Approval Package for:

APPLICATION NUMBER:
NDA 20-164/S-051

Name:  Lovenox® (Enoxaparin Sodium) Injection

Sponsor:  Aventis Pharmaceuticals Products, Inc.

Approval Date:  June 20, 2003
# Reviews / Information Included in this Review

<table>
<thead>
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<td>Approvable Letter</td>
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<td>Medical Review</td>
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<td>X</td>
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</tbody>
</table>
APPLICATION NUMBER:
NDA 20-164/S-051

APPROVAL LETTER
NDA 20-164/S-051

Aventis Pharmaceuticals, Inc.
Attention: Shaler G. Smith, III, Ph.D.
Global Drug Regulatory Director and Liaison
200 Crossing Boulevard
P.O. Box 6890
Bridgewater, NJ 08807-0890

Dear Dr. Shaler:


We acknowledge receipt of your submissions dated April 16 and 18, May 9 and June 5, 2003.

This “Changes Being Effect” supplemental new drug application provides for the addition of an automatic safety device to all presentations of Lovenox® pre-filled syringes.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with minor editorial revisions listed below.

Include the manufacturing information on the Lovenox multiple-dose vial in the **HOW SUPPLIED** section at your next printing of the package insert.

All previous revisions as reflected in the most recently approved labeling, specifically Supplement S-043 approved January 23, 2003, must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

The final printed labeling (FPL) must be identical, and include the minor editorial revision indicated, to the text for the package insert submitted December 19, 2002, carton labels submitted December 19, 2002, immediate container labels for the 30 mg, 80 mg, 100 mg, 120 mg and 150 mg strength prefilled syringes submitted December 19, 2002, and immediate container labeling for the 40 mg and 60 mg strength prefilled syringes submitted June 5, 2003. This revision is terms of the approval of this application.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper 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-051." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Diane Moore, Regulatory Project Manager, at (301) 827-7476.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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Joyce Korvick
6/20/03 02:21:13 PM
for Dr. Robert Justice
Lovenox® (enoxaparin sodium injection)

Factor Xa activity versus time curve (AUC) was approximately 15% greater than the mean Day 1 AUC value. In subjects with moderate renal impairment (intrinsic clearance 30 to 80 mL/min), anti-Factor Xa CL/F values were similar to those in healthy subjects. However, mean CL/F values of subjects with severe renal impairment (intrinsic clearance <30 mL/min) were approximately 10% lower than the mean CL/F value of control group subjects. [See DOSAGE AND ADMINISTRATION.]

Although not studied clinically, the 150 mg/mL concentration of enoxaparin sodium is projected to result in anticoagulant activities similar to those of 100 mg/mL, and 200 mg/mL concentrations at the same enoxaparin dose. When a daily 1.5 mg/kg SC injection of enoxaparin sodium was given to 25 healthy male and female subjects using a 100 mg/mL, or a 200 mg/mL concentration the following pharmacokinetic profiles were obtained (see Table 4).

Pharmacokinetic Parameters* After 5 Days of 1.5 mg/kg SC Once Doses of Enoxaparin Sodium Using 100 mg/mL or 200 mg/mL Concentrations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Concentration</th>
<th>Day 1</th>
<th>5 Days</th>
<th>90% CI</th>
<th>2 CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amax 100 mg/mL</td>
<td>100 mg/mL</td>
<td>1.37 (0.72)</td>
<td>0.95 (0.69)</td>
<td>104.5 (116.4)</td>
<td>19.4 (44.7)</td>
</tr>
<tr>
<td>Amax 100 mg/mL</td>
<td>200 mg/mL</td>
<td>1.45 (0.72)</td>
<td>0.95 (0.69)</td>
<td>119.0 (127.1)</td>
<td>22.6 (44.7)</td>
</tr>
<tr>
<td>Amax 100 mg/mL</td>
<td>30 mg/mL</td>
<td>0.9 (0.56)</td>
<td>0.56 (0.32)</td>
<td>103.11 (109.8)</td>
<td>103-110%</td>
</tr>
<tr>
<td>Amax 100 mg/mL</td>
<td>150 mg/mL</td>
<td>1.46 (0.82)</td>
<td>0.56 (0.32)</td>
<td>103.11 (109.8)</td>
<td>103-110%</td>
</tr>
</tbody>
</table>

* Median ± SD at Day 5 and 90% Confidence Interval (CI) of the ratio

** Median (range)

Clinical Trials

Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery in Patients at Risk for Thromboembolic Complications: Abdominal surgery patients at risk, include those who are over 40 years of age, obese, undergoing surgery under general anesthesia lasting longer than 30 minutes or who have additional risk factors such as malignancy or a history of deep vein thrombosis or pulmonary embolism. In a double-blind, parallel group study of patients undergoing elective cancer surgery of the gastrointestinal, urological, or gynecological tract, a total of 1116 patients were enrolled in the study, and 1115 patients were treated. Patients ranged in age from 32 to 97 years (mean age 67 years). 52.7% men and 47.3% women. Patients were 98% Caucasian, 1.1% Black, 0.4% Oriental, and 0.4% others. Lovenox Injection 40 mg/mL, administered once a day, beginning 2 hours prior to surgery and continuing for a maximum of 12 days after surgery, was comparable to heparin 5000 IU every 8 hours SC in reducing the risk of deep vein thrombosis (DVT). The efficacy data are provided below.

Efficacy of Lovenox Injection in the Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery

** Median (range)

<table>
<thead>
<tr>
<th>Dosing Regimen</th>
<th>Lovenox Inj.</th>
<th>Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 mg q. d. SC</td>
<td>500 U/kg SC</td>
<td></td>
</tr>
</tbody>
</table>

Indication

All Treated Abdominal Surgery Patients

<table>
<thead>
<tr>
<th>Treatment Failures</th>
<th>Total VTE (%)</th>
<th>95% CI: 9 to 15</th>
<th>95% CI: 9 to 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT Only (%)</td>
<td>54 (9.7)</td>
<td>95% CI: 9 to 12</td>
<td>95% CI: 9 to 12</td>
</tr>
</tbody>
</table>

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

** Confidence Interval

In a second double-blind, parallel group study, Lovenox Injection 40 mg/mL once a day was compared to heparin 5000 IU every 6 hours SC in patients undergoing colorectal surgery (one-third with cancer). A total of 1347 patients were randomized in the study and all patients were treated. Patients ranged in age from 18 to 92 years (mean age 61 years). 54.2% men and 45.8% women. Treatment was initiated approximately 24 hours prior to surgery and continued for approximately 7 to 10 days after surgery. The efficacy data are provided below.

Efficacy of Lovenox Injection in the Prophylaxis of Deep Vein Thrombosis Following Colorectal Surgery

** Median (range)

<table>
<thead>
<tr>
<th>Dosing Regimen</th>
<th>Lovenox Inj.</th>
<th>Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 mg q. d. SC</td>
<td>5000 U/kg SC</td>
<td></td>
</tr>
</tbody>
</table>
Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery: Lovenox Injection has been shown to reduce the risk of post-operative deep vein thrombosis (DVT) following hip or knee replacement surgery.

In a double-blind, multicenter study, 100 patients were randomized to either Lovenox Injection 40 mg once a day SC or placebo (n = 90) for 3 weeks. A total of 179 patients were randomized in the double-blind phase of the regimen of either Lovenox Injection 40 mg (n = 90) once a day SC or to placebo (n = 89) study of extended prophylaxis for patients undergoing hip replacement surgery, patients with hip replacement surgery, patients undergoing knee replacement surgery, and patients with knee replacement surgery.

**Efficacy of Lovenox Injection in the Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery**

<table>
<thead>
<tr>
<th>Treatment Failure</th>
<th>Placebo</th>
<th>Lovenox Inj.</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Treated Hip Replacement Patients</td>
<td>0 (0)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Total DVT (%)</td>
<td>43 (12.3%)</td>
<td>16 (4.4%)</td>
</tr>
<tr>
<td>Total VTE (%)</td>
<td>47 (100)</td>
<td>52 (100)</td>
</tr>
</tbody>
</table>

Treatment continued for a maximum of 14 days (median duration 7 days). When given at a dose of 40 mg once a day SC, Lovenox Injection significantly reduced the incidence of DVT as compared to placebo. The efficacy data are provided below.

**Prophylaxis of Deep Vein Thrombosis (DVT) in Medical Patients With Severely Restricted Mobility During Acute Illness:** In a double-blind, multicenter, parallel group study, Lovenox Injection 20 mg or 40 mg once a day SC was compared to placebo in the prophylaxis of DVT in medical patients with severely restricted mobility during acute illness (defined as walking distance < 200 meters for < 3 days). This study included patients with heart failure (NYHA Class III or IV), acute respiratory failure or complicated chronic respiratory insufficiency (not requiring ventilatory support), acute infection (excluding septic shock), or acute thrombotic disorder (acute lumbar or sciatic pain, vertebral compression [due to intervertebral herniation or tumor], acute atherothrombotic episodes of the lower extremities). A total of 1102 patients were enrolled in the study, and 1073 patients were treated. Patients ranged in age from 40 to 87 years (mean age 75 years) with equal proportions of men and women. Treatment (continued for a maximum of 14 days [median duration 7 days]) was initiated at a dose of 40 mg once a day SC. Lovenox Injection significantly reduced the incidence of DVT as compared to placebo. The efficacy data are provided below.

**Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction:** In a multicenter, double-blind, parallel group study, patients who recently experienced unstable angina or non-Q-wave myocardial infarction were randomized to either Lovenox Injection 1 mg/kg every 12 hours SC or heparin i.v. bolus (5000 U) followed by a continuous infusion (adjusted to achieve an aPTT of 55 to 85 seconds). A total of 453 patients were randomly assigned to either treatment and all patients were treated. Patients ranged in age from 38 to 89 years (mean age 68.5 years) with 43.7% men and 56.3% women. Patients were randomized to either Lovenox Injection 8 (6%) versus placebo 28 (21%); P = .001. Prophylaxis of Deep Vein Thrombosis in Medical Patients With Severely Restricted Mobility During Acute Illness. 1 Treatment failures during therapy, between Days 1 and 14. VTE = Venous thromboembolic events which included DVT, PE, and death considered to be thromboembolic in origin. 2 CI = Confidence Interval. 3 Treatment failures during therapy, between Days 1 and 14. VTE = Venous thromboembolic events which included DVT, PE, and death considered to be thromboembolic in origin.
Efficacy of Lovenox Injection in Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction

(Combined Endpoint of Death, Myocardial Infarction, or Recurrent Angina)

**Dosing Regimen**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Lovenox®</th>
<th>Heparin</th>
<th>Reduction</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Treated Unstable Angina and Non-Q-Wave MI Patients</td>
<td>1 mg/kg q12h SC</td>
<td>apPT Adjusted</td>
<td>0.7</td>
<td>0.047</td>
</tr>
</tbody>
</table>

**Timepoint**

<table>
<thead>
<tr>
<th></th>
<th>(n)</th>
<th>(n)</th>
<th>(%)</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total VTE</td>
<td>329 (100)</td>
<td>339 (100)</td>
<td>96.8</td>
<td>93.0</td>
</tr>
<tr>
<td>VTI</td>
<td>105 (32)</td>
<td>115 (34)</td>
<td>90.6</td>
<td>86.6</td>
</tr>
<tr>
<td>DVT</td>
<td>214 (65)</td>
<td>224 (67)</td>
<td>95.3</td>
<td>92.3</td>
</tr>
<tr>
<td>PE</td>
<td>27 (8)</td>
<td>36 (11)</td>
<td>96.4</td>
<td>97.2</td>
</tr>
</tbody>
</table>

All patients were also treated with aspirin 160 to 325 mg per day.

**Evaluation timepoints** after initiation of therapy. Therapy continued for up to 30 days (median duration of 2.6 days).

