Approval Package for:

APPLICATION NUMBER:
NDA 20-164/S-009

Name:  Lovenox® (Enoxaparin Sodium) Injection

Sponsor:  Rhone-Poulenc Rorer Pharmaceuticals

Approval Date:  June 26, 1996
APPLICATION NUMBER:
NDA 20-164/S-009

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-164/S-009

APPROVAL LETTER
NDA 20-164/S-009

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

Dear Dr. Donnelly:

Please refer to your December 17, 1995 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox (enoxaparin sodium) Injection.

We acknowledge receipt of your amendments dated June 5, 11, 12, and 14, 1996.

The supplemental application provides for a change in the approved pre-filled syringe, replacing the 26 gauge needle with a 27 gauge needle. During the review process, it was determined that the supplemental application also included a request for a new needle shield manufacturer, and that new needle cover supplier was included in the supplemental request. This additional information was reviewed as provided in the supplement.

We have completed the review of this supplemental application, including the submitted draft labeling, 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 draft labeling in the submission dated December 27, 1995. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft package insert labeling submitted on December 27, 1995, with the following revisions:

1. In the WARNINGS section, insert the closing parentheses in the phrase (platelet counts between 100,000/mm³).

2. In the DOSAGE AND ADMINISTRATION section, the "Adult Dosage:" subsection, insert the following words at the beginning of the first sentence: "In patients undergoing hip or knee replacement surgery, the recommended dose of Lovenox".

Please submit sixteen 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. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 20-164/S-009. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that 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

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,

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-009
HFD-180/Div. files
HFD-180/CSO/K.Oliver
HFD-180/S.Fredd
HFD-180/E.Duffy
HFD-180/J.Sieczkowski
HFD-180/L.Talarico
HFD-103/P.Botstein
HFD-820/Yuan Yuan Chiu
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-80/DDIR (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613 (with labeling)
HFD-638/generics (with labeling)
HFD-735/(with labeling) - for all NDAs and supplements for adverse reaction changes.
HFD-560/D.Bowen (with labeling - for OTC Drug Products Only)

drafted: KO/June 20, 1996
r/d Initials: J.Sieczkowski 06/24/96
r/d Initials: E.Duffy 06/24/96
r/d Initials: S.Fredd 06/25/96
final: KO/06/25/96/c:\wpwin\karenfil\nda\20164606.3ko

APPROVAL

\[\text{Signature}\] 6/25/96
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-164/S-009

LABELING
LOVENOX®
(enoxaparin sodium) Injection

APPROVED Rev 9989

JAN 29 1997

Approval

INGREDIENTS

Enoxaparin sodium is a sterile, low molecular weight heparin for injection. Each vial contains 30 mg enoxaparin sodium in 0.3 mL Water for Injection. The approved Anti-Xa activity per vial is 200 International Units (IU) of Heparin. The Enzymatic Activity is 200 International Units (IU).

CLINICAL PHARMACOLOGY

Enoxaparin is a low molecular weight heparin which has anticoagulant properties. In man, enoxaparin characterized by a higher ratio of anti-Xa to anti-IIa activity (0.3:1:0.9) than unfractionated heparin (1:2:1). Following the administration of a single subcutaneous dose up to 40 mg of enoxaparin to healthy subjects, no appreciable change was observed in fibrinogen level and other parameters of fibrinolysis. At the recommended dose, single injections of enoxaparin do not significantly influence platelet aggregation or affect the clotting times (i.e., prothrombin time [PT] or activated partial thromboplastin time [APTT]).

Pharmacodynamics

Maximum Anti-Xa and anti-Factor Xa activity occurs 3 to 5 hours after subcutaneous injection of enoxaparin. More peak anti-Xa activity (1.63 IU/mL, 1.58 IU/mL and 1.48 IU/mL) was observed with 30 mg, 40 mg and 50 mg doses, respectively. Mean absolute bioavailability of enoxaparin based on anti-Xa activity is 93% in healthy volunteers. The volume of distribution of anti-Xa activity is about 6.8 L. Following i.v. dosing, the total body clearance of enoxaparin is 25.1 mL/min. Elimination halflife based on anti-Xa activity was about 4.6 hours after subcutaneous administration. Following a 40 mg dose significant anti-Xa activity persisted in plasma for about 12 hours. There appears to be no appreciable interaction between enoxaparin and other currently used oral anticoagulants or with oral anticoagulants in elderly patients. Enoxaparin has been studied in elderly patients with renal insufficiency. The heparin-like activity after dosing for 3 days in young healthy subjects. Clearance analysis based on anti-factor Xa activity decreased in elderly patients, and patients with renal impairment of enoxaparin Xa values for elderly patients was 90% lower than that observed in normal subjects. An increase in dose of 20% of those under the age of 65.

