

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 020304/S004**

**ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE**

NDA 20-304/S-004

ALD - 5 1997

*Submitt*

Bayer Corporation Pharmaceutical Division  
Attention: Lee Scaros, Pharm.D.  
400 Morgan Lane  
West Haven, CT 06516

Dear Dr. Scaros:

Please refer to your supplemental new drug application dated October 29, 1996, received October 31, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trasylol® (aprotinin) Injection.

We also refer to our November 22, 1996, letter notifying you that all fees owed under the Prescription Drug and User Fee Act of 1992 were received by the Agency on November 6, 1996, and therefore, the new receipt date of your submission was November 6, 1996. The User Fee goal date for this application is November 6, 1997.

We acknowledge receipt of your amendments dated November 7, December 10, and December 19, 1996, and February 19, 1997.

This supplemental application provides for a broadening of the indication from repeat CABG and high risk primary CABG patients to all CABG patients. In addition, the package insert has been revised to include changes made to the CLINICAL TRIALS, ADVERSE REACTIONS (addition of "Myocardial Infarction" and "Graft Patency" subsections, inclusion of information on additional Trasylol-treated and placebo-treated primary and repeat CABG patients, and exclusion of patients who underwent other thoracic surgeries), and WARNINGS: Re-exposure of patients (to include data from a retrospective review of 387 European case studies) sections. During the review process, it was determined that revisions to the CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, PRECAUTIONS, DOSAGE AND ADMINISTRATION, and COMPATIBILITY sections of the package insert were also included in the application.

We have completed our review of the application and it is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The information presented is inadequate to support the proposed, broadened indication for the use of Trasylol® in all CABG patients. Specifically, the pivotal study D92-016, entitled "A Multi-center, Randomized, Double-Blind, Placebo-Controlled Group Comparison Study to Investigate the Efficacy and Safety of Aprotinin in Reducing Blood Loss and Transfusion Requirement in Patients Undergoing Primary Cardiopulmonary Bypass Surgery for Myocardial Revascularization (CABG)," failed to support the efficacy of Trasylol® in the low bleeding risk subgroup of CABG patients. In

addition, the increased risk of allergic/anaphylactic reactions on re-exposure to Trasylo<sup>®</sup> further limits the benefit of Trasylo<sup>®</sup> for patients, not at high risk of bleeding, undergoing primary CABG surgery.

Further, we note that supplement 005, submitted May 2, 1997, (received 05/05/97) as "Special Supplement-Changes Being Effected" under 21 CFR 314.70(c), provides for revisions to the WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the package insert similar to the revisions of those sections submitted in S-004. Please be advised, that S-005 is currently under review. The Agency requests that you consider withdrawing the labeling revisions to the WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of S-004, as all comments on the labeling revisions submitted in this supplement will be reserved until the application is otherwise approvable.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, please contact:

Julieann DuBeau, RN, MSN  
Regulatory Health Project Manager  
(301) 443-0487

APPEARS THIS WAY  
ON ORIGINAL

Sincerely yours,

*/s/ 8-5-97*

APPEARS THIS WAY  
ON ORIGINAL

Lilia Talarico, M.D.  
Acting Director  
Division of Gastrointestinal  
and Coagulation Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

*ASO/Dubeau*

**Division of Gastrointestinal & Coagulation Drug Products**

**CONSUMER SAFETY OFFICER REVIEW**

**Application Number:** NDA 20-304/SE1-004

**Name of Drug:** Trasylo<sup>®</sup> (aprotinin) Injection

AUG 25 1998

**Sponsor:** Bayer Corporation

**Material Reviewed**

**Submission Date(s):** March 11, 1998 (draft labeling)

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**Receipt Date(s):** March 12, 1998

**Background and Summary Description:** This supplemental application, submitted October 29, 1996, provides for a broadening of the indication from repeat CABG and high risk primary CABG patients to all CABG patients. The application was NOT APPROVABLE on August 5, 1997, due to clinical and statistical deficiencies.

Following the initial labeling submitted with the supplement, SLR-005 and SLR-006 were approved August 8, 1997, and September 30, 1997, respectively. A meeting was held with the firm in which labeling issues were discussed. Amendments dated November 10, 1997 (clinical), and February 27, 1998 (labeling), in combination, constituted a full response to the NOT APPROVABLE action. On March 11, 1998, the firm submitted a more recent version of the labeling than that submitted on February 27, 1998, and requested that the Agency review the more recent version. a teleconference was held with the firm to discuss further revisions to the proposed labeling submitted on March 11, 1998.

**Review**

The submitted draft labeling (no identifier) for the package insert was compared to the package insert approved September 30, 1997, (SLR-006), identified as "PZ500074, 9/97". Note: Due to the extensive labeling revisions, a copy of the firm's labeling (which includes inserted and deleted text) is attached. This review will address the labeling revisions in three parts. Part I will include those revisions which are included in the labeling contained in the attachment. Part II will address those revisions which the firm did not identify in the labeling contained in the attachment. Part III will address recommendations for further revisions to the labeling.