**Efficacy of Lovenox Injection in Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction**

<table>
<thead>
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<th>Reduction</th>
<th>p Value</th>
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<td>36 (11)</td>
<td>96.4</td>
<td>97.2</td>
</tr>
</tbody>
</table>

**Indications and Usage**

- Lovenox Injection is indicated for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism.
  - In patients undergoing abdominal surgery who are at risk for thromboembolic complications.
  - In patients undergoing hip replacement surgery, during and following hospitalization.
  - In patients undergoing knee replacement surgery.
  - In medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

**Contraindications**

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

- Hemitremor: Lovenox injection, like other anticoagulants, should be used with extreme caution in patients with increased risk of hemorrhage such as bacterial endocarditis, congenital or acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disease, hemorrhagic stroke, or shortly after brain, spinal, or ophthalmological surgery, or patients treated concomitantly with platelet inhibitors.

- Cases of epidermal or visceral hematomas have been reported with the associated use of Lovenox injection and spinal/epidural anesthesia or spinal puncture resulting in long-term or permanent paralysis. The risk of these events is higher with the use of postoperative indwelling epidural catheters or by the concomitant use of additional drugs affecting hemostasis such as NSAIDs (see boxed WARNING; ADVERSE REACTIONS, Ongoing Safety Surveillance; and PRECAUTIONS, Drug Interactions).

- Major hematomas including intradural and intracranial bleeding have been reported. Some of these cases have been fatal.

- Bleeding can occur at any site during therapy with Lovenox injection. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

- Thrombocytopenia: Thrombocytopenia can occur with the administration of Lovenox injection.

- Moderate thrombocytopenia (platelet counts between 100,000/mmcu and 50,000/mmcu) occurred in 1.3% of patients given Lovenox injection, 1.2% in patients given heparin, and 0.7% in patients given placebo in clinical trials. Platelet counts less than 50,000/mmcu occurred in 0.0% of patients given Lovenox injection, in 0.0% of patients given heparin, and in 0.0% of patients given placebo in the same trials. Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mmcu, Lovenox injection should be discontinued. If new or life-threatening bleeding occurs, prophylactic heparin should be administered until the bleeding stops. Some of these cases were complicated by organ infarction, limb ischemia, or death.

- Prophylactic Heart Valves: The use of Lovenox injection is not recommended for thromboprophylaxis in patients with prosthetic heart valves. Cases of prostatic heart valve thrombosis have been reported in patients with prosthetic valve who have received enoxaparin for thromboprophylaxis. Some of these cases were complicated by organ infarction, limb ischemia, or death.

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Lovenox®

(Enoxaparin sodium injection)

Cautions

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

PRECAUTIONS

Lovenox Injection should be used with care in patients with a bleeding diathesis, uncontrolled and/or for patients with severe renal impairment (creatinine clearance <30 ml/min).

Drug Interactions: Unless really needed, agents which may enhance the risk of hemorrhage should be discontinued prior to initiation of Lovenox Injection Therapy. These agents include medications such as: anticoagulants, platelet inhibitors including aspirin, salicylic acid, salicylates, NSAIDs (including ketorolac tromethamine), diuretics, and sulfonpyrazone. If co-administration is essential, conduct close clinical and laboratory monitoring (see PRECAUTIONS: Laboratory Tests).

Respiratory: Lovenox Injection-associated bleeding increased with age. Serious adverse events were always considered major although none were reported during the trial. The rates reported major bleeding on study medication up to 24 hours after last dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of enoxaparin. Enoxaparin was not mutagenic in in vitro tests, including the Ames test, mouse lymphoma cell forward mutation test, and human lymphocyte chromosomal aberration test, and the in vivo bone marrow chromosomal aberration test. Enoxaparin was found to have no effect on fertility or reproductive performance of male and female rats at SC doses of up to 20 mg/kg or IV doses of up to 15 mg/kg body weight. The mean human dose in clinical trials was 2.0 mg/kg/day or 78 mg/m²/day (for an average body weight of 70 kg, height of 170 cm, and body surface area of 1.8 m²).

Laboratory Tests: Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with Lovenox injection. When administered at recommended prophylactic doses, routine coagulation tests such as prothrombin time (PT), activated partial thromboplastin time (aPTT), and factor VIII levels are not affected. Baseline coagulation parameters or bleeding should occur. In older patients, use caution in patients with renal impairment, severe hematologic disease or the need for anticoagulation may be used to reduce the risk of anticoagulant effects of enoxaparin (see CLINICAL PHARMACOLOGY: Pharmacodynamics).

Drug Interactions: Unless really needed, agents which may enhance the risk of hemorrhage should be discontinued prior to initiation of Lovenox Injection Therapy. These agents include medications such as: anticoagulants, platelet inhibitors including aspirin, salicylic acid, salicylates, NSAIDs (including ketorolac tromethamine), diuretics, and sulfonpyrazone. If co-administration is essential, conduct close clinical and laboratory monitoring (see PRECAUTIONS: Laboratory Tests).

Elevations of Serum Aminotransferases: Asymptomatic increases in aspartate (AST) (SGOT) and alanine (ALT) (SGPT) transaminase levels have also been observed in patients and healthy volunteers (see CLINICAL PHARMACOLOGY: Pharmacokinetics and General and Laboratory Tests subsections of PRECAUTIONS).

ADVERSE REACTIONS

Hemorrhage: The incidence of major hemorrhagic complications during Lovenox Injection treatment has been low. The following series of major bleeding events have been reported during clinical trials with Lovenox injection.

Major Bleeding Episodes Following Hip or Knee Replacement Surgery

The following table summarizes the major bleeding episodes following hip or knee replacement surgery during clinical trials with Lovenox injection.

1 Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥2 g/dL or transfusion of 2 or more units of blood products. Retropertoneal, intracranial and intracardiac hemorrhages were always considered major, in the knee replacement surgery trials, intracranial hemorrhages were also considered major hemorrhages.

2 Lovenox injection 30 mg every 12 hours SC initiated 12 to 24 hours after surgery and continued for up to 14 days after surgery.

3 Lovenox injection 40 mg SC once a day initiated up to 12 hours prior to surgery and continued for up to 7 days after surgery.

4 Lovenox injection 40 mg SC once a day for up to 21 days after discharge.

FLIGHT STATUS OF HEMORRHAGES DURING THE EXTENDED PROPHYLAXIS PERIOD AFTER HIP REPLACEMENT SURGERY OCCURRED IN 9% OF THE Lovenox injection patients versus 1.8% of the placebo patients.

Major Bleeding Episodes in Patients With Severely Restricted Mobility During Acute Illness

The following table summarizes the major bleeding episodes in patients with severely restricted mobility during acute illness.

1 Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥2 g/dL or transfusion of 2 or more units of blood products. Retropertoneal and intracranial hemorrhages were always considered major although none were reported during the trial.

2 The rates represent major bleeding on study medication up to 24 hours after last dose.

Thrombolytic agents are contraindicated in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, elevations that might be caused by drugs like Lovenox injection should be interpreted with caution. Other clinical experience related to gastrointestinal bleeding or local irritation, pain, hematuria, ecchymosis, and rhinorrhea may follow SC injection of Lovenox injection.

Dosing Regimen

Injections

Lovenox Injection

40 mg 5 mL SC

150 mg 15 mL SC

Repare

Without Extended

Prophylaxis

Lovenox Injection

Prophylaxis

Extended Prophylaxis

90 mg 30 mL SC

120 mg 30 mL SC

n = 225

n = 221

n = 208

n = 441

n = 225

1 mg/kg q12h SC

1.5 mg/kg q.d. SC

Lovenox Injection

Lovenox Injection

15,000 U/24h SC

Heparin

1 mg/kg q12h SC

1.5 mg/kg q.d. SC

Heparin

aPTT Adjusted

i.v. Therapy

Treatmen of DVT and PE

n = 298

1 mg/kg q12h SC

n = 559

n = 594

2 mg/kg q.d. SC

n = 667

n = 674

2 mg/kg q.d. SC

n = 667

n = 674

Notes:

1. Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥2 g/dL or transfusion of 2 or more units of blood products. Retropertoneal, intracranial and intracardiac hemorrhages were always considered major, in the knee replacement surgery trials, intracranial hemorrhages were also considered major hemorrhages.

2. Lovenox injection 30 mg every 12 hours SC initiated 12 to 24 hours after surgery and continued for up to 14 days after surgery.

3. Lovenox injection 40 mg SC once a day initiated up to 12 hours prior to surgery and continued for up to 7 days after surgery.

4. Lovenox injection 40 mg SC once a day for up to 21 days after discharge.

5. FLIGHT STATUS OF HEMORRHAGES DURING THE EXTENDED PROPHYLAXIS PERIOD AFTER HIP REPLACEMENT SURGERY OCCURRED IN 9% OF THE Lovenox injection patients versus 1.8% of the placebo patients.

6. The rates represent major bleeding on study medication up to 24 hours after last dose.
Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Patients

Undergoing Abdominal or Colorectal Surgery

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Lovenox Injection</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage</td>
<td>&lt;1%</td>
<td>7%</td>
</tr>
<tr>
<td>Anemia</td>
<td>&lt;1%</td>
<td>3%</td>
</tr>
<tr>
<td>Escherichia</td>
<td>0%</td>
<td>3%</td>
</tr>
</tbody>
</table>

1 Excluding unrelated adverse events.

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

Undergoing Hip or Knee Replacement Surgery

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Lovenox Injection</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage</td>
<td>&lt;1%</td>
<td>7%</td>
</tr>
<tr>
<td>Anemia</td>
<td>&lt;1%</td>
<td>3%</td>
</tr>
<tr>
<td>Escherichia</td>
<td>0%</td>
<td>3%</td>
</tr>
</tbody>
</table>

1 Excluding unrelated adverse events.

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

With Severely Restricted Mobility During Acute Illness

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Lovenox Injection</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage</td>
<td>&lt;1%</td>
<td>2%</td>
</tr>
<tr>
<td>Anemia</td>
<td>&lt;1%</td>
<td>3%</td>
</tr>
<tr>
<td>Escherichia</td>
<td>0%</td>
<td>3%</td>
</tr>
</tbody>
</table>

1 Excluding unrelated and unlikely adverse events.

OVERDOSAGE

Symptoms/Treatment: Accidental overdose following administration of Lovenox Injection may lead to hemorraghic complications. Injected Lovenox Injection may be neutralized by the intravenous administration of protamine sulfate (1 mg per 100 mg of Lovenox Injection, 9% solution). The dose of protamine sulfate should be equal to the dose of Lovenox Injection injected: 1 mg protamine sulfate should be administered to neutralize 1 mg Lovenox Injection. A second infusion of 0.5 mg protamine sulfate per kilogram Lovenox Injection may be administered if the aPTT measured 2 to 4 hours after the first infusion remains prolonged. However, with higher doses of protamine, the aPTT may remain prolonged under normal conditions following administration of heparin. In all cases, the anti-Factor Xa activity is nearly completely neutralized (maximum about 80%). Particular caution should be taken to avoid overdose with protamine sulfate. Administration of protamine sulfate can cause severe hypotensive and anaphylactic reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulfate, it should be given only when reulation techniques and treatment of anaphylactic shock are readily available.

