Approval Package for:

APPLICATION NUMBER:
NDA 20-164/S-012

Name: Lovenox® (Enoxaparin Sodium) Injection

Sponsor: Rhone-Poulenc Rorer Pharmaceuticals

Approval Date: October 23, 1996
APPLICATION NUMBER:
NDA 20-164/S-012

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APPLICATION NUMBER:
NDA 20-164/S-012

APPROVAL LETTER
October 23, 1996

Rhone-Poulenc Rorer
Attention: Thomas E. Donnelly, Jr., Ph.D.
P.O. Box 1200
500 Arcola Road,
Collegeville, Pennsylvania 19426-0107

Dear Dr. Donnelly:

Please refer to your May 24, 1996 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium) Injection.

We also acknowledge receipt of your amendments dated June 20, and August 7, 1996.

The supplemental application provides for the addition of a new filling line for Lovenox® (enoxaparin sodium) Injection (30 mg/0.3 mL prefilled syringes) in the manufacturing facility at Rhone-Poulenc Rorer, Propharmaspecialities, Maisons-Alfort, 180, rue Jean Jaures, 94700 Maisons-Alfort, France.

We have completed the review of this supplemental application and it is approved.

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, (301) 443-0487.

Sincerely yours,

Eric P. Duffy, Ph.D.
Chemistry Team Leader
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
cc:
Original NDA 20-164/S-012
HFD-180/Division Files
DISTRICT OFFICE
HFD-180/CSO/KOliver
HFD-232
HFD-820/ONDC/Div Dir
HFD-180/JSieczkowski
R/D init: EDuffy/10-22-96
dob DRAFT 10-7-96/F/T 10-22-96/WP: c:\wpfiles\Chem\S\20164012.AJS

APPROVAL
APPLICATION NUMBER:
NDA 20-164/S-012

CHEMISTRY REVIEW
CHEMIST REVIEW: #1
1. Organization: HFD-180
2. NDA Number: 20-164
3. Name and Address of Applicant (City & State):
   Rhone-Poulenc Rorer
   Arcola Road, P. O. Box 1200
   Jegeville, PA 19426-0107
4. AF Number: OCT 23 1996
5. Supplement(s)
   Number(s): Dates(s):
   SCM-012 24 MAY 1996
   BC 20 JUN 1996
   BC 7 AUG 1996
6. Name of Drug:
   Lovenox® Injection
7. Nonproprietary Name:
   enoxaparin sodium
8. Supplement Provides for: the addition of a new filing line
   for Lovenox® (enoxaparin sodium) Injection (30 mg/0.3 mL prefilled
   syringes) in the manufacturing facility at Rhone-Poulenc Rorer,
   Propharma specialities, Maisons-Alfort, 180 rue Jean Jaures,
   94700 Maisons-Alfort, France.
9. Amendments and Other (Reports, etc.) Dates:
   Microbiologist's Review #1 dated 16 SEP 1996 by
   Brenda Uratani, Ph.D.
10. Pharmacological Category:
    Anticoagulant
11. How Dispensed:
    RX XX OTC ___
12. Related IND/NDA/DMF(s):
    SE 1-008
    SE 1-010
    SCM-011
13. Dosage Form:
    SVS (Parenteral)
14. Potency:
    100 mg/mL
15. Chemical Name and Structure: See The Merck Index, Twelfth
    Edition.
16. Records and Reports:
    Current
    _____ Yes _____ No
    Reviewed
    _____ Yes _____ No
17. Comments:
    See Review Notes
    cc: NDA 20-164
    HFD-180/Div/File
    HFD-181/CSO/KOlive
    HFD-180/SFredd
    HFD-180/JSieczkowski
    R/D init: E Duffy
    dob DRAFT 10-7-96/FT 10-22-96WP: c:\wpfiles\chem\S\20164012.1JS
    EDuffy 01/23/96

18. Conclusions and Recommendations: Based on the submitted CMC information, the Microbiologist's Review #1 and
    the acceptance by compliance (HFD-324) of the manufacturing facility at Maisons-Alfort, it is recommended that this
    supplement be approved. Rhone-Poulenc Rorer should be notified of the supplement approval via letter.
    (See attached APPROVAL letter.)

[Reviewer]

Signature: [Signature]
Date Completed: October 3, 1996
Redacted 2 page(s)
of trade secret and/or confidential commercial information from

CHEMISTRY REVIEW #1
A. Microbiologist's Review #1 recommends approval of the supplement for issues concerning microbiology.

B. EER for NDA 20-164/S-007 for both the Rhone-Poulenc Rorer Limited, Dagenham Essex, England and the Rhone-Poulenc Rorer Propharmaspecialites, Maisons-Alfort, France sites were noted by Compliance HFD-324 as "Acceptable" dated 10-1-96.

COMMENT:
Based on the information submitted in the Original Supplement and the Amendments, the information submitted for the CMC of Lovenox® Injection, the Microbiologist's Review #1, and the response by Compliance to the evaluation of the manufacturing facility as acceptable, it is recommended that the supplement be approved.
APPLICATION NUMBER:
NDA 20-164/S-012

MICROBIOLOGY REVIEW
A. 1. APPLICATION NUMBER:

20-164/S-008 and 20-164/S-010: Qualification of a 40 mg pre-filled syringe (Lovenox), the recommended dosage for the new indication of the prevention of deep vein thrombosis after hip replacement surgery.

20-164/S-011: Update specifications and analytical methods for Lovenox to harmonize methods worldwide.

20-164/S-012: Qualification for an additional filling line — in the manufacture of the approved 30 mg/0.3 ml Lovenox.

APPLICANT: Rhone-Poulenc Rorer Pharmaceuticals Inc.
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

2. PRODUCT NAMES: Lovenox (enoxaparin) injection pre-filled syringe

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:

Lovenox is available in prefilled syringes (10 mg enoxaparin sodium per 0.1 ml WFI, anti-Factor Xa activity is 1000 IU per every 10 mg of drug). The solution is preservative free and intended for use only as a single-dose injection.

Lovenox Injection is administered by subcutaneous injection. It must not be administered by intramuscular injection.

4. METHOD(S) OF STERILIZATION: ———

5. PHARMACOLOGICAL CATEGORY: Lovenox is indicated for prevention of deep vein thrombosis following hip replacement surgery.

B. 1. DATE OF INITIAL SUBMISSION:

NDA 20-164/S-008: December 27, 1996
NDA 20-164/S-010: March 29, 1996
NDA 20-164/S-011: April 15, 1996
NDA 20-164/S-012: May 24, 1996
2. **AMENDMENT:** None

3. **RELATED DOCUMENTS:** NDA 20-164

4. **ASSIGNED FOR REVIEW:** July 15, 1996

5. **DATE OF CONSULT REQUEST:**
   - NDA 20-164/S-008, S-010, S-011: July 10, 1996
   - NDA 20-164/S-012: July 5, 1996

C. **REMARKS:**

   Supplement S-008, S-010 and S-011 were submitted in response to the FDA Chemist’s request for additional information. With regard to microbiology issues, these supplements provide the alternate methods used in endotoxin determinations. The same validation data was provided for all three supplements, and they are the subject of this review.

   Supplement S-012 provides for an additional filling line —— | for use in the manufacture of the approved 30 mg/0.3 ml Lovenox.

D. **CONCLUSIONS:**

   The submissions are recommended for approval for issues concerning microbiology.

---

Brenda Uratani, Ph.D. 9/16/96

cc:

- NDA 20-164/S-008, S-010, S-011, S-012
- HFD-180/Div. File
- HFD-805/Uratani
- HFD-180/CSO/ K. Oliver
drafted by: Brenda Uratani, 9/16/96
R/D initialed by P.Cooney, 9/16/96
Redacted 4 page(s)
of trade secret and/or confidential commercial information from
APPLICATION NUMBER:
NDA 20-164/S-012

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
**REQUEST TYPE (Check One):**
- [ ] Final
- [ ] Follow-Up
- [ ] FUR

**DATE:** May 30, 1996

**PHONE NO.:** (301) 443-0487

**EER ID #**

**CHEMIST NAME:** Joseph Sieczkowski, Ph.D.

**DIVISION:** Gastrointestinal and Coagulation Drug Products

**MAIL CODE:** HFD-180

**APPLICATION AND SUPPLEMENT NUMBER:** NDA NDA 20-164/S-012

**BRAND NAME:** Lovenox Injection

**ESTABLISHED NAME:** Enoxaparin Sodium Injection

**DOSAGE STRENGTH:** 30 mg/0.3mL and 40 mg/0.4mL

**STERILE:**
- [ ] Yes
- [ ] No

**PROFILE CLASS:** SVS

**PRIORITY CLASSIFICATION (See SMG CDER-4820.3):** Standard

**APPLICANT'S NAME:** Rhone-Poulenc Rorer Pharmaceuticals Inc.

**ADDRESS:**
500 Arcola Road
Collegeville, PA 19426-0107

**COMMENTS:** Supplement provides for an additional filling line at the Maison-Alfort, France, site to manufacture Lovenox supplied as a 30 mg/0.3mL and a 40 mg/0.4mL pre-filled syringe containing a 100 mg/mL solution of enoxaparin sodium in Water for Injection. **USER FEE DUE DATE:** November 28, 1996. **NOTE:** Firm states filling line was inspected when filling line was inspected (4/25 to 5/3/96) due to

**FACILITIES TO BE EVALUATED**

(Name and Complete Address)  

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<th>RESPONSIBILITY</th>
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| 1. Rhone-Poulenc Rorer Propharm  
Maisons-Alfort  
180, rue Jean Jaures  
94700 Maisons-Alfort  
France  
Line will manufacture Lovenox as a 30mg/0.3mL and 40mg/0.4mL pre-filled syringe containing 100mg/mL solution of enoxaparin sodium in Water for Inj. | N/A | | |
| 2. | | | |
| 3. | | | |
| 4. | | | |

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**CGMP COMPLIANCE STATUS**

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NDA 20-164/S-012

Rhone-Poulenc Rorer Pharmaceuticals Inc.  MAY 3 | 1996
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-012

Therapeutic Classification:  Standard

Date of Supplement:  May 24, 1996

Date of Receipt:  May 28, 1996

This supplement provides for an additional filling line at the Maisons-Alfort, France, site to manufacture Lovenox Injection supplied as a 30 mg/0.3 mL and a 40 mg/0.4 mL pre-filled syringe containing a 100 mg/mL solution of enoxaparin sodium in Water for Injection.

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 July 27, 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-012
HFD-180/Div. Files
HFD-180/CSO/K.Oliver
HFD-180/J.Sieczkowski
HFD-180/L.Talarico
DISTRICT OFFICE

drafted: KO/May 30, 1996  K.Oliver 05/30/96
Final: KO/05/30/96/c:\wpwin\karenfil\nda\20164605.1ko

SUPPLEMENT ACKNOWLEDGEMENT
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