INDICATIONS AND USAGE

Lovenox injection is indicated for prevention of deep vein thrombosis, which may lead to pulmonary embolism, following hip or knee replacement surgery.

CONTRAINDICATIONS

Lovenox injection is contraindicated in patients with active major bleeding, in patients with thrombocytopenia associated with a positive in vitro test for antiplatelet antibodies in the presence of enoxaparin sodium, or in patients with hypersensitivity to enoxaparin sodium.

Patients with low sensitivity to heparin or other products should not be treated with Lovenox injection.

WARNINGS

Lovenox injection is not intended for intramuscular administration. It cannot be used interchangeably with unfractionated heparin or other low molecular weight heparins as they differ in their manufacturing process, molecular weight distribution, and in vitro and in vivo pharmacodynamics. Special attention and compliance with the instructions for use specific to each proprietary product is therefore required.

Lovenox injection should be used with extreme caution in patients with a history of heparin-induced thrombocytopenia. Pregnancy

Hemorrhage

Hemorrhage, like other anticoagulants, should be used with extreme caution in patients with increased risk of hemorrhage, such as anticoagulant neoplastic disease, uncontrolled bleeding diathesis, severe uncontrolled hypertension or bleeding diathesis, or recent fracture or surgery, or after brain, spinal or orthopedic surgery, or in patients treated concomitantly with platelet inhibitors.

Hemorrhage may occur at any site during therapy with enoxaparin. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

Neurological Anesthesia and Postoperative Inebriating Epidural Catheter Use

Sedation/Analgesia. As with other anticoagulants, there have been rare cases of neuropsychiatric hematomas reported with the concurrent use of enoxaparin and spinal/pudendal anesthesia resulting in long-term or permanent Paradox. The use of these rare events may be higher with the use of postoperative inebriating epidural catheters.

Thrombocytopenia

Thrombocytopenia can occur with the administration of Lovenox. Thrombocytopenia, with or without thrombocytopenia, occurs with enoxaparin, and 1% in patients given placebo following hip or knee replacement surgery in clinical trials. Platelet counts were more than 50,000/mcL in 0.1% in patients given enoxaparin, 0.5% in patients given heparin, and 0.5% in patients given placebo in the same trials. Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 80,000/mcL, enoxaparin should be discontinued. Rare cases of thrombocytopenia with thrombosis have also been observed in clinical practice. The rate of incidence of this complication in usual medical practice is unknown at present.

PRECAUTIONS

General

Lovenox injection should not be mixed with other medications or infusions. Lovenox injection should be used with care in patients with a bleeding diathesis, uncontrolled arterial hypertension or a history of severe gastrointestinal ulceration and hematemesis. Elderly patients and patients with renal insufficiency may show delayed elimination of enoxaparin. Enoxaparin should be used with care in these patients.

Thromboembolic events occur despite enoxaparin prophylaxis. Enoxaparin should be discontinued and appropriate management instituted.

Laboratory Tests

Periodic hematologic and biochemical studies, including platelet count, may be performed in response to the course of treatment with Lovenox injection.

Drug Interactions

It is recommended that agents which affect hemostasis be discontinued prior to Lovenox therapy to reduce the risk of hemorrhagic. These agents include medications such as oral anticoagulants, and/or platelet inhibitors including antiplatelet agents, aspirin, NSAIDs and non-steroidal anti-inflammatory drugs (NSAIDs).
Lovenox (enoxaparin sodium) Injection

Final Printed Labeling
For Approved Supplemental NDA 20-164/8-009

Precautions, drug interactions, adverse reactions, dosages and administration, contraindications, clinical trials, and warnings are provided in the text.