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

Undergoing Deep Vein Thrombosis With or Without Pulmonary Embolism

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Lovenox Injection</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage</td>
<td>&lt;1%</td>
<td>1%</td>
</tr>
<tr>
<td>Anemia</td>
<td>&lt;1%</td>
<td>3%</td>
</tr>
<tr>
<td>Escherichia</td>
<td>0%</td>
<td>3%</td>
</tr>
</tbody>
</table>

1 Excluding unrelated adverse events.

Ongoing Safety Surveillance: Since 1993, there have been over 80 reports of epidural or spinal hematoma formation or concurrent use of Lovenox Injection and spinal/epidural anesthesia or spinal puncture. The majority of patients had a post-operative indwelling epidural catheter placed for analgesia or received additional drugs affecting hemostasis such as NSAIDs. Many of the epidural or spinal hematomas caused neurologic injury, including long-term or permanent paralysis. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

DOSAGE AND ADMINISTRATION

Adult Dosage: Adjuvant Surgery: In patients undergoing abdominal surgery who are at risk for thromboembolic complications, the recommended dose of Lovenox Injection is 40 mg once administered by SC injection. The usual duration of administration is 3 to 5 days; up to 6 days administration has been well tolerated in clinical trials. Mip or Knee Replacement Surgery: In patients undergoing hip or knee replacement surgery, the recommended dose of Lovenox Injection is 30 mg given every 12 hours by SC injection. The usual duration of administration is 10 to 14 days; up to 21 days administration has been well tolerated in clinical trials. Medical Patients: During Acute Illness: In medical patients at risk for thromboembolic complications due to severe restricted mobility during acute illness, the recommended dose of Lovenox Injection is 40 mg once administered by SC injection. The usual duration of administration is 6 to 11 days; up to 14 days of Lovenox Injection has been well tolerated in controlled clinical trials.
**Lovenox** (enoxaparin sodium injection)

Treatment of Deep Vein Thrombosis with or Without Pulmonary Embolism: In outpatient treatment, patients with acute deep vein thrombosis with or without pulmonary embolism who can be treated at home, the recommended dose of Lovenox Injection is 1 mg/kg every 12 hours administered SC. In inpatient hospital treatment, patients with acute deep vein thrombosis with or without pulmonary embolism who are not candidates for outpatient treatment, the recommended dose of Lovenox injection is 1 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 treatment, warfarin sodium therapy should be initiated when appropriate (usually within 72 hours of Lovenox injection). Lovenox injection should be continued for a minimum of 5 days and until a therapeutic oral anticoagulant effect has been achieved (International Normalization Ratio 2.0 to 3.0). The average duration of administration is 7 days, up to 17 days of Lovenox injection administration has been well tolerated in controlled clinical trials.

**Administration**: Lovenox injection is a clear, colorless to pale yellow sterile solution, and as with other parenteral drug products, should be inspected visually for particulate matter and discoloration prior to administration. When using Lovenox injection ampules, to assure withdrawal of the appropriate volume of drug, the use of a tuberculin syringe or equivalent is recommended. Lovenox injection is administered by SC injection. It must not be administered by intramuscular injection. Lovenox injection is intended for use under the guidance of a physician. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up, as necessary. Proper training in subcutaneous injection technique (with or without the assistance of an injection device) should be provided.

Subcutaneous Injection Technique: Patients should be lying down and Lovenox injection administered by deep SC injection. To avoid the loss of drug when using the 30 and 40 mg prefilled syringes, do not expel the air bubble from the syringe before the injection. Administration should be alternated between the left and right anterolateral and left and right posterolateral abdominal wall. The whole length of the needle should be introduced into a skin fold held between the thumb and forefinger; the skin fold should be held throughout the injection should be alternated between the left and right anterolateral and left and right posterolateral abdominal wall. The whole length of the needle should be introduced into a skin fold held between the thumb and forefinger; the skin fold should be held throughout the injection. To minimize bruising, do not rub the injection site after completion of the injection. Lovenox injection prefilled syringes and graduated prefilled syringes are available with a system that shields the needle after injection.

- Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.

- Inject using standard technique, pushing the plunger to the bottom of the syringe.

- Remove the syringe from the injection site keeping your finger on the plunger rod.

- Obtain the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm shield activation.

- Immediately dispose of the syringes in the nearest sharps container.

**Directions for use of One Point Cut (OPC) ampules for Lovenox Injection:**

Use aseptic technique throughout the process. Prior to starting, gently tap the top of the ampule to assist the flow of the solution from the upper portion of the ampule to the lower portion.

1. Locate the yellow dot on the upper portion of the ampule. Below this dot is a small score on the neck of the ampule. Hold the ampule with the yellow dot facing away from you. Do not try to break the ampule at the colored rings, which are identification marks used only in manufacturing.
2. Cover yellow dot with your index finger and position your thumb opposite yellow dot.
3. Apply pressure to the top and bottom portions of the ampule to snap the ampule open away from you.

**HOW SUPPLIED**

Lovenox injection (enoxaparin sodium injection) is available in two concentrations:

100 mg/mL Concentration

<table>
<thead>
<tr>
<th>Dosage Unit / Size</th>
<th>Anti-Xa Activity</th>
<th>Package Size (per carton)</th>
<th>Syringe Label Color</th>
<th>NDC #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampules 30 mg / 0.3 mL</td>
<td>3000 U</td>
<td>10 ampules</td>
<td>Medium Blue</td>
<td>0624-03</td>
</tr>
<tr>
<td>Prefilled Syringes 30 mg / 0.3 mL</td>
<td>3000 U</td>
<td>10 syringes</td>
<td>Medium Blue</td>
<td>0624-30</td>
</tr>
<tr>
<td>Prefilled Syringes 40 mg / 0.4 mL</td>
<td>4000 U</td>
<td>10 syringes</td>
<td>Yellow</td>
<td>0620-40</td>
</tr>
</tbody>
</table>

**150 mg/mL Concentration**

<table>
<thead>
<tr>
<th>Dosage Unit / Size</th>
<th>Anti-Xa Activity1</th>
<th>Package Size (per carton)</th>
<th>Syringe Label Color</th>
<th>NDC #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graduated Prefilled Syringes 1 120 mg / 0.8 mL</td>
<td>12,000 U</td>
<td>10 syringes</td>
<td>Purple</td>
<td>2912-01</td>
</tr>
<tr>
<td>150 mg / 1 mL</td>
<td>15,000 U</td>
<td>10 syringes</td>
<td>Navy Blue</td>
<td>2915-01</td>
</tr>
</tbody>
</table>

1. Strength represents the number of milligrams of enoxaparin sodium in Water for Injection.

**Ampules**

Ampules contain 30, 40, 60, 80, and 100 mg enoxaparin sodium per 0.1 mL Water for Injection.

**Syringes**

Approximate Anti-Factor Xa activity based on reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard.

Each Lovenox Injection syringe is labeled with a 27 gauge x 1/2 inch needle.

Store at Controlled Room Temperature, 15-25°C (59-77°F) [see USP]

Keep out of the reach of children.

Lovenox injection prefilled and graduated prefilled syringes manufactured by:

Aventis Pharma Specialties
4470, Maison-Vert
France.

Aventis Pharma
Boulevard Industriel
75004 Le Trefl
France

Lovenox injection ampules manufactured by:

Aventis Pharma LTD
Dagenham Essex RM10 7XS
United Kingdom.

Aventis Pharmaceuticals Inc.
Bridgewater, NJ 08807

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Prescribing information as of September 2002

50069809
LOVENOX®
(Enoxaparin sodium injection)

30 mg/0.3 mL
[100 mg/mL]

Rx ONLY
SINGLE DOSE SYRINGES WITH AUTOMATIC SAFETY DEVICE FOR SUBCUTANEOUS INJECTION

Ten 0.3 mL Syringes

Aventis
Lovenox®
(enoxaparin sodium injection)

Rx ONLY

Each LOVENOX® Syringe contains 30mg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection.

Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use.

WARNING: Keep out of reach of children.

Store at Controlled Room Temperature 15-25°C (59-77°F) [see USP].

Mfd by: Aventis Pharma Specialties
94700 Maisons-Alfort
France

and

Aventis Pharma
Boulevard Industriel
76580 Le Trait
France

Mfd for: Aventis Pharmaceuticals Inc.
Bridgewater, NJ 08807 ©2002

Made in France

www.aventispharma-us.com

50062559

Lovenox®
(enoxaparin sodium injection)

Directions for Use of Lovenox
Single Dose Syringe with Automatic Safety Device:

1. Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.

2. Inject using standard technique, pushing the plunger to the bottom of the syringe.

3. Remove the syringe from the injection site keeping your finger on the plunger rod.

4. Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm shield activation.

5. Immediately dispose of the syringe in the nearest sharps container.

NOTE:
- The safety system can only be activated once the syringe has been emptied.
- Activation of the safety system must be done only after removing the needle from the patient's skin.
- Do not replace the needle shield after injection.

- The safety system should not be sterilized.
- Activation of the safety system may cause minimal splatter of fluid. For optimal safety, activate the system while orienting it downwards away from yourself and others.
LOVENOX 30 mg
Device Label

LOVENOX 30 mg
Blisterfoil

LOVENOX® (enoxaparin sodium injection) Rx Only
Single Use Syringe with Automatic Safety Device
For Subcutaneous Injection

Each LOVENOX® Syringe contains 30mg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection and sodium citrate as a preservative.

Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use.

Store at Controlled Room Temperature 15-25°C (59-77°F) [see USP]. Wipe the tip of each syringe.

WARNING: Keep out of reach of children.

Visit for Aventis Pharmaceuticals Inc.
Bridgeton, NJ 08017 USA

Made in France

NDC 0075-0624-30

Pharmaceuticals Inc.
LOVENOX®
(Enoxaparin Sodium Injection)

40 mg/0.4 mL
[100 mg/mL]

Rx ONLY
SINGLE DOSE SYRINGES WITH AUTOMATIC SAFETY DEVICE
FOR SUBCUTANEOUS INJECTION

Ten 0.4 mL Syringes

Aventis
Lovenox®
(enoxaparin sodium injection)
RX ONLY
Each LOVENOX® Syringe contains 40mg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection.

Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use.

WARNING: Keep out of reach of children.

Store at Controlled Room Temperature 15–25°C (59–77°F) [see USP].


40 mg 0.4 ml
NDC 0174-9204-40

Lovenox®
(enoxaparin sodium injection)

Directions for Use of Lovenox Single Dose Syringe with Automatic Safety Device:

1. Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.

2. Inject using standard technique, pushing the plunger to the bottom of the syringe.

3. Remove the syringe from the injection site keeping your finger on the plunger rod.

NOTE:
• The safety system can only be activated once the syringe has been emptied.
• Activation of the safety system must be done only after removing the needle from the patient’s skin.
• Do not replace the needle shield after injection.

4. Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible “click” will be heard to confirm shield activation.

5. Immediately dispose of the syringe in the nearest sharps container.

• The safety system should not be sterilized.
• Activation of the safety system may cause minimal splatter of fluid. For optimal safety activate the system while orienting it downwards away from yourself and others.
Lovenox® (enoxaparin sodium injection) Rx ONLY
40mg/0.4ml [100mg/ml] For Subcutaneous Injection
Made for: Aventis Pharmaceuticals Inc.
LOVENOX®
(Enoxaparin sodium injection)

60 mg / 0.6 mL
(100 mg/mL)

Rx ONLY

SINGLE DOSE SYRINGES WITH AUTOMATIC SAFETY DEVICE FOR SUBCUTANEOUS INJECTION

Ten 0.6 mL Syringes

Aventis
Lovenox®
(enoxaparin sodium injection)

Rx ONLY
Each LOVENOX® Syringe contains 60mg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection.

Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use. Each 0.025mL graduation equals 2.5mg enoxaparin sodium injection.

WARNING: Keep out of reach of children.

Store at Controlled Room Temperature 15-25°C (59-77°F) [see USP].

Mfd by: Aventis Pharma Specialties
94700 Maisons-Alfort
France
and
Aventis Pharma
Boulevard Industriel
7E800 - Tarbes
France

Lovenox®
(enoxaparin sodium injection)

Directions for Use of Lovenox Single Dose Syringe with Automatic Safety Device:

1. Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.

2. Inject using standard technique, pushing the plunger to the bottom of the syringe.

3. Remove the syringe from the injection site keeping your finger on the plunger rod.

4. Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm shield activation.

5. Immediately dispose of the syringe in the nearest sharps container.

NOTE:
- The safety system can only be activated once the syringe has been emptied.
- Activation of the safety system must be done only after removing the needle from the patient's skin.
- Do not replace the needle shield after injection.
LOVENOX® (enoxaparin sodium injection)

Each LOVENOX® single-dose syringe contains 60 mg of enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection. Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use. Each 0.025 mL graduation equals 2.5 mg enoxaparin sodium injection.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) (see USP Controlled Room Temperature). WARNING: Keep out of reach of children. Mfd for: Aventis Pharmaceuticals Inc. Bridgewater, NJ 08807 (2003 Made in France

LOVENOX® (enoxaparin sodium injection)

Lot G0950.6mL/100mg/mL

Mfd for: Aventis Pharmaceuticals Inc.
Lovenox®
(enoxaparin sodium injection)

Rx ONLY

Each LOVENOX® Syringe contains 80mg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection.

Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use. Each 0.025mL graduation equals 2.5mg enoxaparin sodium injection.

WARNING: Keep out of reach of children.

Store at Controlled Room Temperature 15–25°C (59–77°F) [see USP].

Mfd by: Aventis Pharma Specialties
94700 Maisons-Alfort
France

and

Aventis Pharma
Boulevard Industriel
76580 Le Trait
France

Mfd for: Aventis Pharmaceuticals Inc.
Bridgewater, NJ 08807 ©2002
Made in France
www.aventispharma-us.com
50062754

Directions for Use of Lovenox
Single Dose Syringe with Automatic Safety Device:

1. Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.

2. Inject using standard technique, pushing the plunger to the bottom of the syringe.

3. Remove the syringe from the injection site keeping your finger on the plunger rod.

4. Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible “click” will be heard to confirm shield activation.

5. Immediately dispose of the syringe in the nearest sharps container.

NOTE:
- The safety system can only be activated once the syringe has been emptied.
- Activation of the safety system must be done only after removing the needle from the patient’s skin.
- Do not replace the needle shield after injection.
- The safety system should not be sterilized.
- Activation of the safety system may cause minimal splatter of fluid. For optimal safety activate the system while orienting it downwards away from yourself and others.
Each LOVENOX syringe contains 80 mg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection. 

Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use. Each 0.025 ml graduation equals 2.5 mg enoxaparin sodium injection. 

Store at controlled room temperature 15-30°C (59-86°F) (USP). 

WARNING: Keep out of reach of children. 

Mfd for: Aventis Pharmaceuticals Inc. 

Bridgewater, NJ 08807-8910 

Made in France
Lovenox®
(enoxaparin sodium injection)

Rx ONLY

Each LOVENOX® Syringe contains 100mg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection.

Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use. Each 0.025mL graduation equals 2.5mg enoxaparin sodium injection.

WARNING: Keep out of reach of children.

Store at Controlled Room Temperature 15–25°C (59–77°F) [see USP].

Mfd by: Aventis Pharma Specialties 94700 Maisons-Alfort France

and

Aventis Pharma Boulevard Industriel 76580 Le Trait France


Lovenox®
(enoxaparin sodium injection)

Directions for Use of Lovenox Single Dose Syringe with Automatic Safety Device:

1. Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.

2. Inject using standard technique, pushing the plunger to the bottom of the syringe.

3. Remove the syringe from the injection site keeping your finger on the plunger rod.

4. Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm shield activation.

5. Immediately dispose of the syringe in the nearest sharps container.

NOTE:
• The safety system can only be activated once the syringe has been emptied.
• Activation of the safety system must be done only after removing the needle from the patient’s skin.
• Do not replace the needle shield after injection.
• The safety system should not be sterilized.
• Activation of the safety system may cause minimal splatter of fluid. For optimal safety activate the system while orienting it downwards away from yourself and others.
Lovenox 100 mg
Device Label

Lovenox (enoxaparin sodium injection) is a single-use syringe with automatic safety device for subcutaneous injection. Each LOVENOX syringe contains 100 mg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection. Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use. Each 0.025 ml graduation equals 1.5 mg enoxaparin sodium injection.

LOVENOX®
(Enoxaparin Sodium Injection)

120 mg/0.8 mL
[150 mg/mL]

Rx ONLY
SINGLE DOSE SYRINGES WITH AUTOMATIC SAFETY DEVICE
FOR SUBCUTANEOUS INJECTION

Ten 0.8 mL Syringes

Aventis
1. Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.

2. Inject using standard technique, pushing the plunger to the bottom of the syringe.

3. Remove the syringe from the injection site keeping your finger on the plunger rod.

4. Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible “click” will be heard to confirm shield activation.

5. Immediately dispose of the syringe in the nearest sharps container.

NOTE:
- The safety system can only be activated once the syringe has been emptied.
- Activation of the safety system must be done only after removing the needle from the patient’s skin.
- Do not replace the needle shield after injection.
- The safety system should not be sterilized.
- Activation of the safety system may cause minimal splatter of fluid. For optimal safety activate the system while orienting it downwards away from yourself and others.
Lovenox 120 mg
Device Label

Lovenox 120 mg
Blisterfoil

Each Lovenox Syringe contains 120mg enoxaparin sodium injection derived from porcine intestinal mucos in Water for Injection. For subcutaneous injection.

See package insert for dosage information and directions for use. Each 0.025ml graduation equals 3.75mg enoxaparin sodium injection.

Store at Controlled Room Temperature 15-25°C (59-77°F) (See USP). Keep out of reach of children.

Mfd for: Aventis Pharmaceuticals Inc.
Bridgewater, NJ 08807-0202
Made in France

9087142
LOVENOX®
(Enoxaparin Sodium Injection)

150 mg/1 mL

Rx ONLY
SINGLE DOSE SYRINGES WITH AUTOMATIC SAFETY DEVICE
FOR SUBCUTANEOUS INJECTION

Ten 1 mL Syringes

Aventis
Lovenox®
(enoxaparin sodium injection)

Rx ONLY
Each LOVENOX® Syringe contains 150mg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection.

Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use. Each 0.025mL graduation equals 3.75mg enoxaparin sodium injection.

WARNING: Keep out of reach of children.

Store at Controlled Room Temperature 15-25°C (59-77°F) [see USP].

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and
Aventis Pharma Boulevard Industriel 76580 Le Traîn France

Mfd for: Aventis Pharmaceuticals Inc. Bridgewater, NJ 08807 ©2002
Made in France
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50062651

Lovenox®
(enoxaparin sodium injection)

Directions for Use of Lovenox Single Dose Syringe with Automatic Safety Device:

1. Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.

2. Inject using standard technique, pushing the plunger to the bottom of the syringe.

3. Remove the syringe from the injection site keeping your finger on the plunger rod.

4. Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm shield activation.

5. Immediately dispose of the syringe in the nearest sharps container.

NOTE:
- The safety system can only be activated once the syringe has been emptied.
- Activation of the safety system must be done only after removing the needle from the patient's skin.
- Do not replace the needle shield after injection.
- The safety system should not be sterilized.
- Activation of the safety system may cause minimal splatter of fluid. For optimal safety activate the system while orienting it downwards away from yourself and others.
Lovenox 150 mg
Device Label

Lovenox (enoxaparin sodium injection)

Each LOVENOX (enoxaparin sodium injection) 150 mg device contains 150 mg enoxaparin sodium derived from porcine intestinal mucosa in Water for Injection. Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use. Each 0.025 ml graduation equals 3.75 mg enoxaparin sodium injection.

Store at Controlled Room Temperature 15-30°C (59-86°F) [see USP].

WARNING: Keep out of reach of children.

Mfd by: Aventis Pharmaceuticals Inc.
Bridgewater, NJ 08807 ©2002

Lovenox Blisterfoil

Lovenox 150 mg
Blisterfoil

Intravenous self-contained injectable device
Each LOVENOX (enoxaparin sodium injection) device contains 150 mg enoxaparin sodium. Each LOVENOX device contains a single-dose syringe and a single-dose vial of 150 mg enoxaparin sodium injection. Each LOVENOX device is supplied in a blisterfoil package. Each blisterfoil package contains 1 LOVENOX device.
Division of Gastrointestinal and Coagulation Drug Products (DGICDP)

REGULATORY PROJECT MANAGER LABELING REVIEW

Application Number: NDA 20-164/SLR-051

Name of Drug: Lovenox® (enoxaparin sodium) Injection

Sponsor: Aventis Pharmaceuticals Inc.

Materials Reviewed: Package Insert (PI)
   Container labeling

Submission Date: December 19, 2002
Receipt Date: December 20, 2002
Amendment Date: April 16, 2003
Receipt Date: April 22, 2003
Amendment Date: April 18, 2003
Receipt Date: April 21, 2003
Amendment Date: May 9, 2003
Receipt Date: May 12, 2003
Amendment Date: June 5, 2003
Receipt Date: June 6, 2003

Background and Summary

Background: Lovenox is a low molecular weight heparin (LMWH) which was approved March 29, 1993, for the following indications:

- prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing abdominal surgery who are at risk for thromboembolic complications;
- in patients undergoing hip replacement surgery during and following hospitalization;
- in patients undergoing knee replacement surgery;
- in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness;
- prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin;
- the inpatient treatment of acute DVT with or without PE when administered in conjunction with warfarin sodium; and
- the outpatient treatment of acute DVT without PE when administered in conjunction with warfarin sodium.

The most recent approved labeling for the Lovenox PI and for the immediate container, blister labeling and carton labeling for the Lovenox 300 mg/3.0 mL multiple-dose vial was submitted on September 20, 2002 (received September 23, 2002) to SCM-043 (approved on draft
January 23, 2003. The most recent approved labeling for the immediate containers, blister labeling and carton labeling for Lovenox syringes was submitted on May 23, 2001 (received May 24, 2001) to SCF-030 (acknowledge and retained on June 19, 2001). The most recent approved labeling for the 30 mg/0.3 mg ampule was submitted on May 31, 2000 to the annual report Y-007 (received June 12, 2000).


The sponsor referenced Becton Dickinson’s Device Master File (DMF) 501 in support of the automatic safety device proposed for use with the Lovenox prefilled syringes. A consult was sent to the Center for Devices and Radiological Health (CDRH) on March 18, 2003, requesting review of the revised labeling. On April 16, 2003 (received April 22, 2003), the DMF holder, Becton Dickinson (BD) submitted a clarification to S-051 that the DMF file (DMF-501) referenced in S-051 for the BD HYPAK™ for the Prefillable Syringe System is identical to the DMF (MHF 454) reviewed by CDRH.

A consult review by CDRH for NDA 20-164/S-051 was completed April 17, 2003. From the CDRH perspective, the addition of the safety feature raises no issues of safety and effectiveness and the labeling in this supplement is consistent with the Device Master File (see Memorandum from Patricia Cricenti, Branch Chief, General Hospital Devices Branch (GHDDB), Division of Anesthesiology, General Hospital Infection Control and Dental Devices (DAGID) dated April 17, 2003).

The sponsor submitted a general correspondence to Supplement 051 on April 18, 2003, agreeing to revise the color of the “40 mg/0.4 mL” and the “60 mg/0.6 mL” foil backing and syringe labeling to reflex blue letters in yellow and orange boxes, respectively, at the next printing. On May 9, 2003, the sponsor submitted revised copies of the 40mg/0.4 mL and the 60 mg/0.6 mL pre-filled syringe immediate container label and the 40mg/0.4 mL and 60 mg/mL prefilled syringe foil backing.

On May 16, 2003, Diane Moore, RPM, called Shaler G. Smith III, Director and Regulatory Liaison at Adventis Pharmaceuticals, Inc., to advise the sponsor that the labeling for the 50mg/0.6 mL foil backing submitted on May 9, 2003, was inconsistent with previous versions of the labeling and requested clarification as to which version the sponsor desired. Specifically, in the 60mg/0.6 mL foil backing, the third sentence in the second column that reads “Each 0.025mL graduation equals 2.5 mg enoxaparin sodium injection” was deleted in the labeling submitted May 9, 2003, (received May 12, 2003) and was added in the first column. In the 40mg/0.4 mL foil backing, was added in the first column. On June 5, 2003 (received June 6, 2003) the sponsor submitted
revised foil backing labeling and syringe labeling for the 40mg/0.4 mL and 60 mg/mL pre-filled syringes.

