DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

NOV 19 1998

Ellen R. Westrick
Senior Director
Office of Medical/Legal
Merck & Co., Inc.
Sumneytown Pike
West Point, PA 19486

RE: NDA#20-912/20-913
Aggrastat (tirofiban hydrochloride) Injection
Aggrastat (tirofiban hydrochloride) Injection, Premixed
MACMIS ID #6986

Dear Ms. Westrick:

Reference is made to Merck & Co., Inc.'s (Merck) October 9, 1998 letter, in response to a September 23, 1998 letter from the Division of Drug Marketing, Advertising and Communications (DDMAC). DDMAC's letter concerned the alleged dissemination of several homemade promotional pieces by or on behalf of Merck, that promoted Aggrastat (tirofiban hydrochloride) in violation of the Federal Food, Drug and Cosmetic Act and its implementing regulations. In our letter, DDMAC requested that Merck investigate the extent to which these homemade pieces were used to promote Aggrastat.

In its response, Merck acknowledged that certain Merck sales representatives have been involved in the development and dissemination of these, and other, violative homemade promotional materials. Merck stated that it believed that its sales representatives were responding to requests from hospital employees to develop promotional materials with off-label dosing recommendations for use in the cardiac catheterization laboratory, and that no evidence had been discovered to suggest an organized internal effort by Merck to develop or disseminate these materials. In addition, Merck described its policy for prohibiting dissemination of homemade materials by its sales force, and specified the corrective actions taken to ensure that this activity will not continue. Further, Merck stated its intention to carefully monitor this issue, and to take additional action if necessary.

DDMAC has reviewed these homemade promotional materials and has determined that they are false or misleading because they promote an off-label dosing regimen, contain unsubstantiated comparative claims, and are lacking in fair balance.

Promotion of an off-label dosing regimen

All of these homemade promotional materials present recommendations for the dosing of Aggrastat, when begun in the cardiac catheterization laboratory, to be a 10 mcg/kg bolus over 3 minutes, followed by a maintenance infusion of 0.15 mcg/kg/minute. Although this was the dosing regimen evaluated in the RESTORE clinical trial, it is not the dosing regimen recommended in the approved product labeling (PI) for Aggrastat. The Dosage and Administration section of the PI states that "...Aggrastat should be administered intravenously, at an initial rate of 0.4 mcg/kg/min for 30 minutes, and then continued at 0.1 mcg/kg/min. Therefore, DDMAC considers Merck's presentation of the RESTORE dosing regimen in these promotional pieces to be inconsistent with the PI and promotion of an off-label dosing regimen. DDMAC is concerned with this issue because the incidence of major bleeding with the RESTORE dosing regimen was nearly double the incidence observed with the recommended dosing regimen.

Unsubstantiated comparative claims

In one of these homemade promotional pieces ("Formulary Review GPIIb/IIIa Platelet Inhibitors"), Merck presents comparative claims for Aggrastat versus Integrilin (eptifibatide), a product of COR Therapeutics, Inc. These comparative claims include quoting selective statements from both Aggrastat's and Integrilin's PIs, and presenting claims that suggest that Aggrastat is superior to Integrilin. For example, Merck presents the following information under the heading "PTCA:"

> AGGRASTAT: 46% reduction of cardiac ischemic events after angioplasty 44% reduction in Death and MI at 30 days in patients who underwent PTCA/ Atherectomy. Prism-Plus
>
> INTEGRILIN: Two doses were studied and both struggled to show positive results. Investigators used a post-hoc sub analysis to show positive outcome....

DDMAC considers this presentation to be misleading for the following reasons:

- These claims, and other claims presented in this piece suggest that Aggrastat is superior to Integrilin. However, none of these claims are based on adequate, well-controlled, head-to-head clinical trials. Therefore, these claims are not supported by substantial evidence.

- Further, in the above example, Merck presented the risk reductions in events at 30 days after PTCA. However, the risk reductions for these same events during the first 30 days of the study, the endpoint described in the PI, were lower. The reduction in

risk of cardiac ischemic events (i.e., the composite endpoint of death, myocardial infarction, and refractory ischemia) at 30 days was 32%, rather than 46%, and the reduction in risk of death and MI was 34%, rather than 44%, for this subgroup receiving Aggrastat in combination with heparin. DDMAC considers this presentation to be misleading because Merck selectively presented the more favorable results to imply greater efficacy for Aggrastat than demonstrated by substantial evidence.

Lacking in fair balance

A majority of these homemade promotional materials failed to provide **any** risk information related to the use of Aggrastat (emphasis added). Promotional materials must present information about the risks associated with the use of the drug in a manner reasonably comparable to that of claims concerning the drug's efficacy. Although these homemade promotional materials contain numerous claims related to the efficacy of Aggrastat, information concerning the contraindications, warnings, precautions, and adverse events associated with Aggrastat's use are not presented. Therefore, DDMAC considers these materials to be lacking in fair balance because they fail to disclose the risks associated with Aggrastat's use.

In addition, one piece presented bleeding as most common adverse event associated with the use of Aggrastat, but described it as "oozing or mild." However, Aggrastat when added to heparin and aspirin, is associated with a greater incidence of bleeding (major, minor, and requiring transfusion) and thrombocytopenia, versus heparin and aspirin therapy alone. DDMAC considers this presentation of bleeding information to be misleading because it minimizes the incidence and severity of this important risk information.

DDMAC has reviewed your response and actions taken with respect to the dissemination of these violative promotional materials. Although DDMAC does not wish to comment on the internal processes of Merck, we are very concerned because the dissemination of these materials has been widespread, occurring across many geographic areas. Further, DDMAC has received additional violative homemade materials for Aggrastat that include these same violations.

DDMAC notes Merck's commitment to continue to carefully monitor this situation and that the additional violative pieces mentioned above may have been disseminated prior to Merck's stated corrective actions. In light of Merck's commitment, and actions taken by Merck to date, *DDMAC considers this matter closed.* However, DDMAC will continue to closely monitor this issue and will consider alternative actions if further violative activities occur. In addition, DDMAC requests that Merck provide us with any further information concerning this matter, including any additional homemade materials discovered during its continuing investigation.

If Merck has any questions or comments, please direct them to 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. DDMAC reminds Merck that only written communications are considered official.

In all future correspondence regarding the issues raised in this letter, please refer to MACMIS ID # 6986 in addition to the NDA numbers.

Sincerely,

Janet Norden, MSN, RN
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications