Approval Package for:

APPLICATION NUMBER:
NDA 20-164/S-021

Name: Lovenox® (Enoxaparin Sodium) Injection

Sponsor: Rhone-Poulenc Pharmaceuticals, Inc.

Approval Date: April 20, 1999
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-164/S-021

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

Dear Mr. Babilon:


This supplemental new drug application provides for additional information in the ADVERSE REACTIONS section, the “Ongoing Safety Surveillance” subsection, of the package insert regarding reports of rare cases of hyperlipidemia.

We have completed the review of this supplemental application 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 submitted labeling dated January 12, 1999 with the revisions listed below. Accordingly, the supplemental application is approved effective on the date of this letter.

Very rare cases of hyperlipidemia have been reported, with one case of hyperlipidemia, with marked hypertriglyceridemia, reported in a diabetic pregnant woman; causality has not been determined.

These revisions are terms of the approval.

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. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-164/S-021." Approval of this submission by FDA is not required before the labeling is used.
In addition, please submit three copies of the introductory promotional materials 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 materials and the package insert directly to:

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

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

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,

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
cc:
Archival NDA 20-164/S-021
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/L.Talarico
HFD-180/J.Schmeling
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-103/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-21/ACS (with labeling) - for drug discussed at advisory committee meeting.
HFD-95/DDMS (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: KO/April 19, 1999
final: KO/04/19/99/c:\mydocuments\nda20160-S-021-04-19-99-AP

APPROVAL (AP)
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-164/S-021

LABELING
Lovenox® (enoxaparin sodium) Injection
FINAL PRINTED LABELING
IN-1107 Rev 6/99 : Malson Alfort

SPINAL / EPIDURAL HEMATOMAS.
When spinal or epidural anesthesia (epidural, subarachnoid, or spinal) is performed, patients may be at increased risk of developing these complications. The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesics or by the concurrent use of drugs affecting hemostasis such as oral anti-coagulants, platelet inhibitors, or other antithrombotics. The risk may be increased by traumatic or repeated epidural or spinal punctures.

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

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

DESCRIPTION
Lovenox injection is a sterile solution containing enoxaparin sodium, a low molecular weight heparin. It is available in prefilled syringes (30 and 40 mg), graduated prefilled syringes (60, 80, and 100 mg), and ampules (50 mg). Each syringe contains 10 mg enoxaparin sodium in 0.3 ml; each ampule contains 50 mg enoxaparin sodium in 0.1 ml. For injection, the solution is presented free of stabilizers or excipients (see DOSAGE AND ADMINISTRATION, how supplied).

The pH of the injection is 5.5 to 7.5, with an approximate anti-factor Xa activity per dosage unit of 1000 IU per every 10 mg of enoxaparin sodium (with reference to the N.H.O. anti-factor Xa international normalizat ion control). The molecular weight of enoxaparin sodium is about 4500 daltons. The molecular weight distribution is:

<2000 daltons: 20%
2000 to 8000 daltons: 28%
>8000 daltons: 52%

STRUCTURAL FORMULA

```
|CH=O|-CH2-OH
|O==O|\(-CH_{2}-COO^{-}\)
```

CLINICAL PHARMACOLOGY
Enoxaparin is a low molecular weight heparin which has antithrombotic properties. In humans, enoxaparin given at a dose of 1.5 mg/kg subcutaneously (SC) is characterized by a higher rate of anti-factor Xa vs anti-factor IIa activity (thrombin). 14 (units I.U.) based on area under the curve (AUC) (0.00-10), shown by a peak at 1.8 times the control values were seen at the infusion time (T), and the activated partial thromboplastin time (aPTT).

CLINICAL STUDIES
Efficacy
Patients received subcutaneous enoxaparin sodium 30 mg SC once daily for at least 12 hours after surgery in patients with hip replacement or 5000 IU on days 1 to 5 after surgery. Treatment was initiated within 24 hours after surgery and was continued for 10 to 14 days after surgery. The data are provided below:

Efficacy of Lovenox Injection in Hip Replacement Surgery

<table>
<thead>
<tr>
<th>Dosage Regimen</th>
<th>10 mg a.d. SC</th>
<th>20 mg a.d. SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Failures</td>
<td>3 (10)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Total DVT (%)</td>
<td>5 (10)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Proximal DVT (%)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Mean value versus placebo: p = 0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p value versus placebo: p = 0.034</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A double-blind, multicenter study compared three dosage regimens of Lovenox injection in patients with hip replacement. Treatment was initiated within 24 hours after surgery and was continued for 7 to 11 days after surgery. The data are provided below:

Efficacy of Lovenox Injection in Hip Replacement Surgery

<table>
<thead>
<tr>
<th>Dosage Regimen</th>
<th>15 mg a.d. SC</th>
<th>30 mg a.d. SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Failures</td>
<td>5 (10)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Total DVT (%)</td>
<td>8 (16)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Proximal DVT (%)</td>
<td>4 (8)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Mean value versus placebo: p = 0.002</td>
<td></td>
<td></td>
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<tr>
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<tr>
<td>Treatment Failures</td>
<td>4 (8)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Total DVT (%)</td>
<td>6 (12)</td>
<td>3 (6)</td>
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<tr>
<td>Proximal DVT (%)</td>
<td>3 (6)</td>
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<td>4 (8)</td>
</tr>
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<tr>
<td>Proximal DVT (%)</td>
<td>5 (10)</td>
<td>2 (4)</td>
</tr>
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<tr>
<th>Dosage Regimen</th>
<th>10 mg a.d. SC</th>
<th>20 mg a.d. SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Failures</td>
<td>12 (24)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Total DVT (%)</td>
<td>14 (28)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Proximal DVT (%)</td>
<td>7 (14)</td>
<td>4 (8)</td>
</tr>
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<td></td>
</tr>
<tr>
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<tr>
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<th>15 mg a.d. SC</th>
<th>30 mg a.d. SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Failures</td>
<td>16 (32)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Total DVT (%)</td>
<td>18 (36)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Proximal DVT (%)</td>
<td>9 (18)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Mean value versus placebo: p = 0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p value versus placebo: p = 0.034</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Lovenox® (enoxaparin sodium) Injection

There was no significant difference between the 30 mg every 12 hours and 40 mg once a day regimen.

Extended Prophylaxis in Hip Replacement Surgery: In a study of extended prophylaxis for patients undergoing hip replacement surgery, patients were treated, while hospitalized, with enoxaparin 40 mg SC, initiated up to 12 hours prior to surgery to provide the protection of postoperative deep vein thrombosis. At the end of the peri-operative period, all patients continued their treatment with enoxaparin. 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 = 131) once a day SC or to placebo (n = 88) for 5 days. In the population of patients, the incidence of deep vein thrombosis was significantly lower for enoxaparin compared to placebo.

The data provided below are based on:

**Efficacy of Lovenox Injection in Knee Replacement Surgery**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Lovenox</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Treated Knee Replacement Patients</td>
<td>54 (98.2)</td>
<td>52 (99)</td>
</tr>
<tr>
<td>Total DVT (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Proximal DVT (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

**Efficacy of Lovenox Injection in Abdominal Surgery Patients with Cancer**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Lovenox</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Treated Abdominal Surgery Patients</td>
<td>52 (100)</td>
<td>50 (100)</td>
</tr>
<tr>
<td>Total VTE (%)</td>
<td>23 (45.2)</td>
<td>48 (96)</td>
</tr>
<tr>
<td>DVT Only (%)</td>
<td>23 (45.2)</td>
<td>48 (96)</td>
</tr>
</tbody>
</table>

**Efficacy of Lovenox Injection in Colorectal Surgery**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Lovenox</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Treated Colorectal Surgery Patients</td>
<td>50 (100)</td>
<td>50 (100)</td>
</tr>
<tr>
<td>Total VTE (%)</td>
<td>44 (88)</td>
<td>44 (88)</td>
</tr>
<tr>
<td>DVT Only (%)</td>
<td>44 (88)</td>
<td>44 (88)</td>
</tr>
</tbody>
</table>

**Postdischarge Dosing Regimen**

<table>
<thead>
<tr>
<th>Indication (Post-discharge)</th>
<th>Lovenox (40 mg SC)</th>
<th>Placebo (40 mg SC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Treated Extended Prophylaxis Patients</td>
<td>90 (100)</td>
<td>89 (100)</td>
</tr>
<tr>
<td>Treatment Failure</td>
<td>Total DVT (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Proximal DVT (%)</td>
<td>0 (0)</td>
<td>12 (14)</td>
</tr>
</tbody>
</table>

1) Value versus placebo = 0.008

2) Value versus placebo = 0.007

A second study, patients undergoing hip replacement surgery were treated, while hospitalized, with enoxaparin 40 mg SC, initiated up to 12 hours prior to surgery. All patients were examined for clinical signs and symptoms of venous thromboembolic disease in a double-blind design, those patients with no venous thromboembolic disease were randomly assigned to post-discharge regimen of either enoxaparin 40 mg (n = 131) once a day SC or to placebo (n = 88) for 5 days. The incidence of deep vein thrombosis during extended prophylaxis was significantly lower for enoxaparin compared to placebo, with a statistically significant difference in both total DVT (enoxaparin 27 (18%) versus placebo 46 (32%) p = 0.003) and proximal DVT (enoxaparin 8 (6%) versus placebo 28 (21%) p = 0.001).

In a double-blind study, Lovenox injection 40 mg every 12 hours SC was compared to enoxaparin 5 days postoperative knee replacement surgery. After bronchoscopic treatment, treatment was initiated 12 to 24 hours after surgery and was continued 12 to 18 days after surgery. The incidence of proximal and total deep vein thrombosis after surgery was significantly lower for enoxaparin compared to placebo. The data are provided below.

**Postdischarge Dosing Regimen**

<table>
<thead>
<tr>
<th>Indication (Post-discharge)</th>
<th>Lovenox (40 mg SC)</th>
<th>Placebo (40 mg SC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Treated Knee Replacement Patients</td>
<td>54 (100)</td>
<td>52 (100)</td>
</tr>
<tr>
<td>Total DVT (%)</td>
<td>0 (0)</td>
<td>25 (28)</td>
</tr>
<tr>
<td>Proximal DVT (%)</td>
<td>0 (0)</td>
<td>12 (14)</td>
</tr>
</tbody>
</table>

1) Value versus placebo = 0.001

C1 = Confidence Interval

Additionally, in an open-label, parallel group, uncontrolled clinical study, Lovenox injection 36 mg every 12 hours SC in patients undergoing elective knee replacement surgery was compared to heparin 5000 U every 8 hours SC. Treatment was initiated after surgery and continued up to 14 days. The incidence of deep vein thrombosis was significantly lower for enoxaparin compared to heparin.

Abdominal Surgery: In a double-blind, parallel group study of 1115 patients undergoing elective open surgery in the gastrointestinal, urological, or gynecological tract, Lovenox injection 40 mg SC, administered once a day, beginning 6 hours prior to surgery and continuing for a maximum of 12 days after surgery, was compared to heparin 5000 U every 8 hours SC in preventing deep vein thrombosis (DVT). The data are provided below.

**Postdischarge Dosing Regimen**

<table>
<thead>
<tr>
<th>Indication (Post-discharge)</th>
<th>Lovenox (40 mg SC)</th>
<th>Placebo (5000 U Q8H SC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Treated Abdominal Surgery Patients</td>
<td>52 (100)</td>
<td>50 (100)</td>
</tr>
<tr>
<td>Total VTE (%)</td>
<td>23 (45.2)</td>
<td>48 (96)</td>
</tr>
<tr>
<td>DVT Only (%)</td>
<td>23 (45.2)</td>
<td>48 (96)</td>
</tr>
</tbody>
</table>

1) VTE = Venous thromboembolic events which included DVT, PE, and death considered to be thromboembolic in origin.

C1 = Confidence Interval

In a second double-blind, parallel group study, Lovenox injection 40 mg SC once a day was compared to heparin 5000 U every 8 hours SC in 1547 patients undergoing colorectal surgery. Treatment was initiated approximately 2 hours prior to surgery and continued for approximately 7 to 10 days after surgery. The data are provided below.

**Postdischarge Dosing Regimen**

<table>
<thead>
<tr>
<th>Indication (Post-discharge)</th>
<th>Lovenox (40 mg SC)</th>
<th>Placebo (5000 U Q8H SC)</th>
</tr>
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<tbody>
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<td>All-Treated Colorectal Surgery Patients</td>
<td>52 (100)</td>
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</tbody>
</table>

1) VTE = Venous thromboembolic events which included DVT, PE, and death considered to be thromboembolic in origin.

C1 = Confidence Interval
### Lovanox® (exosporum sodium) Injection

**Efficacy of Lovanox Injection in Treatment of Deep Vein Thrombosis and Pulmonary Embolism**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Lovanox (mg/kg SC)</th>
<th>Heparin (mg/kg IV adj. Therapy)</th>
<th>Reduction %</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Treated DVT Patients with and without PE</td>
<td>1.0 mg/kg SC</td>
<td>1 mg/kg IV adj. Therapy</td>
<td>54.7</td>
<td>0.00002</td>
</tr>
</tbody>
</table>

**Dosage Regimen**

<table>
<thead>
<tr>
<th>Lovanox (mg/kg SC)</th>
<th>Heparin (mg/kg IV adj. Therapy)</th>
<th>Reduction %</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 mg/kg SC</td>
<td>1 mg/kg IV adj. Therapy</td>
<td>54.7</td>
<td>0.00002</td>
</tr>
</tbody>
</table>

**SIDE EFFECTS**

- **General:** The most frequent side effects were dizziness, headache, and nausea.
- **Local:** Injection site reactions were uncommon.
- **Laboratory:** A slight increase in liver enzymes was observed.

**CONTRAINdications**

- Patients with a history of heparin-induced thrombocytemia or heparin-induced thrombocytopenia.
- Patients with a history of malignancy.
- Patients with a history of bleeding disorders.
- Patients with a history of hepatic impairment.

**WARNINGS**

- **Serious:** The use of Lovanox must be monitored closely and adjusted as needed.
- **Caution:** In the event of bleeding, Lovanox should be discontinued.

**Pharmacology**

- Lovanox is a direct thrombin inhibitor that acts by inhibiting thrombin's ability to activate platelets and fibrinogen.

**References**


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### Lovanox® (exosporum sodium) Injection

**See DOSAGE AND ADMINISTRATION**

**Adult Dosage for appropriate dosage regimens.**

### CONTRAINDICATIONS

Lovanox injection is contraindicated in patients with active major bleeding, in patients with thrombocytopenia or in patients with history of hypersensitivity to exosporum sodium, or in patients with hypersensitivity to exosporum sodium.

### WARNINGS

Lovanox injection cannot be administered intramuscularly (via needle) with either heparin or other low molecular weight heparins, or with other thrombolytic agents. If a thrombolytic agent has previously been used, the patient should not receive Lovanox injection and anti-platelet agents, and until heparin-induced thrombocytopenia has resolved, or until the patient has completed 14 days of Lovanox injection.

### CASES OF EPISOMATIC OR SPINAL HEMATOMAS

Cases of episomatic or spinal hematomas have been reported with the associated use of anticoagulants or antithrombotic agents. These include cases involving major trauma, neurosurgery, or anticoagulation as part of the management of intracranial or intraspinal hematomas such as SAHs. (see WARNING, ADVERSE REACTIONS, Ongoing Safety Surveillance, and PRECAUTIONS). Drug interactions may occur. Drug interactions may occur. Drug interactions may occur. Drug interactions may occur.

### PRECAUTIONS

**General:** Lovanox injection should not be mixed with other injections or infusions. Lovanox injection should be used with care in patients with a bleeding diathesis, uncontrolled hypertension, or severe renal impairment. Lovanox injection should not be used in patients with renal impairment, or in patients with severe renal impairment.

**Laboratory Tests:** Routine complete blood counts, platelet count, and coagulation studies may be performed. Lovanox injection has been associated with transient increases in creatine kinase (CK) and creatine kinase-MB (CK-MB) levels. Lovanox injection has been associated with transient increases in creatine kinase (CK) and creatine kinase-MB (CK-MB) levels. Lovanox injection has been associated with transient increases in creatine kinase (CK) and creatine kinase-MB (CK-MB) levels.

**Drug Interactions:** Drug Interactions: Drug Interactions: Drug Interactions: Drug Interactions:

- **Allergies:** There have been no reports of allergic reactions with Lovanox injection.
- **Immunologic:** There have been no reports of immunologic reactions with Lovanox injection.
- **Pharmacologic:** There have been no reports of pharmacologic interactions with Lovanox injection.
- **Non-Specific:** There have been no reports of non-specific interactions with Lovanox injection.

**Cardiovascular:** Lovanox injection has been associated with transient increases in blood pressure. Lovanox injection has been associated with transient increases in blood pressure. Lovanox injection has been associated with transient increases in blood pressure.

**Other:** Lovanox injection has been associated with transient increases in blood pressure. Lovanox injection has been associated with transient increases in blood pressure. Lovanox injection has been associated with transient increases in blood pressure.

**Pharmacologic:** There have been no reports of pharmacologic interactions with Lovanox injection.

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**Pharmacologic:** There have been no reports of pharmacologic interactions with Lovanox injection.

**Non-Specific:** There have been no reports of non-specific interactions with Lovanox injection.

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Lovenox® (enoxaparin sodium) Injection

**Major Bleeding Episodes in Abdominal and Colorectal Surgery**

<table>
<thead>
<tr>
<th>Lovenox®</th>
<th>Naprosin 40 mg/0.2 SC</th>
<th>Naprosin 500 06/0.2 SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Surgery</td>
<td>n = 595</td>
<td>n = 589</td>
</tr>
<tr>
<td>Colorectal Surgery</td>
<td>n = 674</td>
<td>n = 674</td>
</tr>
</tbody>
</table>

**Bleeding complications were considered major:** 1) if the hemorrhage caused a significant clinical event, or 2) if it accompanied a hemorrhage of at least 2 ml of blood (in addition to overt clinical bleeding of at least 2 ml units of blood products). Retropertitoneal, intravisceral, and intramural hemorrhages were always considered major.

1 All patients also receivedwarfarin sodium (dose-adjusted according to PT to achieve an INR of 2.0 to 3.0) commencing within 72 hours of Lovonox or standard heparin therapy and continuing for up to 8 days.

Major Bleeding Episodes in Unstable Angina and Non-Q-Wave Myocardial Infarction

<table>
<thead>
<tr>
<th>Lovenox® (SC)</th>
<th>Naprosin 1 mg 06/0.2 SC</th>
<th>Naprosin 1 mg 06/0.2 SC aPTT Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovenox®</td>
<td>n = 1078</td>
<td>n = 1078</td>
</tr>
<tr>
<td>Non-Q-Wave MI</td>
<td>n = 1019</td>
<td>n = 1019</td>
</tr>
</tbody>
</table>

2 The rates represent major bleeding on study medication up to 12 hours after dose.

3 Aspirin therapy was administered concurrently (100 to 325 mg per day).

4 Bleeding complications were considered major: 1) if the hemorrhage caused a significant clinical event, or 2) if it accompanied a hemorrhage of at least 2 ml of blood (in addition to overt clinical bleeding of at least 2 ml units of blood products). Retropertitoneal, intravisceral, and intramural hemorrhages were always considered major.

5 All patients also received warfarin sodium (dose-adjusted according to PT to achieve an INR of 2.0 to 3.0) commencing within 72 hours of Lovonox or standard heparin therapy and continuing for up to 8 days.

**Lovenox® (SC) Injection**

Lovenox® (SC) Injection may be administered once daily after the first 24 hours if the patient is hemodynamically stable. The injection should be administered at the same site each day. The usual duration of therapy is at least 5 to 7 days; up to 14 days of administration has been well tolerated in clinical trials.

Unstable Angina and Non-Q-Wave Myocardial Infarction: In patients with unstable angina or non-Q-wave myocardial infarction, Lovenox® (SC) Injection is administered subcutaneously at the dose of 40 mg every 12 hours, or 1 mg every 12 hours, as necessary, in increments of 40 mg or 1 mg, respectively, to a maximum daily dose of 240 mg or 12 mg, respectively.

**Adverse Events Adverse Effects Occurring at <0.1% Incidence in Lovonox Injection Treated Patients**

<table>
<thead>
<tr>
<th>Lovenox®</th>
<th>Naprosin 1 mg 06/0.2 SC</th>
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<td>n = 1019</td>
</tr>
</tbody>
</table>

2 Adverse effects observed in <0.1% of Lovonox Injection treated patients. The incidence of each adverse effect is shown as a percentage of patients treated.

**Adverse Events Adverse Effects Occurring at >2% Incidence in Lovonox Injection Treated Patients Undergoing Abdominal or Colorectal Surgery**

<table>
<thead>
<tr>
<th>Lovenox®</th>
<th>Naprosin 1 mg 06/0.2 SC</th>
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2 Adverse effects observed in >2% of Lovonox Injection treated patients. The incidence of each adverse effect is shown as a percentage of patients treated.

