CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020164/S010

Trade Name: LOVENOX

Generic Name: ENOXAPARIN SODIUM INJECTION

Sponsor: RHONE-POULENC RORER PHARMACEUTICALS INC.

Approval Date: 01/30/98

INDICATION(s): PROVIDES FOR THE USE OF LOVENOX INJECTION DURING AND FOLLOWING HOSPITALIZATION FOR THE PREVENTION OF DEEP VEIN THROMBOSIS, WHICH MAY LEAD TO PULMONARY EMBOLISM, IN PATIENTS UNDERGOING HIP REPLACE SURGERY

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APPLICATION: 020164/S010

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Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI	X			
Pharmacology Review(s)				X
Statistical Review(s)	X			
Microbiology Review(s)	X			
Clinical Pharmacology Biopharmaceutics Review(s)				X
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Application Number: 020164/S010

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-164/S-010

Rhone-Poulenc Rorer Pharmaceuticals Inc.
Attention: Thomas E. Donnelly, Jr., Ph.D.
500 Arcola Road
P.O. Box 5096
Collegeville, PA 19426-0107

JAN 30 1998

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, March 7, May 23 and 28, July 8, 22, 23, August 14 and 15, October 16, December 16, 1997, and January 19 and 27, 1998. The User Fee goal date for this application is July 20, 1998.

The supplemental application provides for the use of Lovenox Injection during and following hospitalization for the prevention of deep vein thrombosis, which may lead to pulmonary embolism, in patient undergoing hip replacement surgery.

Further, the supplement provides for revisions to the labeling to warn health care practioners of the potential for spinal/epidural hematomas with concurrent use of Lovenox Injection and spinal/epidural anesthesia or spinal puncture. These revisions were in response to Agency letters dated December 11, 1997 and January 14, 1998 issued to all manufacturers of low molecular weight heparins and heparinoids. Specifically, the Agency requested the addition of a boxed warning to the package insert and revisions to the PRECAUTIONS section, the "Laboratory Tests" subsection, and the WARNINGS section, the "Hemorrhage" subsection.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on January 19, 1998. Accordingly, the supplemental application is approved effective on the date of this letter.

We request that at the next printing of the package insert, you revise the tables to provide a consistent format throughout the text as follows: (1) in the CLINICAL TRIALS section, delete the current first column title "Dosing Regimen" and replace with the word "Indication" (2) in the CLINICAL TRIALS section, delete the second and third column title "Treatment Group" and replace with the words "Dosing Regimen"; (3) in the ADVERSE REACTIONS

section, insert the word "Indication" in the "title" section of the first column in the table titled "Major Bleeding Episodes in Abdominal & Colorectal Surgery"; (4) in the ADVERSE REACTIONS section, insert the title "Dosing Regimen" above the appropriate columns in all the tables; and (5) throughout the text, provide horizontal and vertical line "grids" similar to the grids in the table titled "Major Bleeding Episodes in Hip or Knee Replacement Surgery" in the ADVERSE REACTIONS section.

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

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely yours,

/S/

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

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020164/S010

APPROVABLE LETTER

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NDA 20-164/S-010

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

DEC 11 1997

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, May 23 and 28, July 8, 22, 23, August 14 and 15, and October 16, 1997. The User Fee goal date for this application is January 9, 1998.

The supplemental application provides for the use of Lovenox Injection 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 as submitted with draft labeling, and it is approvable. Before this supplement may be approved, however, it will be necessary for you to submit final printed labeling (FPL). The labeling should be identical in content to the draft labeling submitted on October 16, 1997 with the following revisions:

1. In the CLINICAL TRIALS section:

   a. In the second table titled "Efficacy of Lovenox in Hip Replacement Surgery", reference the "**p value versus Lovenox 10 mg q.d.=0.0168" in the body of the table by a "**".

   b. For consistency throughout the section and throughout the package insert, tables should be formatted consistently, by containing or not containing a black box outline. In addition, grid lines should be added to all tables to enhance readability, clarity, and uniformity.

   c. In the "Extended Prophylaxis in Hip Replacement Surgery" subsection, in the paragraph beginning with the words "In a second study, patients undergoing...", in the last sentence of the paragraph, change "placebo 35" to "placebo 45" to read: "...(enoxaparin 21 [16%] versus placebo 45 [34%]; p =0.001) and ..."

d. In the "Abdominal Surgery" subsection, reinstate the words "once daily" and use it consistently throughout the package insert text.

2. In the ADVERSE REACTIONS section, the "Hemorrhage" subsection, the "Major Bleeding Episodes in Hip or Knee Replacement Surgery" table, in the first column, delete the column headings and replace with the following: "Hip Replacement Surgery Without Extended Prophylaxis**" and "Hip Replacement Surgery With Extended Prophylaxis***" and provide appropriate information for the column headings. In the footnotes for the asterisks, state all the dosing regimens used in the clinical trials.