- I. See the attachment in which the firm specifies inserted and deleted text.

**The Medical Officer, Dr. Lilia Talarico, requested that the firm revise the labeling as follows**

II. Revisions which the firm did not identify in the labeling contained in the attachment.

A. In the WARNINGS section, in the "Re-exposure to aprotinin" subsection:

III. Recommendations for further revisions to the labeling.

**Conclusion**

Supplement 004 should be approved on draft labeling as submitted on March 11, 1998, with revisions as stated in IA, IB, IC, IIA3, IIA4, and III above.

**APPEARS THIS WAY  
ON ORIGINAL**

*/S/*

*8/25/98*

Julieann DuBeau, RN, MSN  
Regulatory Health Project Manager

*/S/*

*8-25-98*

Attachment: Firm's labeling submitted March 11, 1998, which includes inserted and deleted text.

cc:

- Original NDA 20-304/S-004
- HFD-180/Div. Files
- HFD-180/DuBeau */S/ 8-25-98*
- HFD-180/Talarico
- r/d Init: Talarico 8/17/98, 8/25/98
- JD/August 7, 1998 (drafted)
- JD/8/25/98/c:\mydocs\20304808-rjd.doc

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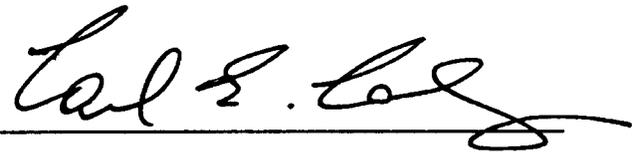
CSO REVIEW

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Section 13: Patent Information

The following information is hereby provided pursuant to 21 CFR 314.53(c) and (d)(2)(iii):

The undersigned declares that there are no U.S. patents covering the drug, drug product, or method of use of the aprotinin product that is the subject of this application for which approval is being sought.



Carl E. Calcagni, R. Ph.  
Vice President, Regulatory Affairs  
Pharmaceutical Division  
Bayer Corporation

APPEARS THIS WAY

APPEARS THIS WAY  
ON ORIGINAL

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**EXCLUSIVITY SUMMARY for NDA # 20-304 SUPPL # 004**

**Trade Name Trasylol® Generic Name (aprotinin)  
Applicant Name Bayer Corporation Pharmaceutical Division HFD-180**

**Approval Date August 28, 1998**

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA?  
YES /     / NO / X /

b) Is it an effectiveness supplement?  
YES / X / NO /     /

If yes, what type? (SE1, SE2, etc.) SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / X / NO /     /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

\_\_\_\_\_  
\_\_\_\_\_  
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /\_\_/\_/ NO /\_X\_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

\_\_\_\_\_

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /\_\_/\_/ NO /\_X\_/

If yes, NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

3. Is this drug product or indication a DESI upgrade?

YES /\_\_/\_/ NO /\_X\_/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).**

**APPEARS THIS WAY  
ON ORIGINAL**

**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO / \_\_\_ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-304 Trasylol® (aprotinin) Injection

NDA # \_\_\_\_\_

NDA # \_\_\_\_\_

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / \_\_\_ / NO / \_\_\_ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # \_\_\_\_\_

NDA # \_\_\_\_\_

NDA # \_\_\_\_\_

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.**

### **PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /  / NO /  /

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /  / NO /  /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

\_\_\_\_\_  
\_\_\_\_\_

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /\_\_\_/ NO /\_X\_/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /\_\_\_/ NO /\_\_\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/ NO /\_X\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # D92-048- "A Multi-Center Randomized Double-Blind Placebo-Controlled Group Comparison Study to Investigate the Effect of Aprotinin on Graft Patency in Patients Undergoing Primary Coronary Artery Bypass Surgery (CABG) for Myocardial Revascularization."

Investigation #2, Study # D92-016- "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Group Comparison Study to Investigate the Efficacy and Safety of Aprotinin in Reducing Blood Loss and Transfusion Requirement in Patients Undergoing Primary Cardiopulmonary Bypass Graft Surgery for Myocardial Revascularization (CABG)."

Investigation #3, Study # D91-007- "A Pilot Study of Aprotinin Prevention of Platelet Dysfunction During Cardiopulmonary Bypass."