Review

1. PACKAGE INSERT

The PI to S-051 submitted on December 19, 2002, received December 20, 2002 (identified as “50066809”) was compared to the draft labeling to SCM-043 (submitted September 20, 2002; received September 23, 2002) approved on draft January 23, 2003 (no identifier). The PIs are identical except for the following:

A. DESCRIPTION section

The sponsor has not included the following revisions to the DESCRIPTION section of the PI that were made in S-043, submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003:

1. The sponsor has not added the term “aqueous” following the term “sterile” in the first paragraph, first sentence that reads “Lovenox Injection is a sterile, aqueous solution containing enoxaparin sodium, a low molecular weight heparin.” as revised in the approved labeling to S-043.

2. In the second paragraph, first sentence that reads, “Lovenox Injection is available in two concentrations: 1. 100mg per mL of Water for Injection,” the sponsor has not included the period following the number “1” and has not deleted the phrase, “of Water for Injection” so that the sentence reads “Lovenox Injection is available in two concentrations: 1. 100 mg per mL” as revised in the PI labeling to S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003.

3. In the second paragraph, the sixth line, the sponsor has not added “Multiple-Dose Vials 300 mg/3.0 mL” to the list of available syringes and ampules as revised in the PI labeling to S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003.

4. In the fourth paragraph, first line that reads, “2. 150 mg per mL of Water for Injection,” the sponsor has not added the period after the number “2” and has not deleted the phrase “of Water for Injection,” as revised in the PI labeling for S-043.

5. In the sixth paragraph, first sentence that begins, “The solutions are preservative-free . . .” the sponsor has not deleted the term “solutions” and has not added the phrase, “Lovenox prefilled syringes, graduated prefilled syringes, and ampules” so that the sentence reads, “The Lovenox prefilled syringes, graduated prefilled syringes, and ampules are preservative-free and intended for use only as a single-dose injection.” as
revised in the PI labeling in S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2002.

6. The sponsor has not added the second sentence in the sixth paragraph that reads, “The multiple-dose vial contains 15 mg/1.0 mL benzyl alcohol as a preservative.” that was added in the PI to S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003.

7. In the sixth paragraph, the sponsor has not deleted the third sentence that reads, “Nitrogen is used in the headspace to inhibit oxidation.” that was deleted in the PI to S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003.

8. In the seventh paragraph, the first sentence that begins, “Enoxaparin is obtained by . . .” the sponsor has not added the term “sodium” after “Enoxaparin” so that the sentence reads, “Enoxaparin sodium is obtained by alkaline degradation of heparin benzyl ester derived from porcine intestinal mucosa.” as was added in the PI to S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003.

9. In the seventh paragraph, the third sentence that begins, “The drug is the sodium . . .” The term “drug” has not been added before the term “substance” so that the sentence reads, “The drug substance is the sodium salt.” as in the PI to S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003.

The above revisions (I.A. 1.-9.) were made to the PI in SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003. The revisions should be included in the PI to SLR-051.

B. CONTRAINDICATIONS section

In the second paragraph, first sentence that begins, “Patients with known hypersensitivity . . .” the sponsor has not added the phrase, “or any of its constituents” so that the sentence reads, “Patients with known hypersensitivity to heparin or pork products should not be treated with Lovenox Injection or any of its constituents.” as revised in the PI to S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003.

The addition of the phrase “or any of its constituents” in the second paragraph, first sentence was made in SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003. The addition should be included in the PI to SLR-051.

C. WARNINGS section:
The sponsor has not added the Miscellaneous subsection following the Prosthetic Heart Valves subsection in the WARNINGS section that was added to the PI in SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003. The Paragraph reads as follows:

“Miscellaneous: Lovenox multiple-dose vials contain benzyl alcohol as a preservative. The administration of medications containing benzyl alcohol as a preservative to premature neonates has been associated with a fatal “Gasping Syndrome”. Because benzyl alcohol may cross the placenta, Lovenox multiple-dose vials, preserved with benzyl alcohol, should be used with caution in pregnant women and only if clearly needed (see PRECAUTIONS, Pregnancy).”

The addition of the Miscellaneous subsection following the Prosthetic Heart Valves subsection of the WARNINGS section of the PI was made in SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003. The addition should be included in the PI to SLR-051.

D. PRECAUTIONS section

The sponsor has not added the paragraph following the Pregnancy subsection, Non-teratogenic Effects subsection in the PI to S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003. The Paragraph reads as follows:

“Cases of “Gasping Syndrome” have occurred in premature infants when large amounts of benzyl alcohol have been administered (99-405 mg/kg/day). The multiple-dose vial of Lovenox solution contains 15 mg/1.0 mL benzyl alcohol as a preservative (see WARNINGS, Miscellaneous).”

The addition of the paragraph regarding “Gasping Syndrome” at the end of the PRECAUTIONS section, Pregnancy Non-teratogenic Effects subsection of the PI was made in SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003. The addition should be included in the PI to SLR-051.

E. DOSAGE AND ADMINISTRATION section

1. In the third paragraph, first sentence that begins, “1. 100 mg/mL Concentration: 30 mg/0.3 mL ampules, . . .” the sponsor has not added the period following the number “1” and has not added “300 mg/3.0 mL multiple-dose vials” at the end of the first item. Item 1. should read as follows:

“1. 100 mg/mL Concentration: 30 mg/0.3 mL ampules, 30 mg/0.3 ml and 40 mg/0.4 mL prefilled single-dose syringes, 60 mg/0.6 mL, 80 mg/0.8 mL, and 100 mg/1 mL prefilled, graduated, single- dose syringes, 300 mg/3.0 mL multiple-dose vials.”
The addition of the period after the number "1" and the phrase "300 mg/3.0 mL multiple-dose vials" in the DOSAGE AND ADMINISTRATION section were made in SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003. The additions should be included in the PI to SLR-051.

2. In the fourth paragraph that begins, "2. 150 mg/mL Concentration . . . ." the sponsor has not added the period following the number "2." Item 1. should read as follows:

"2. 150 mg/mL Concentration: 120 mg/0.8 mL and 150 mg/1mL prefilled, graduated, single-dose syringes."

The addition of the period after the number "2" in the DOSAGE AND ADMINISTRATION section was made in SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003. The addition should be included in the PI to SLR-051.

3. In the Administration subsection, second paragraph, the sponsor has not revised the first sentence that reads as follows:

"When using Lovenox Injection ampules to assure withdrawal of the appropriate volume of drug, the use of a tuberculin syringe or equivalent is recommended."

To:

"The use of a tuberculin syringe or equivalent is recommended when using Lovenox ampules or multiple-dose vials to assure withdrawal of the appropriate volume of drug."

This revision was made in SCM-043 submitted September 20, 2002 (received September 13, 2002) and approved January 23, 2003. The revision should be included in the PI to SLR-051.

4. Subcutaneous Injection Technique sub-subsection, of the Administration subsection

a. In the first paragraph, the sponsor has deleted the sixth and seventh sentences that read as follows:

"An automatic injector, Lovenox EasyInjector™, is available for patients to administer Lovenox Injection packaged in 30 mg and 40 mg prefilled syringes. Please see directions accompanying the Lovenox EasyInjector™ automatic injection device."
Since the sponsor is discontinuing the EasyInjector™ product, the deletion of these two sentences is acceptable.

b. In the first paragraph, following the fifth sentence that begins “To minimize bruising, . . .” the sponsor has added the following section to describe the use of the needle safety system to shield needle after injection (based on manufacturer’s device labeling):

“Lovenox Injection prefilled syringes and graduated prefilled syringes are available with a system that shields the needle after injection.

- Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.

- Inject using standard technique, pushing the plunger to the bottom of the syringe.

- Remove the syringe from the injection site keeping your finger on the plunger rod.

- Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible “click” will be heard to confirm shield activation.
• Immediately dispose of the syringe in the nearest sharps container.

NOTE:
• The safety system can only be activated once the syringe has been emptied.
• Activation of the safety system must be done only after removing the needle from the patient’s skin.
• Do not replace the needle shield after injection.
• The safety system should not be sterilized.
• Activation of the safety system may cause minimal splatter of fluid. For optimal safety activate the system while orienting it downwards away from yourself and others."

This addition is acceptable per Dr. Ruyi He, Medical Officer, in a verbal comment to Diane Moore, RPM on April 18, 2003.

F. HOW SUPPLIED section

1. The sponsor has not included the following revisions that were made in SCM-043, submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003:

   a. In the table entitled, “100 mg/mL Concentration”:
      
   b. In the fourth column, first row, the sponsor has not deleted the term “syringe.”

   c. In the first column, fifth row, the sponsor has not added the title, “Multiple-Dose Vial. 300 mg/3.0 mL.”

   d. In the second column, fifth row, the sponsor has not added “30,000 IU.”

   e. In the third column, fifth row, the sponsor has not added “1 vial.”

   f. In the fourth column, fifth row, the sponsor has not added the term “Red.”
g. In the fifth column, fifth row, the sponsor has not added “0626-03.”

2. In the footnotes to the table entitled, “100 mg/mL Concentration” the sponsor has not added the footnote that reads, “Each Lovenox multiple-dose vial contains 15 mg/1.0 mL of benzyl alcohol as a preservative.” as in the PI labeling to SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003.

3. In the first paragraph after the table entitled, “150 mg/mL Concentration,” the sponsor has not revised the phrase, “Store at Controlled Room Temperature 15-25°C (59-77°F) [see USP]” to ”Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [see USP Controlled Room Temperature].” as revised in the PI labeling in SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003.

The above revisions (I.F.1.-3.) were made in SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003. The revisions should be included in the PI-to SLR-051.

4. In the table entitled, “100 mg/mL Concentration,” the sponsor has added additional lines between the rows to separate the 30 mg/0.3 mL Prefilled Syringes from the 40 mg/0.4 mL Prefilled Syringes and the 60 mg/0.6 mL, 80 mg/0.8 mL and100 mg/1 mL Graduated Prefilled Syringes

This makes the table clearer. The revisions are editorial and acceptable.

5. After the second sentence of the first paragraph following the second table entitled “150 mg/mL Concentration,” that reads “Keep out of the reach of children,” the sponsor has revised the manufacturing information for Lovenox from:

“Lovenox Injection prefilled and graduated prefilled syringes manufactured in France.
Lovenox Injection ampules manufactured in England.
Lovenox multiple-dose vial manufactured for Aventis Pharmaceuticals products Inc. by DSM Pharmaceuticals, Inc. Greenville, NC 27835.
Aventis Pharmaceuticals Products Inc.
BRIDGEWATER, NJ 08807
© 2002 Aventis Pharmaceuticals Inc.
Prescribing information as of XXXX”

to:

“Lovenox Injection prefilled and graduated prefilled syringes manufactured by:
Aventis Pharma Specialties
94700 Maisons-Alfort
France.
And
Aventis Pharma
Boulevard Industriel
76580 Le Trait
France
Lovenox Injection ampules manufactured by:
Aventis Pharma LTD
Dagenham Essex RM 10 7XS
United Kingdom.

Aventis Pharmaceuticals, Inc.
Bridgewater, NJ 08807

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Prescribing information as of September 2002”

The revisions are editorial and acceptable, however, the sponsor should be requested to include the manufacturing information on the Lovenox multiple-dose vial in the HOW SUPPLIED section of the PI at the next printing.

II. IMMEDIATE CONTAINER LABEL

A. All Prefilled Syringe Device Dosage Strengths Labels:

The following prefilled syringe device labels in SLR-051 (submitted December 19, 2002; received December 20, 2002) were compared to the respective prefilled syringe labels in the Final Printed Labeling (FPL) to SCF-030 (submitted May 23, 2001; received May 24, 2001; acknowledged and retained on June 19, 2001). (See chart below for identification and lot numbers):

<table>
<thead>
<tr>
<th>Labeling Item</th>
<th>SLR-051 identification number</th>
<th>SCF-030 Approved labeling identification number</th>
<th>Lot number added to SLR-051 labeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>30mg/0.3 mL Pre-filled Syringe immediate container label</td>
<td>50067912</td>
<td>50062330</td>
<td>512106A</td>
</tr>
<tr>
<td>40mg/0.4 mL Pre-filled Syringe immediate</td>
<td>50067913</td>
<td>50057403</td>
<td>512107A</td>
</tr>
</tbody>
</table>
The sponsor made the following revisions to all of the above syringe immediate container labels in the December 19, 2002, submission:

1. The sponsor revised the tradename “LOVENOX® (enoxaparin sodium) Injection” to **LOVENOX® (enoxaparin sodium injection).”**

   Note: The numbers “120” and “150” after the tradename “Lovenox” for the 120 mg and 150 mg dosage strengths were deleted.