3. The Agency has received more than 30 spontaneous safety reports describing patients who have developed epidural or spinal hematomas with the concurrent use of Lovenox® Injection and spinal/epidural anesthesia or spinal puncture. Many of the hematomas caused neurologic injury, including long-term or permanent paralysis. The Agency is asking all manufacturers of low molecular weight heparins and heparinoids to revise their package inserts to provide further information for the safe and effective use of these drugs. Therefore, please revise the package insert as follows:

a. Insert the following boxed warning at the beginning of the package insert:

> SPINAL/EPIDURAL HEMATOMAS
>
> When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at 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).

b. In the PRECAUTIONS section, the "Laboratory Tests" subsection, insert the following information: "When administered at recommended prophylaxis doses, routine coagulation tests (e.g. Prothrombin Time [PT], Activated Partial Thromboplastin Time [APTT], Kaolin Cephalin Clotting Time [KCCT], Whole Blood Clotting Time [WBCT], and Thrombin Time [TT]) are relatively insensitive measures of Lovenox activity and, therefore, unsuitable for monitoring."

c. In the WARNINGS section, "Neuraxial Anesthesia" subsection:

(1) Delete the subsection title "Neuraxial Anesthesia" and the information contained within the subsection.

(2) In the "Hemorrhage" subsection, insert the following information in bolded type: **"Cases of epidural or spinal hematomas have been reported with the concurrent use of enoxaparin and spinal/epidural anesthesia or spinal puncture resulting in long-term or permanent paralysis. The risk of these events is higher with the use of post-operative indwelling epidural catheters or by the concomitant use of additional drugs affecting hemostasis such as NSAIDs (see boxed WARNING; ADVERSE REACTIONS, Ongoing Safety Surveillance; and PRECAUTIONS, Drug Interactions)."**

d. In the ADVERSE REACTIONS section, revise and bold the "Ongoing Safety Surveillance" subsection to read:

"Ongoing Safety Surveillance: Since 1993, there have been more than 30 reports of epidural or spinal hematoma formation with concurrent use of enoxaparin and spinal/epidural anesthesia or spinal puncture. The majority of patients had a post-operative indwelling epidural catheter placed for analgesia or received additional drugs affecting hemostasis such as NSAIDs. Many of the epidural or spinal hematomas caused neurologic injury, including long-term or permanent paralysis. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made."

e. In the DOSAGE AND ADMINISTRATION, the "Adult Dosage" subsection, delete the second sentence of the second paragraph "There is usually no need..." and replace with the following sentence: "Since coagulation parameters are unsuitable for monitoring Lovenox activity, routine monitoring of coagulation parameters is not required (see PRECAUTIONS, "Laboratory Tests").

In addition, all previous revisions as reflected in the most recently approved package inserts must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Please submit twenty copies of the printed labeling, ten of which are individually mounted on heavy-weight paper or similar material.

Further, due to the serious nature of the adverse events, we are requesting that all manufacturers of approved low molecular weight heparins and heparinoids issue a "Dear Doctor" letter immediately to inform health professionals of these important labeling changes. The letter distribution should include at least anesthesiologists, nurse anesthetists, general surgeons, orthopedic surgeons, nurses, pharmacists, pain management specialists, and hematologists. Enclosed is our recommendation for the wording of this letter. The "Dear Doctor" letter may be issued by each manufacturer separately, or, if you wish to collaborate with the other manufacturers, one letter could be issued jointly. Agency concurrence with the content of the "Dear Doctor" letter is requested prior to issuance of the letter.

Again, due to the seriousness of the risk of spinal or epidural hematoma formation following concurrent use of Lovenox and spinal/epidural anesthesia or spinal puncture, the labeling changes should be implemented as soon as possible. If you anticipate a delay in responding to the portion of the letter pertaining to S-010, you may submit the labeling changes specified under item #3 separately as a "Special Supplement - Changes Being Effected" under 21 CFR 314.70(c).

Following implementation of the above labeling changes, we request under 21 CFR 314.80(c)(2), that you submit monthly periodic adverse drug experience reports of spinal or epidural hematomas, with a cumulative summary. The FDA will continue to closely monitor post marketing reports for these events.

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 Project Manager, at (301) 443-0487.

Sincerely yours,

/S/ 12-11-97

Lilia Talarico, 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/L.Talarico
HFD-180/N.Markovic
HFD-103/P.Botstein
HFD-103/B.Collier
HFD-733/D.Wysowski
HFD-44/N.Drezen
HFD-44/S.Sherman
HFI-20/S.Cruzan
HFI-20/J.Brodsky
HFY-1/C.Kimbrough
HFY-1/J.Fourcroy
HFD-344/A.Burnett
HFD-002/M.Lumpkin
HFD-200/L.Rose
HFD-560/OTC

Drafted by: KO/December 3, 1997
Initialed by: L.Talarico 12/03/97
Initialed by: P.Botstein `12/03/97
Final: KO/12/11/97/c:\wpwin\karenm\nda\20164712.0ko

/S/ 12/11/97

APPROVABLE (AE)