DEPARTMENT OF HEALTH & HUMAN SERVICES
HFD-40 FOI
Public Health Service

Food and Drug Administration
Rockville MD 20857

JAN 23 1997

TRANSMITTED VIA FACSIMILE

Carol A. Sever
Assistant Director, Regulatory Services
Bayer Corporation, Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516-4175

Re: NDA 20-304
Trasylol (aprotinin) Injection
MACMIS File ID #4898

Dear Ms. Sever:

This letter is in reference to Bayer Corporation's (Bayer) submissions (dated October 8, 1996, and October 18, 1996) of promotional materials under cover of FDA Form 2253 for Trasylol (aprotinin injection). These submissions included a reprint article entitled "Aprotinin Use in Patients with Dialysis-Dependent Renal Failure Undergoing Cardiac Operations by Lemmer et al. (TO5126) and an issue of Advances in Cardiovascular Surgery & Anesthesiology (TO6046). The Division of Drug Marketing, Advertising, and Communications (DDMAC) considers the use of these materials in promotion of Trasylol to be false and/or misleading under the Federal Food, Drug, and Cosmetic Act and the regulations promulgated thereunder.

Specifically, the Lemmer article discusses uses other than those for which aprotinin has demonstrated safety and efficacy. This article presents efficacy data for patients who undergo operations other than coronary artery bypass grafts. Lemmer describes the outcome of patients undergoing valve replacement operations. However, the use of aprotinin in valve replacement operations is not an approved use for aprotinin. Therefore, use of this reprint article promotes the use of aprotinin for unapproved uses.

DDMAC is also concerned that this article presents efficacy parameters that were not provided for in the approved product label and which DDMAC objected to previously during its review of the launch materials for aprotinin in a letter dated March 14, 1994. The data DDMAC objected to consisted of the mean total post-operative thoracic drainage volume instead of the total blood loss, the use of blood products instead of units of donor blood, and the percentage of patients undergoing reoperation for bleeding.

Similarly, the article entitled "Aprotinin Reported to Diminish Bypass-Induced Inflammation" contained in Advances in Cardiovascular Surgery & Anesthesiology, promotes the use of aprotinin in myocardial revascularization operations. The overly broad use of aprotinin in all myocardial revascularization operations is inconsistent with the approved product labeling. The approved product labeling limits the use of aprotinin to those patients where the risk of bleeding is especially high or in repeat coronary artery bypass graft surgery. Additionally, this article promotes the use of aprotinin to reduce bypass-induced inflammation for which Bayer has not submitted data to demonstrate the efficacy or safety thereof.

Moreover, another article in TO6046 suggests that the use of aprotinin allows the use of higher doses of heparin in cardiac surgery. Again, Bayer has submitted no data to the Agency to document the use of aprotinin allows for the use of higher doses of heparin. Therefore, use of both of these articles promotes the use of aprotinin for unapproved uses.

Bayer should immediately suspend all promotional activities and materials that convey or contain the allegedly violative claims or information identified in this letter until these allegations are resolved. Bayer should submit a written response to DDMAC on or before February 7, 1997, describing the steps that it has taken to ensure that these activities and the use of these materials have been suspended.

Bayer should address any correspondence or additional questions 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-240, Rm 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 both the NDA number and MACMIS File ID number 4898.

Sincerely,

Stephen W. Sherman

Stephen W. Sherman
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

File name: Trsnovii

Draft: Sherman - 11/21/96
Comment: Hankin - 11/21/96
Comment: Abrams - 11/25/96
Revised: Sherman - 11/27/96
Comment: Abrams - 12/9/96
Revised: Sherman - 12/13/96
Comment: Talarico - 12/17/96
Concur: Abrams - 1/22/96

cc:
HFD-240/NDA 20-304
HFD-240/Chron/Sherman/Drezin
HFD-180/Talarico
HFD-180/NDA 20-304

MACMIS ID #4898

MACMIS Type Code: LETT
MACMIS Action Code: VIOL
2253 ID#: 20959
Material ID#(s): TO9264, TO9274

Due Date: 2/7/97

Close Out: **NO** (circle one)

FOI Status: **RELEASEABLE**