CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020164/S010

CORRESPONDENCE

NDA 20-164/S-010

MAR 21 1997

Rhone-Poulenc Rorer Pharmaceuticals Inc.
Attention: Thomas E. Donnelly, Jr., Ph.D.
500 Arcola Road
P.O. Box 5096
Collegeville, PA 19426-0800

Dear Dr. Donnelly:

Please refer to your supplemental new drug application dated March 29, 1996, received April 1, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium) Injection.

We acknowledge receipt of your submissions dated May 17, June 11 and 24, 1996, and March 7, 1997. The User Fee goal date for this application is April 1, 1997.

The supplemental application provides for a proposed new indication: Lovenox Injection is indicated during and following hospitalization for the prevention of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing hip replacement surgery.

We have completed the review of this supplemental application with draft labeling submitted March 29, 1996, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit draft labeling with revisions to the currently approved labeling as follows:

1. Incorporate the changes approved on January 30, 1996 and January 27 and March 7, 1997 in supplements 005, 014, and 007 respectively.

2. In the CLINICAL TRIALS section:

   a. Delete the proposed section titled "Long Term Prevention Following Hip Replacement Surgery."

   b. After the table and text for the "Efficacy of Lovenox in Hip Replacement Surgery," insert information regarding the "Extended Prophylaxis in Hip Replacement Surgery."

c. The specific text in the "Extended Prophylaxis" subsection should read: "In a study of extended prophylaxis for patients undergoing hip replacement surgery, patients were treated, while hospitalized, with enoxaparin for the prevention of post-operative deep vein thrombosis. All patients underwent bilateral venography. In a double-blind design, those patients with no venous thromboembolic disease were randomized to a post-discharge regimen of either enoxaparin 40 mg (n = 90) once daily sc or to placebo (n = 89) for 3 weeks. In this population of patients, the incidence of deep vein thrombosis during extended prophylaxis was significantly lower for enoxaparin compared to placebo."

d. Following the text describing the study, insert a chart of the study results.

e. After the chart, insert the following text: "In a second study, patients undergoing hip replacement surgery were treated, while hospitalized, with enoxaparin. All patients were examined for clinical signs and symptoms of venous thromboembolic disease. In a double-blind design, patients without clinical signs and symptoms of venous thromboembolic disease were randomized to a post-discharge regimen of either enoxaparin 40 mg once daily sc or to placebo for 3 weeks, with results similar to the first study."

3. In the INDICATIONS AND USAGE section:

a. Retain the wording "Lovenox Injection is indicated for prevention of deep vein thrombosis, which may lead to pulmonary embolism: in patients undergoing knee replacement surgery."

b. Delete all the information regarding the hip replacement indication and replace with the words: "in patients undergoing hip replacement surgery, during and following hospitalization (see DOSAGE AND ADMINISTRATION)."

4. In the WARNINGS section, the "Thrombocytopenia" subsection, revise the section to include the findings regarding thrombocytopenia in patients receiving Lovenox for extended prophylaxis in hip replacement surgery.

5. In the ADVERSE REACTIONS section:

   a. In the "Hemorrhage" subsection:

      (1) Retain the approved table title "Major Bleeding Episodes*" and delete the subsection titles "Hip/Knee Replacement Surgery*" and "Long Term Prevention (LTP)".

      (2) In the left column of the table, between "Hip Replacement Surgery" and "Knee Replacement Surgery," insert "Hip Replacement Surgery, Extended Prophylaxis" and provide the relevant data in the body of the table.

   b. In the "Thrombocytopenia" subsection, delete the words "see WARNINGS: Thrombocytopenia" and replace with the approved descriptive text, with revisions as stated in 4.

   c. In the "Other" subsection:

      (1) Delete the descriptive text and replace with the following: "Other adverse effects that were thought to be possibly or probably related to treatment with Lovenox Injection, heparin or placebo in clinical trials with patients undergoing hip replacement surgery during and following hospitalization and knee replacement surgery, and that occurred at a rate of at least 2% in the enoxaparin group, are shown below."

      (2) Delete the title of the table, "Adverse Events Occurring at ≥ 2% Incidence in Enoxaparin Treated Patents* Undergoing Hip or Knee Replacement Surgery," and retain the approved title of the table, "Adverse Events Occurring at ≥ 2% Incidence in Enoxaparin Treated Patents*".

      (3) Add the subheading "Enoxaparin 40 mg" and add the clinical trials data for patients undergoing hip replacement surgery and receiving enoxaparin following hospitalization in the table.

6. In the DOSAGE AND ADMINISTRATION section:

   a. In the "Adult Dosage" subsection:

(1) Delete the sub-subsection "*Long Term Prevention Following Hip Replacement Surgery*".

(2) In the "*Hip or Knee Replacement Surgery*" sub-subsection, after the sentence, "The average duration of administration is 7 to 10 days," add the following sentences: "For hip replacement surgery, a dose of 40 mg once daily subcutaneously, given within 12 hours prior to surgery, may be considered. Continued therapy with Lovenox Injection 40 mg once daily administered by subcutaneous injection for 3 weeks following the initial therapy is recommended."

b. In the "Administration" subsection, delete the following sentence: "An automatic injection device (TRADENAME) is available for use with Lovenox syringes."

In addition, we note that supplement 008, submitted December 27, 1995, which provides for enoxaparin sodium in a new 40 mg pre-filled syringe, should be approved prior to the approval of supplement 010, which includes a 40 mg dosing regimen during and following hospitalization for the prevention of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing hip replacement surgery.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

1. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs now will certainly facilitate review.

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings, if any.

4. Summarize worldwide experience on the safety of this drug.

5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

This change may not be implemented until you have been notified in writing that this supplemental application is approved.

If you have any questions, please contact Karen Oliver, Regulatory Health Project Manager, at (301) 443-0487.

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Original NDA 20-164/S-010
HFD-180/Div. Files
HFD-002/ORM
HFD-103/Office Director
HFD-101/L.Carter
HFD-92/DDM-DIAB
HFD-40/DDMAC (with draft labeling)
DISTRICT OFFICE
HFD-180/K.Oliver
HFD-180/S.Fredd
HFD-180/N.Markovic
HFD-180/L.Talarico
HFD-180/E.Duffy
HFD-180/J.Sieczkowski
HFD-720/M.Huque
HFD-720/Rahid
HFD-160/P.Cooney
HFD-160/B.Urtani
HFD-560/OTC (with labeling - for OTC Drug Products Only)

Drafted by: KO/March 14, 1997 /S/
Initialed by: S.Fredd 03/21/97
Final: KO/03/21/97/c:\wpwin\karenfil\20164307.4ko 03/21/97

APPROVABLE (AE) /S/ 3/21/97

DEPARTMENT OF HEALTH & HUMAN SERVICES

Oliver

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-164

Rhone-Poulenc Rorer Pharmaceuticals Inc.
Attention: Thomas E. Donnelly, Jr., Ph.D.
500 Arcola Road
P.O. Box 5096
Collegeville, PA 19426

JAN 14 1998

Dear Dr. Donnelly:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium) Injection.

We also refer to the January 9, 1998, meeting between FDA and manufacturers of low molecular weight heparins and heparinoids approved in the U.S., Rhone-Poulenc Rorer, Pharmacia & Upjohn, Wyeth Laboratories, and Organon. The purpose of the meeting was to discuss the Agency's request, forwarded separately to each company in a letter dated December 11, 1997, for revisions to the labeling for low molecular weight heparins and heparinoids to warn health care practitioners of the potential for spinal/epidural hematomas with concurrent use of these drugs and spinal/epidural anesthesia or spinal puncture. This request was made in response to over 30 recent post marketing reports of patients who have developed epidural or spinal hematomas, some resulting in long-term or permanent paralysis, with the concurrent use of a low molecular weight heparin and spinal/epidural anesthesia or spinal puncture. Although the postmarketing reports received by the agency involved patients who were treated with Lovenox (enoxaparin sodium) Injection, the adverse event would be expected to occur if drugs with similar pharmacological activity were used in the same manner.

Subsequent to the January 9, 1998 meeting, a request to revise the agreements reached in the meeting was received from Dr. Thomas Donnelly of Rhone-Poulenc Rorer in a telephone call on January 13, 1998, with Bronwyn Collier, Associate Director, Office of Drug Evaluation III. Dr. Donnelly stated that he represented Rhone-Poulenc Rorer, Pharmacia & Upjohn, Wyeth Laboratories, and Organon. The specific request was to revert back to the original wording of the boxed warning and the WARNINGS section, "Hemorrhage" subsection, specified in the Agency's December 11, 1997 letters.