Enoxaparin "subcutaneous injection" is a product of Genentech. The text includes a list of contraindications, precautions, adverse reactions, and dosages.

Lovenox is a subcutaneous injection that is administered to patients with deep vein thrombosis. The text provides information about the drug's mechanism of action, effects on the coagulation system, and how it should be administered.

The text also states that Lovenox is indicated for the prevention of deep vein thrombosis in patients undergoing hip or knee replacement surgery and for the treatment of deep vein thrombosis and pulmonary embolism.

Other sections of the document provide information on the drug's mechanism of action, dosage, and administration. The text also includes a list of adverse effects and precautions for use.

The text concludes with a section on the drug's warnings and precautions, including the potential for bleeding and the need for close monitoring in patients with a history of bleeding disorders.

In summary, the text provides comprehensive information about Lovenox, including its indications, dosages, and precautions, as well as detailed information on the drug's mechanism of action and effects on the coagulation system.

The text also includes a list of adverse effects and precautions for use. It provides information on the drug's mechanism of action, dosage, and administration.

The text concludes with a section on the drug's warnings and precautions, including the potential for bleeding and the need for close monitoring in patients with a history of bleeding disorders.

In summary, the text provides comprehensive information about Lovenox, including its indications, dosages, and precautions, as well as detailed information on the drug's mechanism of action and effects on the coagulation system.

The text also includes a list of adverse effects and precautions for use. It provides information on the drug's mechanism of action, dosage, and administration.

The text concludes with a section on the drug's warnings and precautions, including the potential for bleeding and the need for close monitoring in patients with a history of bleeding disorders.
Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW  

Application Number: 20-164/S-009  

Name of Drug: Lovenox® (enoxaparin sodium) Injection  

Sponsor: Rhone-Poulenc Rorer Pharmaceuticals Inc.  

Material Reviewed

Submission Date(s): December 27, 1995  

Receipt Date(s): December 27, 1995  

Background and Summary Description: This supplement provides for a change in the approved pre-filled syringe, replacing the 26 G needle with a 27 G needle. 

Review

The submitted annotated draft package insert labeling was compared to the final printed labeling (FPL) approved in Supplement 005 on January 30, 1996, identified as "IN-1107H Rev.11/95". The inserts are identical except for the following:

1. In the WARNINGS section, the closing parentheses in the phrase (platelet counts between 100,000/mm³) has been deleted.  

This is UNACCEPTABLE. Request that the firm re-insert the closing parentheses.

2. In the DOSAGE AND ADMINISTRATION section, the "Adult Dosage:" subsection, the words "In patients undergoing hip or knee replacement surgery, the recommended dose of Lovenox" have been deleted from the first sentence of the subsection.  

This is UNACCEPTABLE. Request that the firm re-insert the deleted words.

3. In the HOW SUPPLIED section, the words "26 gauge" were replaced with the words "27 gauge".  

This change is ACCEPTABLE.
4. The recycled logo and words "Printed on recycled paper" were deleted.

*This change is ACCEPTABLE.*

5. The identification code and revision date to be updated.

*This change is ACCEPTABLE.*

**Conclusions**

The firm should be requested to:

1. In WARNINGS section, insert the closing parentheses.

2. In the first sentence of the DOSAGE AND ADMINISTRATION section, the "Adult Dosage:" subsection, insert the words "In patients undergoing hip or knee replacement surgery, the recommended dose of Lovenox".

[Signature]
Karen Oliver
Consumer Safety Officer

**cc:**
Original NDA 20-164/S-009
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/S.Fredd
HFD-180/J.Sieczkowski
HFD-180/L.Talarico

r/d Init: J.Sieczkowski 06/06/96
r/d Init: E.Duffy 06/06/96
r/d Init: S.Fredd 06/07/96

draft: KO/June 4, 1996
final: KO/06/07/96/c:\wpwin\karenfil\rev\20164606.0ko

CSO REVIEW
Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-164/S-009
NDA 20-164/S-014

Name of Drug: Lovenox (enoxaparin sodium) Injection

Sponsor: Rhone-Poulenc Rorer Pharmaceuticals Inc.

