

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020164, S015

Trade Name: LOVENOX INJECTION

Generic Name: ENOXAPARIN SODIUM

**Sponsor: RHONE-POULENC RORER
PHARMACEUTICAL, INC.**

Approval Date: 12/31/98

INDICATION(s): (1) THE INPATIENT TREATMENT OF ACUTE DEEP VEIN THROMBOSIS WITH AND WITHOUT PULMONARY EMBOLISM, WHEN ADMINISTERED IN CONJUNCTION WITH WARFARIN SODIUM, AND (2) THE OUTPATIENT TREATMENT OF ACUTE DEEP VEIN THROMBOSIS WITHOUT PULMONARY EMBOLISM WHEN ADMINISTERED IN CONJUNCTION WITH WARFARIN SODIUM.

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APPLICATION: 020164, S015

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020164, S015

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 20-164/S-015

Food and Drug Administration
Rockville MD 20857

Rhone-Poulenc Rorer Pharmaceuticals Inc.
Attention: Mr. Robert W. Babilon
500 Arcola Road
P.O. Box 5096
Collegeville, PA 19426-0800

DEC 31 1998

Dear Mr. Babilon:

Please refer to your supplemental new drug application dated February 28, 1997, received February 28, 1997, 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 February 28, March 5, 14, and 26, May 7 and 16, June 17 and 18, July 10, and October 8 and 23, 1997, and February 10, May 19 and 28, June 12 and 23, July 6, September 24, and October 8, 1998.

This supplemental new drug application provides for the use of Lovenox® (enoxaparin sodium) Injection for: (1) the inpatient treatment of acute deep vein thrombosis with and without pulmonary embolism, when administered in conjunction with warfarin sodium; and (2) the outpatient treatment of acute deep vein thrombosis without pulmonary embolism when administered in conjunction with warfarin sodium.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and submitted draft labeling (immediate container and carton labels submitted May 19, 1998). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Since there are currently two approved package inserts for Lovenox Injection (printed in Mason Alfort and Dagenham), please submit the appropriate number of copies of each of the package inserts. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-164/S-015." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your facsimile dated December 29, 1998. These commitments, along with any completion dates agreed upon, are listed below.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

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.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is 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 20857

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, contact Karen Oliver, Regulatory Health Project Manager,
at (301) 827-7310.

Sincerely,

LT

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

Enclosure: package insert labeling text

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER : 020164, S015

APPROVABLE LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-164/S-015

FEB 27 1998

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 February 28, 1997, received February 28, 1997, 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 February 28, March 5, 14, and 26, May 7 and 16, June 17 and 18, July 10, August 14, and October 8, 9, and 23, 1997, and February 10, 1998. The User Fee goal date for this application is February 28, 1998.

The supplemental application provides for: the inpatient treatment of acute deep vein thrombosis with and without pulmonary embolism, when administered in conjunction with warfarin sodium; and the outpatient treatment of acute, symptomatic deep vein thrombosis without pulmonary embolism when administered in conjunction with warfarin sodium.

We have completed the review of this supplemental application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to note the following and provide the requested information:

Biopharmaceutics

1. In a July 24, 1997 letter, the Agency communicated to Rhone-Poulenc Rorer their concern regarding gender effect and gender and treatment interaction observed in RP54563Q-133. Possible approaches to further explore gender effect in anti-Xa derived parameters were considered and it is unclear whether these approaches were discussed with Rhone-Poulenc Rorer Pharmaceuticals. Therefore, the Agency

re-analyzed the submitted data using Type III MS from subject within sequence as the error term. The gender effect was no longer statistically significant. In future analyses, please use Type III MS from subject within sequence as the error term for evaluating gender effect.