The nature of the adverse events is serious and there should be no further delay in implementing the labeling revisions and carrying out the agreements reached in the January 9, 1998, meeting. Accordingly, we are documenting, with this letter, the agreements and our conclusions regarding your request for further consideration of the wording for the boxed warning and PRECAUTIONS section, "Hemorrhage" subsection, of the labeling. In future interactions between industry representatives and FDA, the Agency expects that industry representatives be empowered to make binding decisions.

At the January 9, 1998, meeting the following agreements were reached by all attendees:

1. Regarding the boxed warning, the words "low molecular weight heparins or heparinoids" will be replaced with the individual product name and the word "greater" will be inserted in the first sentence before "risk". The boxed warning is reproduced below with the deleted words indicated by a line through them and added words by shading:

SPINAL/EPIDURAL HEMATOMAS

When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with Trade name (established name) dosage form for prevention of thromboembolic complications are at greater risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurologic compromise is noted, urgent treatment is necessary.

The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (see also WARNINGS, Hemorrhage and PRECAUTIONS, Drug Interactions).

2. Regarding the added wording for the PRECAUTIONS section, "Laboratory Tests" subsection, the examples of routine coagulation tests will be limited to Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT). The text with the deleted words indicated by a line through them and added words indicated with shading is reproduced below:

When administered at recommended prophylaxis doses, routing coagulation tests such as (Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT)) are relatively insensitive measures of *Trade name* activity and, therefore, unsuitable for monitoring.

3. Regarding the added wording for the WARNINGS section, "Hemorrhage" subsection (to be inserted as the second paragraph), the words "low molecular weight heparins or heparinoids" will be replaced with the individual product name and the word "concurrent" will be replaced with "associated". The added bolded paragraph with the deleted words indicated by a line through them and added words by shading is reproduced below:

Spinal or epidural hematomas can occur with the associated use of ; Trade name and neuraxial (spinal/epidural) anesthesia or spinal puncture which can result in long-term paralysis. The risk of these events is higher with the use of post-operative indwelling epidural catheters or concomitant use of additional drugs affecting hemostasis such as NSAIDs (see boxed WARNING).

4. The requested labeling revisions with the changes specified above will be instituted as soon as possible.

5. Regarding the "Dear Doctor" letter also requested in the Agency's December 11, 1997 letter:

   a. The Health Advisory on the potential for spinal or epidural hematomas associated with the concurrent use of low molecular weight heparins or heparinoids and spinal/epidural anesthesia or spinal puncture issued by FDA on December 15, 1997 may be substituted for an individual or joint "Dear Doctor" letter. No alterations to the Health Advisory are permissible.

   b. Plans and any drafts for the "Dear Doctor" letter, or individual mailing of the FDA Health Advisory will be submitted to the agency by Rhone-Poulenc Rorer,

   c. Individual mailing of the "Dear Doctor" letter or FDA Health Advisory will target anesthesiologists, nurse anesthetists, general surgeons, orthopedic surgeons, hospital nurses, hospital pharmacists, pain management specialists, hematologists, obstetricians/gynecologists, emergency room physicians, neurosurgeons, family practitioners, critical care specialists, and neurologists.

6. Promotional materials will incorporate the information from the boxed warning concerning the potential for spinal or epidural hematomas associated with the concurrent use of low molecular weight heparins or heparinoids and spinal/epidural anesthesia or spinal puncture within 30 days of receipt of the December 29, 1997, letter from the

Division of Drug Marketing, Advertising, and Communications (DDMAC). Exceptions for use of materials without this information will be negotiated between the individual company and DDMAC prior to use.

7. Regarding the February 5, 1998, meeting of the Anesthetic and Life Support Drugs Advisory Committee, the following topics will be addressed:

   a. Adequacy of the boxed warning versus a labeled contraindication for concurrent use of low molecular weight heparin and heparinoid drugs with spinal/epidural anesthesia or spinal puncture.

   b. Whether the class warning should be extended to other anticoagulants, such as warfarin sodium and heparin sodium.

   c. Additional use information that may be appropriate for labeling.

   NDA holders for heparin sodium, heparin calcium, and warfarin sodium will be invited to address the committee, in the public forum session, on the possible extension of the class warning to their drugs.

   Total scheduled time for presentation(s) from Rhone-Poulenc Rorer will be approximately equal to presentation time allotted to the Agency and our expert consultants. The Agency and expert consultant presentations will cover the pharmacology of low molecular weight heparins and heparinoids, clinical use of these drugs, surgical practices associated with the use of spinal catheters.