Material Reviewed

Submission Date(s): September 19, 1996 (S-009)
September 20, 1996 (S-014)

Receipt Date(s): September 20, 1996
September 23, 1996

Background and Summary Description: Supplement 009 provides for a change in the approved pre-filled syringe, replacing the 26 G needle with a 27 G needle and for a new needle shield manufacturer, --- The September 20, 1996 submission provides for final printed labeling (FPL) for supplement 009. Supplement 014, submitted September 20, 1996 as "Special Supplement - Changes Being Effected, provides for changes in the PRECAUTIONS section, the "Pediatric Use" subsection, and the ADVERSE REACTIONS, the "Ongoing Safety Surveillance" subsection. The FPL submitted for supplements 009 and 014 are identical, identified as "IN-1107L Rev. 8/96", incorporating the changes approved June 26, 1996 for S-009 and the "Special Supplement - Changes Being Effected" changes in S-014.

Review

The package insert, identified as "IN-1107L Rev. 8/96" submitted September 19 and September 20, 1996 in Supplements 009 and 014, respectively, was compared to the draft package insert submitted December 27, 1995 and the revisions listed in the June 26, 1996 approval letter. The package inserts were identical except for the following:

1. The identification number has been changed.

This change is ACCEPTABLE.
2. In the CLINICAL PHARMACOLOGY section, the "i.e." has been italicized to read "i.e."

This change is ACCEPTABLE.

3. In the WARNINGS section, the "Neuraxial Anesthesia and Post-operative Indwelling Epidural Catheter Use" subsection, the underlining from the sub-subheading was deleted to read: "Spinal/Epidural Anesthesia".

This change is ACCEPTABLE.

4. A solid-black, rectangular box was added to the front of the package insert, the bottom right corner.

This addition is ACCEPTABLE.

5. In the PRECAUTIONS section:

a. In the "Drug/Laboratory Test Interactions: Elevations of Serum Aminotranferases" subsection, the "®" symbol was added after the word "Lovenox" to read "Lovenox®".

This addition is ACCEPTABLE.

b. In the "Pediatric Use" subsection, the underlined words in the following sentence have been changed in response to the Federal Register Notice of December 13, 1994 regarding: "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of 'Pediatric Use' Subsection in the Labeling; Final Rule".

from: "Safety and effectiveness of enoxaparin in children has not been established."

to: "Safety and effectiveness of enoxaparin in pediatric patients has not been established."

This change should be reviewed by the MEDICAL OFFICER.
6. In the ADVERSE REACTIONS section:
   a. In the "Thrombocytopenia" subsection, the "®" symbol was deleted after the word "Lovenox®" to read "Lovenox".
      
      This deletion is ACCEPTABLE.
   b. In the "Ongoing Safety Surveillance" subsection, the following was added:
      "Other reports include: skin necrosis at the injection site, inflammatory nodules at the injection site, purpura, systemic allergic reactions, and thrombocythemia."
      
      This addition should be reviewed by the MEDICAL OFFICER.

Conclusions

1. The following changes are ACCEPTABLE: 1., 2., 3., 4., 5.a. and 6.a.

2. The following changes should be reviewed by the MEDICAL OFFICER: 5.b. and 6.b.

Karen Oliver 01/23/97
Regulatory Health Project Manager

cc: Original NDA 20-164/S-009
    NDA 20-164/S-014
    HFD-180/Div. Files
    HFD-180/K.Oliver
    HFD-180/S.Fredd
    HFD-180/L.Talarico
    HFD-180/N.Markovic
draft: KO/January 3, 1997
final: KO/01/23/97/c:\wpwin\karenfil\rev\20164701.0ko

CSO REVIEW
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

Application Number: NDA 20-164/S-009
NDA 20-164/S-014

JAN 15 1997

Subject: Proposal for Final Printed Labeling for Supplement 009.

Drug: Lovenox® (enoxaparin sodium) Injection

Sponsor: Rhone-Poulenc Rorer Pharmaceuticals Inc.

Submission Date: September 20, 1996

Assignment Date: 01/03/97
Completion Date: 01/10/97

Medical Officer: Nenad Markovic, M.D.