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X_/
Investigation #3	YES /___/	NO /_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
 NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
 NDA # \_\_\_\_\_ Study # \_\_\_\_\_

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X_/
Investigation #3	YES /___/	NO /_X_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
 NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
 NDA # \_\_\_\_\_ Study # \_\_\_\_\_

**APPEARS THIS WAY  
ON ORIGINAL**

- c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # D92-048

Investigation #2, Study # D92-016

Investigation #3, Study # D91-007

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

- a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # \_\_\_\_\_ YES / X / NO / \_\_\_ / Explain: \_\_\_\_\_

Investigation #2

IND # \_\_\_\_\_ YES / X / NO / \_\_\_ / Explain: \_\_\_\_\_

Investigation #3

IND # \_\_\_\_\_ YES / X / NO / \_\_\_ / Explain: \_\_\_\_\_

- (b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES / \_\_\_ / Explain \_\_\_\_\_ NO / \_\_\_ / Explain \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_

Investigation #2

YES /\_\_\_/ Explain \_\_\_\_\_ NO /\_\_\_/ Explain \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /\_\_\_/ NO /\_X\_/

If yes, explain: \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_

/S/

\_\_\_\_\_  
Signature

8/28/98  
\_\_\_\_\_  
Date

APPEARS THIS WAY  
ON ORIGINAL

Title: Regulatory Health Project Manager

/S/

\_\_\_\_\_  
Signature of Division Director

8-28-98  
\_\_\_\_\_  
Date

APPEARS THIS WAY  
ON ORIGINAL

cc: Original NDA 20-304/S-004  
HFD-180/Div. File  
HFD/180/DuBeau  
HFD-85 Mary Ann Holovac  
r/d Init: Talarico 8/24/98  
JD/August 21, 1998 (drafted)  
JD/8/28/98/c:\mydocs\20304808-2jd.doc

NDA/PLA  
Action Pkg

# PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

**NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.**

NDA/PLA/PMA # NDA 20-304 Supplement # S-004 Circle one:  SE1 SE2 SE3 SE4 SE5 SE6

HF D-180 Trade and generic names/dosage form: Trasylol (aprotinin) Injection Action:  AP AE NA

Applicant Bayer Corp. Therapeutic Class 1X 8

Indication(s) previously approved Prophylactic use to reduce perioperative blood loss & need for blood  
Pediatric information in labeling of approved indication(s) is adequate  inadequate \_\_\_ transfusion in pts. undergoing cardiopulmo  
Proposed indication in this application Same as above, but ary bypass in the course of repeat CABG su  
"in the course of CABG surgery."

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? \_\_\_ Yes (Continue with questions)  No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

Neonates (Birth-1month)  Infants (1month-2yrs)  Children (2-12yrs)  Adolescents(12-16yrs)

- 1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
- 2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
- 3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.
  - a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
  - b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
  - c. The applicant has committed to doing such studies as will be required.
    - (1) Studies are ongoing,
    - (2) Protocols were submitted and approved.
    - (3) Protocols were submitted and are under review.
    - (4) If no protocol has been submitted, attach memo describing status of discussions.
  - d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
- 4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed. See attached memo.
- 5. PEDIATRIC LABELING MAY NOT BE ADEQUATE.
  - a. Pediatric studies are needed.
  - b. Pediatric studies may not be needed but a pediatric supplement is needed.
- 6. If none of the above apply, attach an explanation, as necessary.

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ON ORIGINAL

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? \_\_\_ Yes  No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/ Pm  
Signature of Preparer and Title

8/25/98  
Date

cc: Orig NDA/PLA/PMA # NDA 20-304/S-004  
HF D-180 Div File  
NDA/PLA Action Package  
HFD-006/ KRoberts (include labeling for all NME approvals; either draft or final)

(revised 9/15/97)

Dubeau

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 25, 1998  
FROM: Julieann DuBeau, Regulatory Health Project Manager  
SUBJECT: Pediatric Use of Trasylol® (aprotinin) Injection  
TO: NDA 20-304/S-004

IS/ 8/25/98

Pediatric studies are not needed with Trasylol® (aprotinin) Injection for prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft (CABG) surgery since there is little potential use of Trasylol® (aprotinin) Injection in pediatric patients for this indication.

APPEARS THIS WAY  
ON ORIGINAL

cc:  
Original NDA 20-304/S-004  
HFD-180/Div. files  
HFD-180/DuBeau  
r/d Init: Talarico 8/25/98  
JD/August 24, 1998 (drafted)  
JD/8/25/98/c:\mydocs\20304808-1mjd.doc

IS/

8-25-98

December 10, 1996

**Pharmaceutical  
Division**

Bayer Corporation  
400 Morgan Lane  
West Haven, CT 06516-4175

Stephen B. Fredd, M.D., Director  
Division of Gastrointestinal and  
Coagulation Drug Products  
Office of Drug Evaluation III (HFD-180)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
**ATTN: DOCUMENT CONTROL ROOM 6B-45**  
5600 Fishers Lane  
Rockville, MD 20857

**RE: Trasylo<sup>®</sup> (aprotinin injection)  
NDA #20-304  
Debarment Statement**

**APPEARS THIS WAY  
ON ORIGINAL**

Dear Dr. Fredd:

Bayer Corporation, formerly Miles Inc., certifies that it did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306(a) or (b)], in connection with NDA #20-304.

If you have any questions regarding this information, please contact Maureen Garvey, Ph.D. at (203) 812-5145.

Sincerely,



Carl E. Calcagni, R.Ph.  
Vice President, Regulatory Affairs

CEC:pc

**APPEARS THIS WAY  
ON ORIGINAL**