8. Following implementation of the labeling changes, each company will submit monthly periodic adverse drug experience reports of spinal or epidural hematomas, with a cumulative summary.

After carefully considering your request, FDA does not object to reverting to the wording for the boxed warning and the WARNINGS section, "Hemorrhage" subsection, exactly as stated in the Agency's December 11, 1997 letters except that in the WARNINGS section, "Hemorrhage" subsection, the word "concurrent" should be replaced with "associated" (refer to item #3 above). The wording for these sections discussed at the January 9, 1998, meeting is no longer an alternative. This decision affects only the wording of the boxed warning and WARNINGS section, "Hemorrhage" subsection. The balance of the agreements or any other requests made in the Agency's December 11, 1997, letters are not altered.

We respectfully request that you submit to the Agency, within 24 hours, your written agreement to 1) institute the labeling changes as described above within 5 business days, 2) issue an individual mailing of a "Dear Doctor" letter to notify health care practitioners of the potential for spinal or epidural hematomas associated with the use of low molecular weight heparins or heparinoids and spinal/epidural anesthesia or spinal puncture, or, the December 15, 1997 FDA Health Advisory, by January 20, 1998, and 3) incorporate the information from the boxed warning into promotional materials within 30 days of receipt of the December 29, 1997, letter from DDMAC. Exceptions for use of materials without this information will be negotiated between the individual company and DDMAC prior to use. If you elect to issue the FDA Health Advisory in lieu of a "Dear Doctor" letter it will be issued in the same manner as a "Dear Doctor" letter as described under 21 CFR 200.5(c)(1) bearing on the envelope the legend "IMPORTANT DRUG WARNING" in red. The individual mailing will include anesthesiologists, nurse anesthetists, general surgeons, orthopedic surgeons, hospital nurses, hospital pharmacists, pain management specialists, hematologists, obstetricians/gynecologists, emergency room physicians, neurosurgeons, family practitioners, critical care specialists, and neurologists. The individual mailing may be undertaken by each manufacturer separately, or, in collaboration with the other manufacturers.

Please be informed that this letter serves as documentation of the agreements reached at the January 9, 1998, meeting. A list of attendees and meeting logistics is attached.

Should additional information become available concerning the use of low molecular weight heparins and heparinoids, further changes to the labeling may be necessary.

If you have any questions, please contact Karen Oliver, Project Manager, at (301) 443-0487.

Sincerely yours,

/S/ 1/14/98

APPEARS THIS WAY
ON ORIGINAL

Paula Botstein, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 20-164
HFD-180/Div. Files
HFD-180/CSO/K.Oliver
L.Talarico
N.Markovic
K.Sizer
HFD-103/P.Botstein
B.Collier
HFD-002/ORM/M.Lumpkin
HFD-40/DDMAC/N.Drezin
S.Sherman
T.Abrams

Drafted by: B.Collier & K.Oliver /January 14, 1998
Initialed by: P.Botstein 1/14/98
L.Talarico 1/14/98
S.Sherman 1/14/98
final: KO/01/14/98/c:\wpwin\karenfil\misc\20164801.0ko /S/ 01/14/98

GENERAL CORRESPONDENCE

ATTACHMENT

Meeting Date: January 9, 1998
Time: 12:30pm-2:00pm
Location: 13B-45 Conference Room, Parklawn Building

Applications: Fragmin® (dalteparin sodium injection); NDA 20-287
Lovenox® (enoxaparin sodium) Injection; NDA 20-164
Normiflo® (ardeparin sodium) Injection; NDA 20-227
Orgaran™ (danaparoid sodium) Injection; NDA 20-430

Type of Meeting: Discussion of Labeling Revisions with Industry Representatives

Meeting Chair: Paula Botstein, Acting Division Director, ODE III

Meeting Recorder: Karen Oliver, Regulatory Health Project Manager

FDA Attendees, titles, and Office/Division:

Office of Review Management, HFD-002

M Lumpkin, M.D., Deputy Center Director, Review Management

Office of Drug Evaluation III, HFD-103

P. Botstein, M.D., Acting Director
B. Collier, Special Associate Director for Regulatory Affairs

Division of Gastrointestinal and Coagulation Drug Products

L. Talarico, M.D., Division Director
K. Sizer, M.D., Medical Reviewer
N. Markovic, M.D., Medical Reviewer
K. Oliver, Regulatory Health Project Manager

Division of Drug Marketing, Marketing, and Communications HFD-40

N. Drezin, R.Ph, J.D., Deputy Director
T. Abrams, R.Ph., MBA, Branch Chief
S. Sherman, Regulatory Review Officer

External Constituent Attendees and titles:

Pharmacia & Upjohn

K. King. Ph.D., Vice President Global Regulatory Affairs
J. Luderer, M.D., Vice President US Clinical Development

Rhone-Poulenc Rorer Pharmaceuticals Inc.