Review Number: 2016414.R46

Background:

The supplement S-014 provides for final printed labeling (FTP) for supplement S-009, NDA 20-164. This supplement was submitted (September 19, 1996) for a change in the approved pre-filled syringe replacing the 26G needle with a 27G needle and for a needle shield manufacturer. The Supplement 014 (September 20, 1996) provides for changes in the Labeling, section PRECAUTIONS, subsection Pediatric Use, and the section ADVERSE REACTIONS, subsection Ongoing Safety Surveillance.

Both supplements have been previously reviewed by the Consumer Safety Officer, except the changes identified in her review as #5b (PRECAUTIONS), and 6b (ADVERSE REACTIONS). This two particulars are the subject of this review.

Requested Change of the Labeling for Lovenox(enoxaparin sodium) Injection, identified as "IN-1107L Rev. 8/96."

#1. Section PRECAUTIONS, subsection Pediatric Use.


This change is acceptable
#2. Section ADVERSE REACTIONS, subsection Ongoing Safety Surveillance.

A new text was added as a paragraph 2 from above: "Other reports include: skin necrosis at the injection site, inflammatory nodules at the injection site, purpura, systemic allergic reactions, and thrombocytopenia."

This change is not sufficient.

Comment:

The change is not sufficient due to new information. The FDA Postmarketing and Pharmacovigilance group have analyzed safety record of Lovenox Injection and have made their recommendation.

In a Memorandum signed by Carol Pamer, R.Ph., Postmarketing Safety Evaluator, HFD-735, through Vincent Guinee, M.D., M.P.H., Director, Division of Pharmacovigilance and Epidemiology, HFD-730 to Steven Fredd, M.D., Director DGCDP, from December 31, 1996, the following recommendations were made:

a. "The following localized dermatological adverse events were thought to have sufficient documentation to merit consideration for inclusion in the next labeling for Lovenox injection: skin necrosis at injection site, prolonged bleeding at injection site, hypersensitivity reaction at or near injection site, and possible scarring, masses resulting from injection site reactions."

b. "The following generalized dermatological adverse events were put in the same category: vesiculobullous rash, urticaria. Three cases of epidermal necrolysis were reported but without sufficient documentation to be labeled."

The sponsor's and Pharmacovigilance proposed texts are compared with the COSTART terminology (Table 1).
Table 1.
ONGOING SAFETY SURVEILLANCE Section in the Rhone-Poulenc Rorer current version, proposal by FDA Pharmacovigilance, and COSTART-based terminology for the proposed changes in Labeling.

<table>
<thead>
<tr>
<th>RPR</th>
<th>Pharmacovigilance</th>
<th>Relevant COSTART terminology</th>
<th>Injection site reactions</th>
</tr>
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<tbody>
<tr>
<td>skin necrosis</td>
<td>skin necrosis</td>
<td>necro skin or skin necrosis</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>masses resulting from injection site reactions</td>
<td>nodule skin</td>
<td></td>
</tr>
<tr>
<td>inflammatory nodules</td>
<td>-</td>
<td>injection site inflammation</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>hypersensitivity reaction at or near injection site and possible scarring</td>
<td>hysn</td>
<td></td>
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<tr>
<td>-</td>
<td>prolonged bleeding at injection site</td>
<td>prolonged hem</td>
<td></td>
</tr>
<tr>
<td>purpura</td>
<td>-</td>
<td>purpura</td>
<td></td>
</tr>
<tr>
<td>systemic allergic reactions</td>
<td>vesiculobullous rash, urticaria</td>
<td>allergic reactions (vesiculobullous rash, urticaria)</td>
<td></td>
</tr>
<tr>
<td>thrombocythemia</td>
<td>-</td>
<td>thrombocythemia</td>
<td></td>
</tr>
</tbody>
</table>

The table suggests that the sponsor and Pharmacovigilance have separately collected information of adverse events. Some of the events are identical, but some are different. The difference can also be seen by separate COSTART terms. Since it may be considered as important for the Labeling to include all meaningful available information for newly reported adverse events, the easiest way to go would be to add adverse events cited in the Pharmacovigilance report to the sponsor's text. However, a simple addition would produce semantically awkward text. Some editing is necessary.

**Recommendation**

Change #1 (#5b from CSO Review) is acceptable.