2. During review of the Summary Table provided in your August 7, 1997 submission, several discrepancies between the information in the table and the printouts in the attachment were noted. In the table, it is stated that the p values are from the final model. However, based on the entry for "weight" and "Subject (gender*sequence)" in the Summary Table, this statement appears to be incorrect. Furthermore, the sequence effect appears to be inaccurately represented in the table. Based on the SAS printouts provided in the Attachment of the letter dated August 7, 1997 from Rhone-Poulenc Rorer Pharmaceuticals, the sequence effect is not significant for any one of the parameters that were tested.
3. Provide the supporting data and an assessment of the correlation between anti-Xa activity and enoxaparin doses covering the studied dose range (40-mg to 2 mg/kg for an average body-weight of 70 kg).
4. Provide ASCII data files on a disk for anti-Xa activity vs time (and pharmacokinetic parameters if available) from all subjects in RP54563Q-260 and RP54563Q-261 with the patient/subject demographics in the same file.
5. In response to your letter dated August 7, 1997, regarding the observation related to the CL/F values from RP54563Q-260, it is possible that the data from RP54563Q-260 are more variable compared to other studies. However, after reviewing the data, the Agency is not convinced that the differences observed in the mean CL/F values represent variability in the data or an overestimation of anti-Xa derived parameters. A review of enoxaparin sodium studies (100537, 100539, 100541, 100542, 105640, K9001006, and RP54563Q-133) has shown that the anti-Xa derived CL/F values may be lower after administration of high (1mg/kg or higher) enoxaparin sodium doses than the CL/F values obtained after administration of low enoxaparin sodium doses (such as 60 mg in RP54563Q-260).

6.

[REDACTED]

7. [REDACTED]

8. Provide an annotated, tabulated, comprehensive summary of anti-Xa derived pharmacokinetic parameters (grouped by gender) over the studied dose ranges. This table will be reviewed by the Agency for possible inclusion in the package insert.

In addition, it will be necessary for you to submit final printed labeling (FPL) identical in content to the package insert draft labeling submitted on February 10, 1998 and the immediate container label and carton draft labeling submitted on February 28, 1997 with the following revisions:

Package Insert

1. Throughout the text of the package insert:
 - a. Change the abbreviation [REDACTED] except for the initial time the word [REDACTED] is used in the CLINICAL PHARMACOLOGY section which should read: [REDACTED]
 - b. Delete the phrase [REDACTED] and replace with the word [REDACTED]
 - c. Revise all the tables to provide a consistent format throughout the text as requested in the January 30, 1998 approval letter for S-010.
 - d. Change the words [REDACTED] DRAFT LABELING [REDACTED] except when referencing the specific indication of prevention or treatment of post-operative DVT.
 - e. Delete the hyphen between time elements and replace with the word [REDACTED] DRAFT LABELING [REDACTED]
 - f. Change the abbreviation [REDACTED] DRAFT LABELING [REDACTED]
 - g. Change the abbreviation [REDACTED] DRAFT LABELING [REDACTED] DRAFT LABELING [REDACTED]

d. In the "Pharmacodynamics" subsection:

- (1) Provide the reference and information supporting the fifth sentence of the first paragraph related to clearance of enoxaparin including the enoxaparin sodium dose at which this estimate was obtained.
- (2) Provide the reference and the information supporting the first sentence of the second paragraph related to clearance and C_{max} derived from anti-Xa activity after single and multiple doses in elderly subjects and in subjects with renal impairment.
- (3) Provide the data and the method used for calculation of the AUC values that are indicated to be 25% higher on Day 10 compared to Day 1 in the third sentence of the second paragraph.
- (4) Provide the data that supports the third paragraph related to decline of total radioactivity and anti-Factor Xa activity.

4. In the CLINICAL TRIALS section:

- a. Provide the appropriate route of administration to the "dosing regimen" listed in the tables.
- b. Revise the "Hip or Knee Replacement Surgery" subsection as requested in the September 8, 1997 approvable letter for S-016.
- c. In the subsection titled "Treatment of Deep Vein Thrombosis and Pulmonary Embolism":
 - (1) Revise the following sentence in the descriptive paragraph of the first study to read:

DRAFT LABELING

- (2) Insert the word **DRAFT LABELING** in the sentence referencing [REDACTED].
- (3) Revise the descriptive paragraph of the second study to read:

DRAFT LABELING



- (4) The firm should be requested to revise the data table for the second study to be consistent with the table format requested in the January 30, 1998 approval letter for S-010.
5. Revise the **INDICATIONS AND USAGE** section to read:

Lovenox Injection is indicated for:

The prevention of deep vein thrombosis, which may lead to pulmonary embolism (**DOSAGE AND ADMINISTRATION: Adult Dosage**).

