determined." The disclaimer that follows the misleading HDL-C claims, "The effect of Baycol on cardiovascular morbidity and mortality" that appears in very tiny font, in a footnote, does not adequately correct the misleading implication.

Baycol proven significantly better than Pravachol

The presentation under this header is misleading because it implies that Baycol is superior to Pravachol without substantial evidence. More specifically, the presentation of LDL-C reductions for Baycol .3 mg (31%) versus Pravachol 20 mg (26%) in conjunction

with the misleading claim of "19% better efficacy...P<.0001" implies superiority without adequate substantiation. The studies utilized by Bayer to substantiate the superiority of Baycol versus Pravachol are inadequate. For example, the first study compares Baycol .3 mg (at that time—the highest labeled dose) to Pravachol 20 mg (the mid-range dose). Furthermore, the second study yielded no difference (both achieved 30% LDL-C reduction) between Baycol .3 mg and Pravachol 40 mg (the highest labeled dose). Therefore, the presentation of superiority is misleading for the aforementioned reasons. The disclaimer, "The clinical outcomes resulting from differences in LDL-C reductions between Baycol and Pravachol have not been determined" does not adequately correct the unsubstantiated implication of superiority.

Lack of Fair Balance

The presentation of risk information in this promotional piece lacks fair balance. Promotional materials may be lacking in fair balance, or otherwise misleading if they fail to present information relating to side effects and contraindications, with a prominence and readability reasonably comparable to the presentation of efficacy information. In the Sales Aid, Bayer uses several pages, various color patterns, charts, graphs, and the like, to provide emphasis for efficacy information. However, the page seemingly devoted to the presentation of risk information titled, "Baycol offers a proven record of safety" contains mostly additional benefit (safety) claims for Baycol and very little risk information. In fact, Bayer presents the most important risk information (risk of myopathy, rhabdomyolysis, etc...) with much less emphasis, in the middle of the Sales Aid.

Bayer should immediately cease using this, and all other promotional materials for Baycol that contain the same or similar violations. Bayer should submit a written response to DDMAC, on or before November 8, 1999, describing its intent and plans to comply with the above. In its letter to DDMAC, Bayer should include a list of all promotional materials that were discontinued, and the discontinuation date.

Bayer should direct its response to the undersigned by facsimile (301) 594-6771, or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-42; Room 17B-20; 5600 Fishers Lane; Rockville, MD 20857. DDMAC reminds Bayer that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS # 8238 and NDA 20-740.

Sincerely,

/S/

Michael A. Misocky R.Ph., J.D.
Regulatory Review ~~Officer~~
Division of Drug Marketing,
Advertising and Communications