Regarding the Change #2 (#6b from CSO Review), I recommend the current text of the Labeling, section ADVERSE EVENTS, subsection Ongoing Safety Surveillance, paragraph 2 from above, reading "Other reports include . . ." to be replaced with the following text.
"Other reports include the following adverse reactions:"

The sponsor should be advised to consider this text for the next change of the Lovenox (enoxaparin sodium) Injection Labeling.

Nenad Markovic, M.D.

CC:
NDA 20-164/S-009
NDA 20-164/S-014
HFD-180
HFD-180/SRedd
HFD-180/NMarkovic
HFD-181/CSO
HFD-180/JChoudary
HFD-180/EDuffy
f/t 1/15/97 jgw
MED\N\20164701.0NM
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-164/S-009

CHEMISTRY REVIEW
<table>
<thead>
<tr>
<th>CHEMIST REVIEW: #1</th>
<th>1. Organization:</th>
<th>HFD-180</th>
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<tbody>
<tr>
<td>3. Name and Address of Applicant (City &amp; State):</td>
<td>Rhone-Poulenc Rorer Pharmaceuticals Inc.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P.O. Box 1200</td>
<td></td>
</tr>
<tr>
<td></td>
<td>500 Arcola Road</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Collegeville, PA 19426</td>
<td></td>
</tr>
<tr>
<td>2. NDA Number:</td>
<td>20-164</td>
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<td>4. AF Number:</td>
<td>JUN 25 1996</td>
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<td>BC</td>
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<td>6. Name of Drug:</td>
<td>Lovenox Injection</td>
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<tr>
<td>7. Nonproprietary Name:</td>
<td>enoxaparin sodium</td>
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<tr>
<td>8. Supplement Provides for:</td>
<td>a 27G ½&quot; needle and needle shield as alternate syringe components for the previously approved Lovenox Injection Syringe container and the labeling to reflect the proposed use of a 27 gauge needle.</td>
<td>(See BC AM of June 5, 1996.)</td>
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<td>9. Amendments and Other (Reports, etc.) Dates:</td>
<td>CSO's Labeling Review dated June 7, 1996</td>
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<td>10. Pharmacological Category:</td>
<td>Anti-Coagulant</td>
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<td>11. How Dispensed:</td>
<td>RX XXX OTC</td>
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<td>12. Related IND/NDA/DMF(s):</td>
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<td>1. DMF</td>
<td></td>
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<tr>
<td></td>
<td>2. See page 2.</td>
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<tr>
<td>13. Dosage Form:</td>
<td>Parenteral (SVP)</td>
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<tr>
<td>14. Potency:</td>
<td>30 mg/0.3 mL</td>
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<td>Syringe and Ampule</td>
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<td>16. Records and Reports:</td>
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<tr>
<td></td>
<td>Current</td>
<td>Yes No</td>
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<tr>
<td></td>
<td>Reviewed</td>
<td>Yes No</td>
</tr>
<tr>
<td>17. Comments:</td>
<td>See Review Notes</td>
<td></td>
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<td>cc:</td>
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<tr>
<td>NDA 20-164</td>
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<td>HFD-180/Division File</td>
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<td>HFD-180/JSieczkowski</td>
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<td>R/D init.: EDuffy 6-17-96</td>
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<td>dob DRAFT 6-17-96/F/T 6-25-96/WP: c:/wpfiles/chem/S/20164009.1JS</td>
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<tr>
<td>18. Conclusions and Recommendations:</td>
<td>Based on the submitted information in support of the use of a 27G ½&quot; needle and needle shield, it is recommended that the syringe container with the alternate syringe components be approved. The change in the drug product labeling with respect to adding the 27G ½&quot; needle to the How Supplied section is acceptable. Other changes to the labeling which are the purview of the medical officer were not reviewed. The CSO should draft an action letter for the Division Director's signature with respect to the supplements approvability.</td>
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<tr>
<td>19. Reviewer:</td>
<td></td>
<td></td>
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<tr>
<td>Name:</td>
<td>Joseph Sieczkowski, Ph.D.</td>
<td></td>
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<tr>
<td>Signature:</td>
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<tr>
<td>Date Completed:</td>
<td>June 19, 1996</td>
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12. **Rhone-Poulenc Rorer Supplements:**

- **SE2-008**  Prevention of DVT, high risk and surgery (EA)
- **SCP-009**  Replacement of 26G needle with 27G needle/Pre-filled Syringe
- **SE2-010**  Prevention of DVT, Long term therapy (EA)
- **SCS-011**  Updated Specifications, Methods, and Stability protocols and Fulfillment of NDA Commitments.
- **SCM-012**  Add new filling line for 30mg and 40mg prefilled syringes at the Maisons Alfort, France facility.
Redacted ___ page(s) of trade secret and/or confidential commercial information from

CHEMISTRY REVIEW #1
the CSO's new labeling 6/6/96.] with respect to chemistry, the package insert is adequate.