**Adverse Effects Adverse Effects Occurring at >2% Incidence in Lovonox Injection Treated Patients Undergoing Deep Vein Thrombosis and Pulmonary Embolism**

<table>
<thead>
<tr>
<th>Lovenox®</th>
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2 Adverse effects observed in >2% of Lovonox Injection treated patients. The incidence of each adverse effect is shown as a percentage of patients treated.
DESCRIPTION

Lovonox Injection is a sterile solution containing enoxaparin sodium, a low molecular weight heparin. It is available in: prefilled syringes (30 and 40 mg), graduated prefilled syringes (50, 80, and 100 mg), and ampules (30 mg). Each dosage unit contains 10 mg enoxaparin sodium per 0.1 mL, sterile for injection. The solution is in a presentation-free and intended for use only as a single dose. (See DOSAGE AND ADMINISTRATION and HOW SUPPLIED for dosage unit descriptions.)

The pH of the Injection is 5.5 to 7.5, with an approximate anti-Factor Xa activity per dosage unit of 1,000 IU per every 10 mg of enoxaparin sodium (with reference to the IU.U.C. International Normalized Ratio [INR]).
Lovenox® (enoxaparin sodium) Injection

Efficacy of Lovenox Injection with Extended Post-Discharge Follow-Up:

Lovenox® (enoxaparin sodium) Injection

Indication

Post-Discharge Dosing Regimen

| Dosing Regimen | Lovenox® | Heparin
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Post-Discharge Dosing Regimen

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Efficacy of Lovenox Injection in Knee Replacement Surgery:

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Lovenox® (enoxaparin sodium) Injection

Efficacy of Lovenox Injection in Deep Vein Thrombosis:

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All patients were also treated with warfarin sodium commencing on the evening of day 2 of Lovenox injection and continuing for a minimum of 3 months. All patients received deep vein thrombosis event (deep venous thrombosis) and/or pulmonary embolus.

Efficacy of Lovenox Injection in Unstable Angina and Non-Q-Wave Myocardial Infarction:

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Lovenox® (enoxaparin sodium) Injection

Efficacy of Lovenox Injection in Combined Endpoint of Death, Myocardial Infarction, or Rehospitalization:

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Lovenox® (enoxaparin sodium) Injection

Efficacy of Lovenox Injection in Extended Post-Discharge Follow-Up:

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Lovenox® (enoxaparin sodium) Injection

Efficacy of Lovenox Injection in Knee Replacement Surgery:

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Lovenox® (enoxaparin sodium) Injection

Efficacy of Lovenox Injection in Deep Vein Thrombosis:

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Lovenox® (enoxaparin sodium) Injection

Efficacy of Lovenox Injection in Unstable Angina and Non-Q-Wave Myocardial Infarction:

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Lovenox® (enoxaparin sodium) Injection

Efficacy of Lovenox Injection in Combined Endpoint of Death, Myocardial Infarction, or Rehospitalization:

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Lovenox® (enoxaparin sodium) Injection

Efficacy of Lovenox Injection in Combined Endpoint of Death or Myocardial Infarction:

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Efficacy of Lovenox Injection in Extended Post-Discharge Follow-Up:

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Lovenox® (enoxaparin sodium) Injection

Efficacy of Lovenox Injection in Knee Replacement Surgery:

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Lovenox® (enoxaparin sodium) Injection

Efficacy of Lovenox Injection in Deep Vein Thrombosis:

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Lovenox® (enoxaparin sodium) Injection

Efficacy of Lovenox Injection in Unstable Angina and Non-Q-Wave Myocardial Infarction:

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Lovenox® (enoxaparin sodium) Injection

Efficacy of Lovenox Injection in Combined Endpoint of Death, Myocardial Infarction, or Rehospitalization:

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Lovenox® (enoxaparin sodium) Injection

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Lovenox® (enoxaparin sodium) Injection

Patient costs less than $50,000/month occurred at a rate of 0.1% in patients given Lovenox injection, in 0.3% of patients given heparin, and in 0.4% of patients given plain in the selected sites.

Thromboembolic events were infrequent in the post-operative period. The rate of significant thromboembolic events in the post-operative period was approximately 1% in patients treated with Lovenox injection.

Precautions

General: Lovenox injection should not be mixed with other injections or infusions.

Lovenox injection is associated with patient thromboembolic events, including arterial, arterial, and/or subclavian vein thrombosis, and/or pulmonary embolism. Lovenox injection should not be used in patients with known history of arterial, arterial, or subclavian vein thrombosis or pulmonary embolism. Lovenox injection should be used cautiously in patients with a known history of arterial, arterial, or subclavian vein thrombosis or pulmonary embolism.

Overdose: In case of overdose, the patient should be adequately rescued and resuscitated if necessary. Lovenox injection should not be used for the treatment of arterial, arterial, or subclavian vein thrombosis or pulmonary embolism.

Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Patients

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>N/500 ug</th>
<th>Severe</th>
<th>N/5000 ug</th>
<th>Severe</th>
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</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>0%</td>
<td>0%</td>
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<tr>
<td>Diaphoresis</td>
<td>0%</td>
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<tr>
<td>Myalgia</td>
<td>0%</td>
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<tr>
<td>Fatigue</td>
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Laboratory Tests: Complete blood count, including platelet count, and coagulation tests are recommended at the time of treatment with Lovenox injection. When significant laboratory values are noted during Lovenox injection, laboratory tests should be performed at regular intervals throughout the treatment duration. If significant laboratory values are noted during Lovenox injection, laboratory tests should be performed at regular intervals throughout the treatment duration.

Drug Interactions: Lovenox injection is not recommended for use with other anticoagulants or antiplatelet agents. Lovenox injection is not recommended for use with other anticoagulants or antiplatelet agents.

Pharmacodynamics: The pharmacodynamics of Lovenox injection are essentially the same as those of unfractionated heparin. The pharmacodynamics of Lovenox injection are essentially the same as those of unfractionated heparin.