J. Rush, M.D., Vice President Clinical Research/Cardiology
T. Donnelly, Jr., Ph.D., Senior Director Worldwide Regulatory Affairs
C. Brown, M.D., Associate Director of Drug Product Safety

Wyeth-Ayerst Laboratories

D. Mitrione, Director US Regulatory Affairs
D. Humphrey, M.D., Director Clinical Affairs, Medical Affairs Department

Organon Inc.

A. Mayo, Director Regulatory Affairs
H. Magnani, M.D., Head Clinical Development, Atherothromobotic Drugs

Background:

On December 11, 1997, the Agency issues a letter requesting that the manufacturers of the low molecular weight heparins and heparinoids to revise their package inserts and issue a Dear Doctor letter in regards to the risk of epidural/spinal anesthesia and concurrent use of low molecular weight heparins and heparinoids.

Discussion Topics:

1. Proposed package insert labeling changes including the boxed warning and the WARNINGS and PRECAUTIONS sections.

2. Proposed Dear Doctor letter.

3. Promotional materials.

4. Anesthetics and Life Support Drugs Advisory Committee scheduled 02/05/98.

Clear

NDA 20-164/S-010

JUL 14 1997

Rhone-Poulenc Rorer Pharmaceuticals Inc.
Attention: Thomas E. Donnelly, Jr. Ph.D.
500 Arcola Road
P.O. Box 5096
Collegeville, PA 19426-0800

Dear Dr. Donnelly:

We acknowledge receipt on July 9, 1997 of your July 8, 1997 amendment to your supplemental new drug application (NDA) for Lovenox® (enoxaparin sodium) Injection.

This amendment contains additional Chemistry, Manufacturing and Controls information and draft labeling submitted in response to our March 21, 1997 approvable letter.

We consider this a major amendment under 21 CFR 314.60 of the regulations and it constitutes a full response to our letter. Therefore, the due date under the Prescription Drug User Fee Act of 1992 (PDUFA) is January 9, 1998.

If you have any questions, please contact me at (301) 443-0487.

Sincerely yours,

Karen Oliver
Regulatory Health Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-164/S-010
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/L.Talarico
HFD-180/N.Markovic
HFD-180/E.Duffy
HFD-180/J.Sieczkowski

DISTRICT OFFICE

/S/ 07/11/97

Drafted by: KO/July 11, 1997
Final: KO/07/11/97/c:\wpwin\karenfil\nda\20164707.0ko

ACKNOWLEDGEMENT (AC)

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APR -5

NDA 20-164/S-010

Rhone-Poulenc Rorer Pharmaceuticals Inc.
Attention: Thomas E. Donnelly, Jr., Ph.D.
P.O. Box 5096
500 Arcola Road
Collegeville, PA 19426-0800

Dear Dr. Donnelly:

We acknowledge receipt of your supplemental application for the following:

Name of Drug Product: Lovenox (enoxaparin sodium) Injection

NDA Number: NDA 20-164

Supplement Number: S-010

Therapeutic Classification: Standard

Date of Supplement: March 29, 1996

Date of Receipt: April 1, 1996

This supplement provides for a proposed new indication: Lovenox Injection is indicated after hospital discharge for long-term prevention of deep vein thrombosis following hip replacement surgery.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 31, 1996 in accordance with 21 CFR 314.101(a).

All communications concerning this supplemental application should be addressed as follows:

Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation
Drug Products, HFD-180
Attention: DOCUMENT CONTROL ROOM, 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions, please contact me at (301) 443-0487.

Sincerely yours,

Karen Oliver
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-164/S-010
HFD-180/Div. Files
HFD-180/CSO/K.Oliver
HFD-180/S.Sieczkowski
HFD-180/L.Talarico
DISTRICT OFFICE

drafted: KO/April 3, 1996 /S/ 04/03/96
Final: KO/04/03/96/c:\wpwin\karenfil\nda\20164604.0ko

SUPPLEMENT ACKNOWLEDGEMENT