   **The revisions are editorial and acceptable.**

2. The sponsor added the phrase “Rx ONLY” to the top right corner.

   **The addition is acceptable.**

3. The sponsor revised the sponsor information from “Aventis Pharmaceuticals Products Inc.” to “Mfd for: **Aventis Pharmaceuticals Inc.**”

   **The revision is editorial and acceptable.**

4. The identification numbers for each dosage strength was revised (see above chart entitled “IMMEDIATE CONTAINER LABELING CHART”).

   **The revisions are editorial and acceptable.**
5. The lot number for each dosage strength has been added to the left side of the label (see above chart entitled "IMMEDIATE CONTAINER LABELING CHART").

The additions are acceptable.

B. 30mg/0.3 mL Pre-filled Syringe Immediate Container Label

In the section immediately following the trademark "Lovenox® (enoxaparin sodium injection)" the following revision was made to the 30mg/0.3 mL dosage strength:

The sponsor added the phrase "[100mg/mL]" to the phrase that reads "30 mg/0.3 mL" so that the phrase reads "30mg/0.3mL [100mg/mL]."

The addition clarifies the 30 mg/0.3 mL dosage strength. The revision is acceptable.

C. 4mg/0.4 mL Pre-filled Syringe Immediate Container Label

The following revisions were made to the 40mg/0.4 mL dosage strength prefilled syringe:

1. In the section immediately following the trademark "Lovenox® (enoxaparin sodium injection)" the sponsor added the phrase "[100mg/mL]" to the phrase that reads "40 mg/0.4 mL" so that the phrase reads "40mg/0.4mL [100mg/mL]."

The addition clarifies the 40mg/0.4 mL dosage strength. The revision is acceptable.

2. The sponsor revised the color from black numbers inside a yellow rectangular box to letters in a yellow rectangular box.

This is not acceptable. The letters are difficult to distinguish. The sponsor submitted a general correspondence to Supplement 051 on April 18, 2003 agreeing to revise the color of the "40 mg/0.4 mL" and the "60 mg/0.6 mL" the syringe label and foil backing to reflex blue at the next printing. On May 9, 2003, the sponsor submitted revised mock-up labeling for the 40 mg/0.4 mL syringe label. The 40 mg/0.4 mL prefilled syringe label submitted in S-051 on May 9, 2003 (received May 12, 2003; no identifier) was compared to the label submitted in S-051 on December 19, 2002 (received December 20, 2002; identification number 50067913). The sponsor revised the color from the letters in a yellow rectangular box to reflex blue letters in a yellow rectangular box. The reflex blue color gives an acceptable contrast for the 40 mg/0.4 mL prefilled syringe label. This proposed revision is acceptable. Because the labeling was a mock-up representation, the lot number was not included. This is acceptable.
On June 5, 2003, (received June 6, 2003), the sponsor submitted revised labeling for the 40mg/0.4 mL and 60 mg/0.6 mL foil backing and syringe labeling. The syringe label for the 40mg/0.4 mL submitted on June 5, 2003 (received June 6, 2003; no identifier number) is identical to the 40mg/0.4 mL syringe label submitted to S-051 on May 9, 2003 (received May 12, 2003; no identifier number). The label submitted on June 5, 2003 (received June 6, 20003; no identifier number) is acceptable.

D. 60mg/0.6 mL Pre-filled Syringe Immediate Container Label

The following revisions were made to the 60mg/0.6 mL Pre-filled Syringe Label dosage strength:

1. In the section immediately following the trademark “Lovenox® (enoxaparin sodium injection)” the sponsor added the phrase “[100mg/mL]” to the phrase that read “60 mg/0.6 mL” so that the phrase reads “60mg/0.6mL [100mg/mL].”

The addition clarifies the dosage strength. The revision is acceptable.

2. The sponsor revised the color from black numbers inside an orange rectangular box to ——— letters in an orange rectangular box.

This is not acceptable. The numbers are difficult to distinguish. The sponsor submitted a general correspondence to Supplement 051 on April 18, 2003 agreeing to revise the color of the “40 mg/0.4 mL” and the “60 mg/0.6 mL” syringe label and foil backing to reflex blue at the next printing. On May 9, 2003, the sponsor submitted revised mock-up labeling for the 60 mg/0.6 mL syringe label. The 60 mg/0.6 mL prefilled syringe label submitted in S-051 on May 9, 2003 (received May 12, 2003; no identifier) was compared to the label submitted in S-051 on December 19, 2002 (received December 20, 2002; identification number 50067914). The sponsor revised the color from the ——— letters in an orange rectangular box to reflex blue letters in an orange rectangular box. The reflex blue color gives an acceptable contrast for the 60 mg/0.6 mL prefilled syringe label. The proposed revision is acceptable. Because the labeling was a mock-up representation, the lot number was not included. This is acceptable.

On June 5, 2003, (received June 6, 2003), the sponsor submitted revised labeling for the 40mg/0.4 mL and 60 mg/0.6 mL foil backing and syringe labeling. The syringe label for the 60mg/0.6 mL submitted on June 5, 2003 (received June 6, 2003; no identifier number) is identical to the 60mg/0.6 mL syringe label submitted to S-051 on May 9, 2003 (received May 12, 2003; no identifier number). The label submitted on June 5, 2003 (received June 6, 20003; no identifier number) is acceptable.
E. 80mg/0.8 mL Pre-filled Syringe Immediate Container Label

The following revisions were made to the 80mg/0.8 mL Pre-filled Syringe Label dosage strength:

In the section immediately following the trademark “Lovenox® (enoxaparin sodium injection)” the sponsor added the phrase “[100mg/mL]” to the phrase that reads “80 mg/0.8 mL” so that the phrase reads “80mg/0.8mL [100mg/mL].”

The addition clarifies the dosage strength. The revision is acceptable.

F. 120mg/0.8 mL Prefilled Syringe Immediate Container Label

The following revisions were made to the 120mg/0.8 mL Pre-filled Syringe Label dosage strength:

1. The sponsor revised the tradename “LOVENOX 120 (enoxaparin sodium) Inj.” to “LOVENOX (enoxaparin sodium injection).”

The revision is editorial and acceptable.

2. In the section immediately following the trademark “Lovenox® (enoxaparin sodium injection)” the sponsor added the phrase “[150mg/mL]” to the phrase that reads “120 mg/0.8 mL” so that the phrase reads “120mg/0.8mL [150mg/mL].”

The addition clarifies the dosage strength. The revision is acceptable.

G. 150mg/1 mL Prefilled Syringe Immediate Container Label

The following revisions were made to the 150mg/1 mL Pre-filled Syringe Label dosage strength:

The sponsor revised the tradename “LOVENOX® 150 (enoxaparin sodium) Inj.” to “LOVENOX (enoxaparin sodium injection).”

The revision is editorial and acceptable.

III. BLISTER LABELING

A. Prefilled Syringe Blisterfoil Labeling

The following prefilled Syringe Blister backing labeling in SLR-051 (submitted December 19, 2002; received December 20, 2002) was compared to the prefilled Syringe
Blister Labeling in the FPL to SCF-030 (submitted May 23, 2001; received May 24, 2001; acknowledged and retained on June 19, 2001):

<table>
<thead>
<tr>
<th>Labeling Item</th>
<th>SLR-051 identification number</th>
<th>SCF-030 Approved labeling identification number</th>
<th>NDC number</th>
<th>Lot number added to SLR-051 labeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>30mg/0.3 mL Prefilled syringe blister backing labeling</td>
<td>50067137</td>
<td>50062182</td>
<td>NDC 0075-0624-30</td>
<td>512115A</td>
</tr>
<tr>
<td>40mg/0.4 mL Prefilled syringe blister backing labeling</td>
<td>50067138</td>
<td>50062015</td>
<td>NDC 0075-0620-40</td>
<td>512116A</td>
</tr>
<tr>
<td>60mg/0.6 mL Prefilled syringe blister backing labeling</td>
<td>50067139</td>
<td>50062018</td>
<td>NDC 0075-0621-60</td>
<td>512140A</td>
</tr>
<tr>
<td>80mg/0.8 mL Prefilled syringe blister backing labeling</td>
<td>50067140</td>
<td>50062021</td>
<td>NDC 0075-0622-80</td>
<td>512145A</td>
</tr>
<tr>
<td>100mg/1 mL Prefilled syringe blister backing labeling</td>
<td>50067141</td>
<td>50062024</td>
<td>NDC 0075-0623-00</td>
<td>512146A</td>
</tr>
<tr>
<td>120mg/0.8 mL Prefilled syringe blister backing labeling</td>
<td>50067142</td>
<td>50062030</td>
<td>NDC 0075-2912-01</td>
<td>512188A</td>
</tr>
<tr>
<td>150mg/1 mL Prefilled syringe blister backing labeling</td>
<td>50067143</td>
<td>50062034</td>
<td>NDC 0075-2915-01</td>
<td>512189A</td>
</tr>
</tbody>
</table>

The sponsor made the following revisions to all of the above syringe blisterfoil labeling in the December 19, 2002 submission (received December 20, 2003):

1. The NDC number (see above chart for specific NDC numbers for each strength) was moved from the top of the third column to the top of the first column (following the Lovenox tradename) of the blisterfoil labeling.

The revision is editorial and acceptable.
2. In the first column, in the first and second lines, the sponsor revised the tradename from "LOVENOX® (enoxaparin sodium) Injection’ to “LOVENOX® (enoxaparin sodium injection).”

Note: The numbers “120” and “150” after the tradename “Lovenox” for the 120 mg and 150 mg dosage strengths were deleted.

The revisions are editorial and acceptable.

3. The sponsor moved the phrase “Rx ONLY” from the bottom of the second column after the “Store at Controlled Room Temperature” section to the middle of the first column after the “XXmg/YYmL [100mg/mL]” phrase for each strength syringe. (see above chart titled “BLISTER LABELING CHART” for each dosage strength). Herein, the “Y.Y” denotes the syringe amount for each respective syringe size (i.e., 0.3mL, 0.4mL, 0.6mL, 0.8mL, 1.0mL, 0.8mL and 1.0 mL) and “XX” denotes the amount of enoxaparin sodium in each respective syringe (i.e., 30mg, 40mg, 60mg, 80mg, 100mg, 120mg and 150mg, respectively).

The revision is acceptable.

4. The sponsor added the following three phrases below the “Rx ONLY” addition in the left column of the blisterfoil labeling:

“Single Dose Syringe with Automatic Safety Device; One Y.Y mL syringe; For Subcutaneous Injection.” (Where “Y.Y” denotes the syringe amount for each respective syringe size, i.e., 0.3mL, 0.4mL, 0.6mL, 0.8mL, 1.0mL, 0.8mL and 1.0 mL for the 30mg, 40mg, 60mg, 80mg, 100mg, 120mg and 150mg, respectively.)

The additions clarify the number of syringes, type of injection and note the automatic safety device. The additions are acceptable.

5. The sponsor revised the first sentence in the second column that reads “Each Y.Y mL contains XX mg of enoxaparin sodium in Water for Injection. See insert for directions.” to read as follows:

“Each LOVENOX® Syringe contains XX mg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection.”

Herein, the “Y.Y” denotes the syringe amount for each respective syringe size (i.e., 0.3mL, 0.4mL, 0.6mL, 0.8mL, 1.0mL, 0.8mL and 1.0 mL) and “XX” denotes the amount of enoxaparin sodium in each respective syringe (i.e., 30mg, 40mg, 60mg, 80mg, 100mg, 120mg and 150mg, respectively).