Pharmacokinetics: Absorption: Lovenox injection is absorbed rapidly and completely from the subcutaneous injection site. Absorption: Lovenox injection is absorbed rapidly and completely from the subcutaneous injection site.

Parenteral administration is not recommended for use with other anticoagulants or antiplatelet agents. Parenteral administration is not recommended for use with other anticoagulants or antiplatelet agents.

In rare instances, patients may experience allergic reactions such as skin rash, urticaria, or angioedema. In rare instances, patients may experience allergic reactions such as skin rash, urticaria, or angioedema.

Some adverse effects may be reduced by the use of premedication or postmedication. Some adverse effects may be reduced by the use of premedication or postmedication.

Severe adverse effects may be reduced by the use of premedication or postmedication. Severe adverse effects may be reduced by the use of premedication or postmedication.

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The following pages contain additional information on adverse effects, laboratory tests, and drug interactions. The following pages contain additional information on adverse effects, laboratory tests, and drug interactions.

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Lovenox® (enoxaparin sodium) Injection

...uation is 7 to 10 days; up to 12 days administration has been well tolerated in clinical trials.

Treatment of Deep Vein Thrombosis and Pulmonary Embolism: In outpatient treatment, patients with acute deep vein thrombosis without pulmonary embolism who can be treated at home, the recom-

...he recommended dose of Lovenox Injection is 1.8 mg/kg every 12 hours administered SC. In inpatient (hospital) treatment, patients with acute deep vein thrombosis with pulmonary embolism or patients with acute deep vein thrombosis without pulmonary embolism who are not candidates for outpatient treatment, the recommended dose of Lovenox Injection is 1.8 mg/kg every 12 hours administered SC or 1.5 mg/kg once a day administered SC at the same time every day in both outpatient and inpatient (hospital) treatments, without exceeding 75 hours of Lovenox Injection. Lovenox Injection should be continued for a minimum of 5 days after discontinuation of intermittent pneumatic compression. Anticoagulant therapy should be continued for at least 10 days following discontinuation of intermittent pneumatic compression. The duration of administration is 7 to 14 days, up to 17 days Lovenox Injection administration has been well tolerated in controlled clinical trials. Unstable Angina and Non-Q-Wave Myocardial Infarction: In patients with unstable angina or non-

...ve thromboembolic events, the recommended dose of Lovenox Injection is 1 mg/kg administered SC every 12 hours in conjunction with oral antiplatelet therapy (100 to 325 mg daily). Treatment with Lovenox Injection should be continued for a minimum of 5 days and discontinued until clinical stabilization. The usual duration of treatment is 2 to 8 days. To minimize the risk of bleeding following vascular instrumentation during the treatment of unstable angina, administering the medication should be limited to inpatients. The intravenous route of administration should not be used after 48 hours following a dose of Lovenox Injection. The next recommended dose of Lovenox Injection should be administered 24 hours after thrombolytic therapy administration. The preferred route of administration is subcutaneous injection. The patient's abdominal, gluteal, or antecubital region should be selected. The injection should be administered 2 cm below the level of the anterior iliac spine or the lower intercostal space in the lower back. The subcutaneous injection site should be cleaned with alcohol before administration. The injection should be administered using a sterile needle. The subcutaneous injection site should be protected with a sterile dressing.

HOW SUPPLIED

Lovenox® (enoxaparin sodium) injection is available in:

<table>
<thead>
<tr>
<th>Dose Unit</th>
<th>Strength</th>
<th>Package Size</th>
<th>Anti-Xa Activity</th>
<th>NDC # IPEA-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampules</td>
<td>30 mg / 0.3 mL</td>
<td>10 ampules</td>
<td>3000 IU</td>
<td>0524-03</td>
</tr>
<tr>
<td>Pre-filled Syringeα</td>
<td>30 mg / 0.3 mL</td>
<td>10 syringes</td>
<td>3300 IU</td>
<td>0524-30</td>
</tr>
<tr>
<td>Pre-filled Syringeα</td>
<td>40 mg / 0.3 mL</td>
<td>10 syringes</td>
<td>3800 IU</td>
<td>0524-41</td>
</tr>
<tr>
<td>Graded Dose Pre-filled Syringeα</td>
<td>60 mg / 0.6 mL</td>
<td>10 syringes</td>
<td>6000 IU</td>
<td>0524-80</td>
</tr>
<tr>
<td>Graded Dose Pre-filled Syringeα</td>
<td>50 mg / 0.5 mL</td>
<td>10 syringes</td>
<td>6000 IU</td>
<td>0524-80</td>
</tr>
<tr>
<td>Graded Dose Pre-filled Syringeα</td>
<td>100 mg / 1.0 mL</td>
<td>10 syringes</td>
<td>10,000 IU</td>
<td>0524-30</td>
</tr>
</tbody>
</table>

α Strength represents the number of milligrams of enoxaparin sodium in Vial/for injection. Lovenox ampules and pre-filled syringes contain 10 mg enoxaparin sodium per 0.1 mL Water for Injection.

β Approximate anti-Xa activity based on reference to the WHO. First International Low Molecular Weight Heparin Reference Standard.

* Each Lovenox syringe is affixed with a 27-gauge 0.5 inch needle.

Keep out of the reach of children.

Lovenox injection pre-filled and graded pre-filled syringes manufactured in France. Lovenox injection ampules manufactured in England.

PHAEM-POLLING BÖRGER PHARMACEUTICALS INC., COLLEGEVILLE, PA 19426

Rev. 6/99

IN-4382BE
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-164/S-021

LABELING REVIEWS
Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-164/S-021
NDA 20-164/S-031

Name of Drug: Lovenox® (enoxaparin sodium) Injection

Sponsor: Rhone-Poulenc Rorer Pharmaceuticals Inc.

Material Reviewed

Submission Date(s): September 8, 1999 (S-021), Final Printed Labeling
September 8, 1999 (S-031), Final Printed Labeling

Receipt Date(s): September 9, 1999 (S-021)
September 9, 1999 (S-031)

Background and Summary Description:

Supplement -021, submitted September 8, 1999, approved April 20, 1999, provides for the addition of the following information in the ADVERSE REACTIONS section, the “Ongoing Safety Surveillance” subsection, of the package insert:

“Very rare cases of hyperlipidemia have been reported, with one case of hyperlipidemia, reported in a diabetic pregnant woman; causality has not been determined.”

The final printed labeling (FPL), submitted September 8, 1999 to Supplement –021, was in response to the April 20, 1999 approval letter.

Supplement –031, submitted September 8, 1999 under 21 CFR 314.70(c), “Special Supplement—Changes Being Effected” provides FPL, with the following revisions:

1. In the DOSAGE AND ADMINISTRATION section:
   a. The first sentence of the first paragraph reads:
      “All patients should be evaluated for a bleeding disorder before administration of Lovenox Injection, unless the medication is needed urgently.”

   b. The second sentence of the “Subcutaneous Injection Technique:” subsection reads:
      “To avoid the loss of drug when using the 30 and 40 mg prefilled syringes...”
2. In the ADVERSE REACTIONS section, the “Ongoing Safety Surveillance” subsection, the information approved in Supplement –021 regarding hyperlipidemia was provided.

Review

The final printed labeling (FPL) for the package inserts submitted for Supplement –021 and –031 are identical, incorporating the revisions provided for in both supplements. The package inserts, identified as “IN-2828E Rev. 6/99 508539BC” (Maisons Alfort) and “IN-1107T Rev. 6/99” (Dagenham), were compared to the package inserts approved December 31, 1998 in Supplement –015, identified as “IN-1107S Rev. 12/98 508539B” and “IN-2828D-Rev. 12/98”, respectively; the revisions requested in the April 20, 1999 approval letter for Supplement –021; and the changes provided for in CBE Supplement –031. Deletions are shown as strikethroughs and additions shown as double underlines.

1. In the ADVERSE REACTIONS section, the “Ongoing Safety Surveillance” subsection, the following sentence has been added:

“Very rare cases of hyperlipidemia have been reported, with one case of hyperlipidemia, reported in a diabetic pregnant woman; causality has not been determined.”

Comment: This revision, requested in the Agency’s April 20, 1999 approval letter for S-021, is acceptable.

2. In the DOSAGE AND ADMINISTRATION section:

a. The first sentence of the first paragraph has been revised as follows:

“All patients should be evaluated for a bleeding disorder before prophylactic administration of Lovenox Injection, unless the medication is needed urgently.”

b. The second sentence of the “Subcutaneous Injection Technique” subsection has been revised as follows:

“To avoid the loss of drug when using the 30 and 40 mg prefilled syringes, do not expel the air bubbles from the syringe before the injection.”

Comment: These two changes, provided for in S-031, were found acceptable in the medical officer review dated September 13, 1999.

3. The phrase “Rx only” has been moved from after the “HOW SUPPLIED” section to the right side of the title sections.
4. The copyright statement has been revised as follows: "©19982"

5. For the Maisons Alfort package insert,
   a. The identifier at the top of the package insert has been revised from:
      
      "IN-1107S Rev. 12/98 508539B"

      to:
      
      "IN-1107T Rev. 6/99 508539C"

   b. The identifier at the end of the package insert has been revised from:
      
      "IN-1107S Rev. 12/98"

      to:

      "IN-1107T Rev. 6/99"

6. For the Dagenham package insert, the identifier at the top and at the end of the package insert has been revised from:

   "IN-2828D Rev. 12/98"

   to:

   "IN-2828E Rev. 6/99"

Comment: These are appropriate editorial revisions.

Conclusions

The identical FPL submitted for Supplement -021 and Supplement -031 are acceptable. The FPL should be acknowledged and retained for Supplement -021 and approved for Supplement -031.
The currently approved package insert is now considered:

Maisons Alfort: "IN-1107T Rev. 6/99"
Dagenham: "IN-2828E Rev. 6/99"

cc:
Original NDA 20-164/S-021, S-031
HFD-180/Div. Files
HFD-180/A.Kacuba
HFD-180/K.Oliver

Draft: A.Kacuba/September 30, 1999
R/d Initials: K.Oliver/October 4, 1999
Final: AK/October 24, 1999
Filename: c:\wpfiles\20164-S-021-FA&S-031-CBE-lab-review.doc
CSO REVIEW
APPLICATION NUMBER:
NDA 20-164/S-021

MEDICAL REVIEW
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA: 20-164/SLR021

Drug name: Lovenox®

Generic name: Enoxaparin sodium

Other names: PK 10169
Enoxaparine
Pharmuka 10169

Chemical name: Alkaline degradation product of porcine intestinal mucosa characterized by a 2-O-sulfo-4-enepyranosuronic acid group at the non-reducing end and a 2-N,6-O-disulfo-D-glucosamine at the reducing end

Sponsor: Rhône-Poulenc Rorer Pharmaceuticals, Inc.

Pharmacologic Category: Low Molecular Weight Heparin
Anticoagulant
Antithrombotic

(Proposed) Indications: For the prevention of deep veinthrombosis which may lead to pulmonary embolism following hip or knee replacement surgery

Dosage Form(s) and Route(s) of Administration: 40 mg, subcutaneous injection

NDA Drug Classification:

Important Related Drugs: Dalteparin (Fragmin®)
Ardeparin (Normiflo®)
Danaparoid (Orgaran®)

Date of Submission: 1/12/99
Date received by HPD-180: 1/13/99
Date of Review: 4/1/99

Medical Reviewer: John William Schmeling, M.D., Ph.D.
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APPEARS THIS WAY ON ORIGINAL
2. MATERIAL REVIEWED
   A single-volume labeling supplement was reviewed.

3. RELATED REVIEW

4. BACKGROUND
   The Agency, on April 14, 1998, requested that the sponsor review reports
   regarding enoxaparin and hyperlipidemia, especially in pregnancy, and to
determine whether there should be a label revision for Lovenox® regarding
hyperlipidemia in pregnancy.

   The sponsor subsequently, on July 16, 1998, submitted a special supplement,
and indicated that no labeling revision was needed.

   A medical officer’s review, dated August 24, 1998, of this supplement,
disagreed and recommended that the post-marketing label warnings should
include a description of the case reports of hyperlipidemia in association with
Lovenox®. Further, it was recommended that the sponsor should state on the
label that one of the patients in whom marked hyperlipidemia occurred was
pregnant.

5. LABELING REVIEW

1.1 Proposed addition

   Proposed addition to ADVERSE REACTIONS, Ongoing Safety Surveillance
section:

   Other reports include: local reactions at the injection
site (i.e., skin necrosis, nodules, inflammation, oozing),
systemic allergic reactions (i.e., pruritus, urticaria),
vesiculobullous rash, purpura, and thrombocytosis.
Very rare cases of hyperlipidemia have been reported,
with one case of hypertriglyceridemia reported in a
diabetic pregnant woman; causality has not been
determined.
1.2 Comment

The diabetic pregnant woman developed hyperlipidemia, including hypercholesterolemia and hypertriglyceridemia.

The sentence should read:

Very rare cases of hyperlipidemia have been reported, with one case of hypertriglyceridemia–hyperlipidemia, with marked hypertriglyceridemia, reported in a diabetic pregnant woman; causality has not been determined.

John W. Schmeling, M.D., Ph.D.

cc:
NDA 20-164/SLR021
HFD-180
HFD-180/L.Talarico
HFD-180/J.Schmeling
HFD-181/PM
HFD-180/J.Choudary
HFD-180/EDuffy
f/t 4/9/99 jgw
N/20164904.JWS
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-164/S-021

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
NDA 20-164/S-021

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

Dear Mr. Babilon:

We acknowledge receipt of your labeling supplemental application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Lovenox® (enoxaparin sodium) Injection

NDA Number: 20-164

Supplement Number: S-021

Date of Supplement: January 12, 1999

Date of Receipt: January 13, 1999

This supplement proposes the following change(s): the addition of the following sentence to the ADVERSE REACTIONS section, the "Ongoing Safety Surveillance" subsection: "Very rare cases of hyperlipidemia have been reported, with one case of hypertriglyceridemia reported in a diabetic pregnant woman; causality has not been determined."

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 March 14, 1999 in accordance with 21 CFR 314.101(a).

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room, 6B-24
5600 Fishers Lane
Rockville, Maryland 20857
If you have any questions, contact me at (301) 827-7310.

Sincerely,

Karen Oliver, RN, MSN
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
cc:
Archival NDA 20-164/S-021
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/L.Talarico
HFD-180/J.Schmeling
DISTRICT OFFICE

Drafted by: KO/January 22, 1999
final: KO/01/22/99
filename: c:\mydocuments\NDA20164-S-021-01-22-99-ack

SUPPLEMENT ACKNOWLEDGEMENT (AC)
NDA 20-164/S-021

Rhone-Poulenc Rorer Pharmaceuticals Inc.
Attention: Edmond Roland, M.D.
P.O. Box 5096
500 Arcola Road
Collegeville, PA 19426-0800

Dear Dr. Roland:

We acknowledge receipt of your September 8, 1999 submission containing final printed labeling in response to April 20, 1999 letter approving your supplemental new drug application for Lovenox® (enoxaparin sodium) Injection.

We also acknowledge Supplement –031, submitted September 8, 1999 under 21 CFR 314.70(c) and approved October 5, 1999, that provided for changes in the DOSAGE AND ADMINISTRATION section of the package insert.

We have reviewed the labeling that you submitted in accordance with our April 20, 1999 approval letter and the changes approved October 5, 1999 in Supplement –031, and we find it acceptable.

If you have any questions, contact Karen Oliver, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely yours,

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
cc:
Archival NDA 20-164/S-021
HFD-180/division file
HFD-180/K.Oliver
HF-2/MedWatch (with labeling)
HFD-094/DDMS (with labeling)
HFD-103/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/OPDRA (with labeling)
DISTRICT OFFICE

Drafted by: A.Kacuba/September 30, 1999
Initialed by: K.Oliver/October 4, 1999
Final: AK/October 4, 1999
Filename: c:wpfiles\20164-S-021-AR.doc

ACKNOWLEDGE AND RETAIN (AR)