G. Establishment Inspection:

COMMENT:
An inspection was not requested because upon implementation of the proposed changes to the syringe container, the same manufacturing facility will be used.

H. DRAFT DEFICIENCY LETTER: NONE
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-164/S-009

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
NDA 20-164/S-009

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

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-009
Therapeutic Classification: Standard

Date of Supplement: December 27, 1995
Date of Receipt: December 27, 1995

This supplement provides for a change in the approved pre-filled syringe, replacing the 26 g needle with a 27 g needle.

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 February 25, 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
Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

CC:
Original NDA 20-164/S-009
HFD-180/Div. Files
HFD-80
HFD-180/CSO/K.Oliver

drafted: KO/December 29, 1995  \karen\ntime \12/29/95
Final: KO/12/29/95/c:\wpwin\karenfil\nda\20164512.3ko

SUPPLEMENT ACKNOWLEDGEMENT
September 19, 1996

Stephen B. Fredd, M.D., Director
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation
Drug Products (HFD-180)
Document Control Room 6B-24
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Loovoxx (enoxaparin sodium) Injection
FINAL PRINTED LABELING
for approved SNDA 20-164/S-009

Dear Dr. Fredd:

Please refer to your letter of June 26, 1996 which indicated that NDA 20-164/S-009, submitted for a change in the approved pre-filled syringe, replacing the 26 gauge needle with a 27 gauge needle was approved. The supplement also included a request for a new needle shield manufacturer, . As requested, we are providing final printed labeling defining the availability of Lovoxx Injection prefilled syringe with the 27G needle under the section How Supplied.

In addition, the statement under Pediatric Use now describes the age group as "pediatric patients" rather than "children", as required under 21CFR 201.57. Also, please note that as agreed on September 10, 1996 in a phone call to Ms. Karen Oliver, this final printed labeling includes adverse event data collected from post-marketing spontaneous reports. Under Ongoing Safety Surveillance the statement “Other reports include: skin necrosis at the injection site, inflammatory nodules at the injection site, purpura, systemic allergic reactions, and thrombocytopenia” is now written.

These three changes are included in the attached package insert, version IN-1107L. A separate supplement for Changes Being Effected has also been submitted regarding these labeling changes.
Please contact me at (610) 454-3023 with any questions regarding this submission.

Sincerely yours,

[Signature]

Thomas E. Donnelly, Jr., Ph.D.
Group Director
Worldwide Regulatory Affairs

TED/bnh
Attachments
NDA 20-164/S-009

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

Dear Dr. Donnelly:

We acknowledge the receipt of your September 19, 1996 submission containing final printed labeling in response to our June 26, 1996 letter approving your supplemental new drug application for Lovenox (enoxaparin sodium) Injection.

We have reviewed the labeling that you have submitted in accordance with our June 26, 1996 letter, and we find it acceptable. We note that the final printed labeling contains changes approved in supplemental application S-014, submitted as "Special Supplement - Changes Being Effected" under 21 CFR 314.70(c), dated September 20, 1996, approved January 27, 1997.

Sincerely yours,

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-009
  HFD-180/Div. Files
  HF-2/Medwatch (with labeling)
  HFD-103/Office Director (with labeling)
  HFD-180/CSO/K. Oliver
  HFD-40/DDMAC (with labeling)
  HFD-92/DDM-DIAB (with labeling)
  HFD-613/OGD (with labeling)
  HFD-735/DPE (with labeling)

Drafted by: KO/January 27, 1997
final: KO/01/27/97/c:\wpwin\karenhl\nda\20164701.1ko

ACKNOWLEDGE AND RETAIN (AR)