The revisions are acceptable.
6. In the third column, the sponsor deleted the phrase “1 Single Dose Prefilled Syringe – Y.YmL.” Herein, the “Y.Y” denotes the syringe amount for each respective syringe size (i.e., 0.3mL, 0.4mL, 0.6mL, 0.8mL, 1.0mL, 0.8mL and 1.0 mL).

The information was added to the bottom of the first column. The deletions are acceptable.

7. The sponsor revised the second paragraph in the second column that reads “FOR SUBCUTANEOUS INJECTION” to read as follows:

“Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use.”

The revisions are acceptable.

8. In the third column following the storage conditions, the sponsor added the following warning phrase:

“WARNING: Keep out of reach of children.”

The addition is acceptable.

9. The sponsor moved the phrase “Made in France” from the top of the third column (following the NDC number) to the bottom of the third column following the sponsor information.

The revision is editorial and acceptable.

10. The sponsor revised the manufacturer information that reads “Aventis Pharmaceuticals Products Inc. Bridgewater, NJ 08807 USA” to read “Mfd for: Aventis Pharmaceuticals Inc. Bridgewater, NJ 08807 ©2002.”

The revisions are editorial and acceptable.

11. The identification number was revised. (See above chart entitled “BLISTER LABELING CHART” for specific identification numbers for each strength).

The revision is editorial and acceptable.

12. The lot numbers were added on the left end of the blister backing labeling. (See above chart entitled “BLISTER LABELING CHART” for specific identification numbers for each strength).

The additions are acceptable.
B. 30mg/0.3 mL Prefilled Syringe Blisterfoil Labeling

The following revision was made to the 30mg/0.3 mL Pre-filled Syringe blisterfoil labeling:

In the first column, third line, the sponsor added the phrase “[100mg/mL]” to the phrase that reads “30 mg/0.3 mL” so that the phrase reads “30mg/0.3mL [100mg/mL].”

The addition clarifies the dosage strength. The revision is acceptable.

C. 40mg/0.4 mL Prefilled Syringe Blister Backing

The following revisions were made to the 40mg/0.4 mL Pre-filled Syringe blisterfoil labeling:

1. In the first column, third line, the sponsor added the phrase “[100mg/mL]” to the phrase that reads “40 mg/0.4 mL” so that the phrase reads “40mg/04mL [100mg/mL].”

The addition clarifies the dosage strength. The revision is acceptable.

2. The sponsor revised the color from black numbers inside a yellow rectangular box to ——— letters in a yellow rectangular box.

This is not acceptable. The letters are difficult to distinguish.

On April 18, 2003, the sponsor submitted a general correspondence to Supplement 051 agreeing to revise the color of the letters “40 mg/0.4 mL” and “60 mg/0.6 mL” in the syringe label and foil backing to reflex blue at the next printing.

On May 9, 2003, the sponsor submitted revised labeling for the 40 mg/0.4 mL syringe foil backing. The 40 mg/0.4 mL prefilled syringe foil backing submitted in S-051 on May 9, 2003 (received May 12, 2003; no identifier) was compared to the syringe foil backing submitted in S-051 on December 19, 2002 (received December 20, 2002; identification number 50067138). The sponsor revised the color from the——— letters in a yellow rectangular box to reflex blue letters in a yellow rectangular box. The reflex blue color gives an acceptable contrast for the 40 mg/0.4 mL prefilled syringe foil backing. This proposed revision is acceptable. Because the labeling was a mock-up representation, the lot number was not included. This is acceptable. However, the sponsor added ———— on the first line of the foil backing. This is inconsistent with labeling for the other Lovenox strengths and is not recommended by the Division of Medication Errors and Technical Support (DMETS) (see consult to NDA 20-164/S-043 for review of the proprietary name ———— requested May 1, 2002 and completed July 29, 2002). The
addition of ______________________ is not acceptable. In addition, in the first sentence in the second column, the sponsor moved the term ______________________ to after ______________________ so that the sentence reads “________________________________________” derived from porcine intestinal mucosa in Water for Injection.” The revised sentence is acceptable.

The sponsor submitted revised labeling on June 5, 2003 (received June 6, 2003) to S-051. In this revised labeling, the sponsor deleted ______________________ and reverted back to the previous version of the first sentence in the second column that reads “Each LOVENOX® Syringe contains 40 mg enoxaparin sodium Injection derived from porcine intestinal mucosa in Water for Injection.” The foil backing for the 40mg/0.4 mL prefilled syringe submitted June 5, 2003 (received June 6, 2003) is acceptable.

D. 60mg/0.6 mL Prefilled Syringe Blister Backing

The following revisions were made to the 60mg/0.6 mL Pre-filled Syringe blisterfoil labeling in the December 19, 2002 submission (received December 20, 2002):

1. In the first column, third line, the sponsor added the phrase “[100mg/mL]” to the phrase that reads 60 mg/0.6 mL” so that the phrase reads “60mg/0.6mL [100mg/mL].”

   The addition clarifies the dosage strength. The revision is acceptable.

2. The sponsor revised the color from black numbers inside an orange rectangular box to ——— letters in an orange rectangular box.

   This is not acceptable. The letters are difficult to distinguish. The sponsor submitted a general correspondence to Supplement 051 on April 18, 2003 agreeing to revise the color of the “40 mg/0.4 mL” and the “60 mg/0.6 mL” syringe label and foil backing to reflex blue at the next printing.

On May 9, 2003, (received May 12, 2003) the sponsor submitted revised labeling for the 60 mg/0.6 mL syringe foil backing. The 60 mg/0.6 mL prefilled syringe foil backing submitted in S-051 on May 9, 2003 (received May 12, 2003; no identifier) was compared to the syringe foil backing submitted in S-051 on December 19, 2002 (received December 20, 2002; identification number 50067139). The sponsor revised the color from the ——— letters in an orange rectangular box to reflex blue letters in an orange rectangular box. The reflex blue color gives an acceptable contrast for the 60 mg/0.6 mL prefilled syringe foil backing. This proposed revision is acceptable. However, the sponsor added ——— on the first line of the foil backing.
This is inconsistent with labeling for the other Lovenox strengths and is not recommended by the Division of Medication Errors and Technical Support (DMETS) (see consult to NDA 20-164/S-043 for review of the proprietary name completed July 29, 2002). The addition of ________ is not acceptable. In addition, in the first sentence in the second column, the sponsor moved the term ________ to after ________, so that the sentence reads ________, derived from porcine intestinal mucosa in Water for Injection.” The revised sentence is acceptable.

The sponsor submitted revised labeling on June 5, 2003 (received June 6, 2003) to S-051. In this revised labeling, the sponsor deleted ________ and reverted back to the previous version of the first sentence in the second column that reads “Each LOVENOX® Syringe contains 60 mg enoxaparin sodium Injection derived from porcine intestinal mucosa in Water for Injection.” The addition of the sentence is acceptable.

3. The sponsor revised the second paragraph in the second column that reads “FOR SUBCUTANEOUS INJECTION” to read as follows in the December 19, 2002 (received December 20, 2003) submission:

“Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use. Each 0.025 mL graduation equals 2.5 mg enoxaparin sodium injection.”

The revision is acceptable.

On May 9, 2003, (received may 12, 2003) the sponsor submitted revised labeling for the 60 mg/0.6 mL syringe foil backing. The 60 mg/0.6 mL prefilled syringe foil backing submitted in S-051 on May 9, 2003 (received May 12, 2003; no identifier) was compared to the syringe foil backing submitted in S-051 on December 19, 2002 (received December 20, 2002; identification number 50067139). The sponsor deleted the third sentence in the second column that reads “Each 0.025mL graduation equals 2.5 mg enoxaparin sodium injection.” The deletion is acceptable.

The sponsor submitted revised labeling on June 5, 2003 (received June 6, 2003) to S-051. In this revised labeling, the sponsor added back the sentence that reads “Each 0.025mL graduation equals 2.5 mg enoxaparin sodium injection” after the sentence that begins “Dosage and Administration:”

The addition of the sentence is acceptable. The foil backing for the 60mg/0.6 mL prefilled syringe submitted June 5, 2003 (received June 6, 2003) is acceptable.
E. 80mg/0.8 mL Prefilled Syringe Blister Backing

The following revisions were made to the 80mg/0.8 mL Pre-filled Syringe blisterfoil labeling:

1. In the first column, third line, the sponsor added the phrase “[100mg/mL]” to the phrase that reads “80 mg/0.8 mL” so that the phrase reads “80mg/0.8mL [100mg/mL].”

The addition clarifies the dosage strength. The revision is acceptable.

2. The sponsor revised the second paragraph in the second column that reads “FOR SUBCUTANEOUS INJECTION” to read as follows:

“Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use. Each 0.025 mL graduation equals 2.5 mg enoxaparin sodium injection.”

The revisions are acceptable.

F. 100mg/1 mL Prefilled Syringe Blister Backing

The following revisions were made to the 100mg/1 mL Pre-filled Syringe blisterfoil labeling:

1. In the first column, third line, the sponsor revised the phrase “100mg/1.0mL” to read “100 mg/1 mL.”

The revision better clarifies the dosage strength. The revision is acceptable.

2. The sponsor revised the second paragraph in the second column that reads “FOR SUBCUTANEOUS INJECTION” to read as follows:

“Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use. Each 0.025 mL graduation equals 2.5 mg enoxaparin sodium injection.”

The revisions are acceptable.

G. 120mg/0.8 mL Prefilled Syringe Blister Backing

The following revisions were made to the 120mg/0.8 mL Pre-filled Syringe blisterfoil labeling:
1. In the first column, in the first and second line, the sponsor revised the tradename from “LOVENOX® 120 (enoxaparin sodium) Injection” to “LOVENOX® (enoxaparin sodium injection).”

The revision is editorial and acceptable.

2. In the first column, third line, the sponsor added the phrase “[150mg/mL]” to the phrase that read “120 mg/0.8 mL” so that the phrase reads “120mg/0.8mL [150mg/mL].”

The addition clarifies the dosage strength. The revision is acceptable.

3. The sponsor revised the second paragraph in the second column that reads “FOR SUBCUTANEOUS INJECTION” to read as follows:

   “Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use. Each 0.025 mL graduation equals 3.75 mg enoxaparin sodium injection.”

The revisions are acceptable.

H. 150mg/1 mL Prefilled Syringe Blister Backing

The following revisions were made to the 150mg/1 mL Pre-filled Syringe blisterfoil labeling:

1. In the first column, in the first and second line, the sponsor revised the tradename from “LOVENOX®150 (enoxaparin sodium) Injection” to “LOVENOX® (enoxaparin sodium injection).”

The revision is editorial and acceptable.

2. The sponsor revised the second paragraph in the second column that reads “FOR SUBCUTANEOUS INJECTION” to read as follows:

   “Dosage and Administration: For subcutaneous injection. See package insert for dosage information and directions for use. Each 0.025 mL graduation equals 3.75 mg enoxaparin sodium injection.”

The revisions are acceptable.

IV. CARTON LABELING

The prefilled syringe carton labeling in SLR-051 (submitted December 19, 2002; received December 20, 2002) was compared to the prefilled syringe carton labeling in the
FPL to SCF-030 (submitted May 23, 2001; received May 24, 2001; acknowledged and retained on June 19, 2001) (see identification numbers below).