- in patients undergoing hip replacement surgery, during and following hospitalization;
- in patients undergoing knee replacement surgery;
- in patients undergoing abdominal surgery who are at risk for thromboembolic complications.

Patients at risk include patients who are over 40 years of age, obese, undergoing surgery under general anesthesia lasting longer than 30 minutes or who have additional risk factors such as malignancy or a history of deep vein thrombosis or pulmonary embolism.

Lovenox is also indicated for:

- The inpatient treatment of acute deep vein thrombosis with and without pulmonary embolism, when administered in conjunction with warfarin sodium (see DOSAGE AND ADMINISTRATION: Adult Dosage)
- The outpatient treatment of acute, symptomatic deep vein thrombosis without pulmonary embolism when administered in conjunction with warfarin sodium (DOSAGE AND ADMINISTRATION: Adult Dosage).

6. In the WARNINGS section:

a. DRAFT LABELING

DRAFT LABELING

b. In the "Thrombocytopenia" subsection:

(1) DRAFT LABELING

(2) Retain the first sentence of the subsection to read:

DRAFT LABELING

- (3) Retain the last paragraph of the subsection, with revisions, to read:

DRAFT LABELING

DRAFT LABELING

7. In the PRECAUTIONS section:

a. DRAFT LABELING

b. DRAFT LABELING

- c. In the "Carcinogenesis, Mutagenesis, Impairment of Fertility" subsection:

(1) DRAFT LABELING

- (2) Provide the re-calculation, including related formulas and all mathematical processes, for the maximum human dose in clinical trials.

d. DRAFT LABELING
DRAFT LABELING

8. In the ADVERSE REACTIONS section:

- a. Re-insert the word [REDACTED] in the first sentence of the "Hemorrhage" subsection to read:

DRAFT LABELING
DRAFT LABELING

- b. Delete the one large [REDACTED] tables that integrated all the major bleeding episodes for the various indications.

c. **DRAFT LABELING**

d. Re-format the table titled, "Deep Vein Thrombosis and Pulmonary Embolism Treatment", to be consistent with other tables.

(1) Reference all major bleeding criteria in the footnote of the table.

(2) Insert the word **DRAFT LABELING** in the sentence referencing **DRAFT LABELING**.

e. In the subsection titled "Elevations of Serum Aminotransferases":

(1) Re-insert the second paragraph in the subsection to read:

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(2) **DRAFT LABELING**

f. In the "Other" subsection:

(1) **DRAFT LABELING**

(2) The modification of the phrase **DRAFT LABELING**
DRAFT LABELING

9. Implement the changes requested in the September 8, 1997 approvable letter for S-016 in the OVERDOSAGE section, the "Symptoms/Treatment" subsection.

10. In the DOSAGE AND ADMINISTRATION section:

a. Delete the first paragraph and insert the following sentences to read:

DRAFT LABELING
DRAFT LABELING

b. In the "Adult Dosage" subsection:

(1) DRAFT LABELING
DRAFT LABELING

(2) Delete the sub-subsection titled DRAFT LABELING
and insert the following to read:

DRAFT LABELING

11. In the HOW SUPPLIED section, in the "How Supplied" table:
 - a. Delete the graduated prefilled syringe strength [REDACTED] and replace with [REDACTED]
 - b. Insert the title heading **DRAFT LABELING** [REDACTED]
12. After the HOW SUPPLIED section, delete the word [REDACTED] and replace with the word [REDACTED] in the following sentence to read:

DRAFT LABELING

Immediate Container Labels and Cartons

13. Provide the following information:
 - a. Indicate on unit package cartons where the lot number and the expiration date will be displayed.
 - b. Indicate the following on the syringe label:
 - (1) The orientation of the label information on the syringe barrel.
 - (2) Where the expiration date will be displayed.
 - (3) The graduation which will appear on the label (if any).

Please submit 20 copies of the final printed labeling, ten of which are individually mounted on heavy-weight paper or similar material. Since there are currently two approved package inserts for Lovenox Injection, (printed in Maison Alfort and Dagenham), please submit the appropriate number of copies of each of the package inserts. 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.

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,

/s/

/s/

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