### CARTON LABELING CHART

<table>
<thead>
<tr>
<th>Labeling Item</th>
<th>SLR-051 identification number</th>
<th>SCF-030 Approved labeling identification number</th>
<th>Carton color</th>
<th>NDC Number</th>
<th>Lot Number added to SLR-051 labeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg/0.3 mL prefilled Syringe10-count carton labeling</td>
<td>50062559</td>
<td>50062013</td>
<td>Bright Sky Blue</td>
<td>NDC 0075-0624-30</td>
<td>512112A</td>
</tr>
<tr>
<td>40 mg/0.4 mL prefilled Syringe10-count carton labeling</td>
<td>50062611</td>
<td>50062016</td>
<td>Golden Yellow</td>
<td>NDC 0075-0620-40</td>
<td>512113A</td>
</tr>
<tr>
<td>60 mg/0.6 mL prefilled Syringe10-count carton labeling</td>
<td>50062752</td>
<td>50062019</td>
<td>Orange</td>
<td>NDC 0075-0621-60</td>
<td>512136A</td>
</tr>
<tr>
<td>80 mg/0.8 mL prefilled Syringe10-count carton labeling</td>
<td>50062754</td>
<td>50062022</td>
<td>Brown</td>
<td>NDC 0075-0622-80</td>
<td>512137A</td>
</tr>
<tr>
<td>100 mg/1.0 mL prefilled Syringe10-count carton labeling</td>
<td>50062614</td>
<td>50062025</td>
<td>Black</td>
<td>NDC 0075-0623-00</td>
<td>512139A</td>
</tr>
<tr>
<td>120 mg/0.8 mL prefilled Syringe10-count carton labeling</td>
<td>50062618</td>
<td>50062031</td>
<td>Purple</td>
<td>NDC 0075-2912-01</td>
<td>512192A</td>
</tr>
<tr>
<td>150 mg/1.0 mL prefilled Syringe10-count carton labeling</td>
<td>50062651</td>
<td>50062034</td>
<td>Navy Blue</td>
<td>NDC 0075-2915-01</td>
<td>511085B</td>
</tr>
</tbody>
</table>

### A. Carton Front

1. The sponsor made the following revisions to the carton front of all of the above syringe 10-count carton labeling strengths:

   a. The sponsor has deleted the tradename and established name [Lovenox® (*enoxaparin sodium*) Injection] on the top half of the carton front and colored the
entire top half with the color associated with the dosage strength (see above chart entitled "CARTON LABELING CHART").

This part of the carton is perforated for removal after opening for ease of dispensing the syringes. The tradename and established name is on the bottom half of the front of the carton. The revision is cosmetic and acceptable.

b. The sponsor revised the established name from “(enoxaparin sodium) Injection” to “(enoxaparin sodium injection).”

This revision is editorial and acceptable.

c. The sponsor has deleted the box surrounding the phrase “XX mg/X.X mL (where “XX” denotes the amount of enoxaparin sodium in each syringe (i.e., 30mg, 40mg, 60mg, 80mg, 100mg, 120mg or 150mg); and “Y.Y”mL represents the amount of liquid in the syringe for each respective syringe size *(i.e., 0.3 mL, 0.4 mL, 0.6 mL, 0.8 mL, 1 mL, 0.8 mL or 1 mL) and changed the color of the numbers from white to the designated color for each strength (see chart above entitled “CARTON LABELING CHART”).

The colors are easy to identify and read. The revisions are acceptable.

d. The sponsor has deleted the picture of the syringe.

This deletion is editorial and acceptable.

e. The sponsor has added the phrase “Rx ONLY” after the “XXmg/Y.Y mL [ZZZmg/mL].” mL where “XX denotes the amount of enoxaparin sodium in each syringe (i.e., 30mg, 40mg, 60mg, 80mg, 100mg, 120mg or 150mg); and “Y.Y” represents the amount of liquid in the syringe for each respective syringe size (i.e., 0.3 mL, 0.4 mL, 0.6 mL, 0.8 mL, 1 mL, 0.8 mL or 1 mL); and “ZZZ” denotes the concentration of drug in the syringes.

This addition is acceptable.

f. The sponsor has deleted the phrase “10 x XX mg Single Dose Syringes” at the bottom of the carton front for each syringe. Herein “XX” denotes the amount of enoxaparin sodium in each syringe (i.e., 30mg, 40mg, 60mg, 80mg, 100mg, 120mg or 150mg).

The information is added below the following phrase that begins, “SINGLE DOSE SYRINGES . . .” in a different format. The deletion is acceptable.
g. The sponsor has revised the phrase “FOR SUBCUTANEOUS INJECTION” to “SINGLE DOSE SYRINGES WITH AUTOMATIC SAFETY DEVICE FOR SUBCUTANEOUS INJECTION.”

The revision notes the addition of the new automatic safety device. The revision is acceptable.

h. The sponsor has added the phrase “Ten X.XmL Syringes” after the phrase “SINGLE DOSE SYRINGES WITH AUTOMATIC SAFETY DEVICE FOR SUBCUTANEOUS INJECTION” for each strength. (Where “Y.Y” represents the amount of liquid in the syringe for each respective syringe size, i.e., 0.3 mL, 0.4 ml, 0.6 mL, 0.8 mL, 1 mL, 0.8 mL or 1 mL).

This is the same information previously presented higher on the carton front panel. The term “Ten” clearly identifies the number of syringes in the carton. The addition is acceptable.

i. The sponsor has added the sponsor logo and name “Aventis” to the bottom right on the carton front.

The addition of the sponsor’s name is editorial and acceptable.

j. On the front top flap, the lot number for each strength has been added (see above chart titled “CARTON LABELING CHART”).

This addition is editorial and acceptable.

2. The sponsor has made the following revisions to the carton fronts specific for each dosage strength:

a. On the carton for the 30 mg/0.3 mL prefilled Syringe10-count carton labeling, the sponsor has added the phrase “[100 mg/mL]” in blue letters after the phrase “30 mg/0.3 mL.”

b. On the carton for the 40 mg/0.4 mL prefilled Syringe10-count carton labeling, the sponsor has added the phrase “[100 mg/mL]” in yellow letters after the phrase “40 mg/0.4 mL.”

c. On the carton for the 60 mg/0.6 mL prefilled Syringe10-count carton labeling, the sponsor has added the phrase “[100 mg/mL]” in orange letters after the phrase “60 mg/0.6 mL.”

d. On the carton for the 80 mg/0.8 mL prefilled Syringe10-count carton labeling, the sponsor has added the phrase “[100 mg/mL]” in brown letters after the phrase “80 mg/0.8 mL.”
e. On the carton for the 120 mg/0.8 mL prefilled Syringe10-count carton labeling, the sponsor has added the phrase “[150 mg/mL]” in purple letters after the phrase “120 mg/0.8 mL.”

These revisions clearly depict the dose concentration for each respective dosage strength. The revisions are acceptable.

B. Right Carton Side

The right carton side labeling is identical to the carton front labeling for each of the above prefilled 10-count syringes with the following exceptions:

1. The side of the carton is wider than the front of the carton.

2. The right carton side has a barcode on the bottom center of the carton side.

These are not changes to the cartons. All the revisions that are acceptable to the carton front are acceptable to the right carton side. All the revisions that are not acceptable to the carton front are not acceptable to the right carton side.

C. Left Carton Side

The sponsor made the following revisions to the left carton side of all of the above syringe 10-count carton labeling strengths:

1. The sponsor has deleted the following information on the left carton side:

   “Lovenox (enoxaparin sodium) Injection (wavy line™); XX mg/Y.Y mL; FOR SUBCUTANEOUS INJECTION; 10xXX mg Single Dose Syringes”

   where “XX denotes the amount of enoxaparin sodium in each syringe (i.e., 30mg, 40mg, 60mg, 80mg, 100mg, 120mg or 150mg); and “Y.Y” represents the amount of liquid in the syringe for each respective syringe size (i.e., 0.3 mL, 0.4 ml, 0.6 mL, 0.8 mL, 1 mL, 0.8 mL or 1 mL).

   The sponsor has revised this information and included it on the carton front and right carton side and left carton side flap. The inclusion of the information on these areas of the carton is acceptable. The deletion of the information from the carton left side is acceptable.

2. The sponsor has revised the format of the tradename and inserted it onto the top left portion of the carton left side as follows:

   “Lovenox® (enoxaparin sodium injection)”
The addition is editorial and acceptable.

3. The sponsor has added the following directions for use of the Lovenox single dose syringe with automatic safety device on the carton left side:

"Directions for Use of Lovenox
Single Dose Syringe with Automatic Safety Device:
1. Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.

2. Inject using standard technique, pushing the plunger to the bottom of the syringe.

3. Remove the syringe from the injection site keeping your finger on the plunger rod.

4. Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible “click” will be heard to confirm shield activation.

5. Immediately dispose of the syringe in the nearest sharps container.

NOTE:
- The safety system can only be activated once the syringe has been emptied.
- Activation of the safety system must be done only after removing the needle from the patient’s skin.
- Do not replace the needle shield after injection.
- The safety system should not be sterilized.
- Activation of the safety system may cause minimal splatter of fluid. For optimal safety activate the system while orienting it downwards away from yourself and others."

This addition is acceptable per Dr. Ruyi He, Medical Officer, in a verbal comment to Diane Moore, RPM on April 18, 2003.

D. Left Carton Side Flap

The information on the left carton side flap is identical to the revised carton front for each dosage strength. (For dosage strengths, see above chart titled “CARTON LABELING CHART.”) Note: The orientation of the information on the flap has been moved by 90 degrees counterclockwise.
The revision is acceptable.

E. Carton Back

The sponsor made the following revisions to the carton back of all of the above syringe 10-count carton labeling strengths:

1. The sponsor added the tradename to the top of the carton back as follows:

   “Lovonox® (enoxaparin sodium injection)”

   The addition is editorial and acceptable.

2. The sponsor has deleted the first phrase that reads “10 x XX mg Single Dose Syringes.”
   (Where XX denotes the amount of enoxaparin sodium in each syringe, i.e., 30mg, 40mg, 60mg, 80mg, 100mg, 120mg or 150mg).

   This information is included on the carton front and carton right side. The deletion is acceptable.

3. The sponsor moved the phrase “Rx ONLY” from the fifth phrase on the carton backs to the second phrase immediately following the tradename.

   The revisions are acceptable.

4. The second paragraph on the carton box has been revised from:

   “Each Y.Y mL contains XX mg enoxaparin sodium derived from porcine intestinal mucosa in Water for Injection.”

   to:

   “Each LOVENOX® Syringe contains XXmg enoxaparin sodium injection derived from porcine intestinal mucosa in Water for Injection.” for all prefilled syringe cartons (Where “XX denotes the amount of enoxaparin sodium in each syringe, i.e., 30mg, 40mg, 60mg, 80mg, 100mg, 120mg or 150mg and “Y.Y” represents the amount of liquid in the syringe for each respective syringe size, i.e., 0.3 mL, 0.4 mL, 0.6 mL, 0.8 mL, 1 mL, 0.8 mL or 1 mL).”

   The revisions add the tradename and dosage form information. They are editorial and acceptable.

5. The sponsor has revised the third phrase that reads “Directions for Use: See insert.” to the following:
“Dosage and Administration: For subcutaneous injection. See package insert for dosage information and direction for use.”

The revision is editorial acceptable.

6. The sponsor has moved and revised the sixth phrase that reads “Keep out of the reach of children” to follow the Dosage and Administration sentence. The revised phrase reads “WARNING: Keep out of reach of children” for all prefilled syringe cartons.

The revisions are acceptable.

7. The sponsor has bolded the fourth sentence that reads “Store at Controlled room Temperature 15-25°C (59-77°F) [see USP]” for all prefilled syringe cartons.

The revisions are editorial and acceptable.

8. The sponsor has deleted the sponsor’s name “Aventis Pharmaceuticals Products Inc.” and replaced it with the following manufacturing information:


The revision updates the sponsor and manufacturing information. The revision is editorial and acceptable.

9. The sponsor has revised the identification numbers for all prefilled syringe cartons (for specific identification numbers, see above chart entitled “CARTON LABELING CHART”).

The revision is editorial and acceptable.

CONCLUSIONS

2. **Item I.F.5. is acceptable.** However, the sponsor should be requested to add the manufacturing information on the Lovenox multiple-dose vial in the HOW SUPPLIED section of the PI at the next printing.

3. **Items I.E.4.b. and IV.C.3. are acceptable per the medical officer, Dr. Ruiyi He.**

4. **Items I.A., I.B., I.C., I.D., I.E.1.-3., I.F.1.-3., that were approved in SCM-043, submitted September 20, 2002, received September 23, 2002 and approved January 23, 2003 and Item I.F.5. should be incorporated into the PI to SLR-051.**

5. **The labeling for SLR-051 should be approved with revisions noted in Conclusion Items 2. and 4. above to be included at the next printing of the PI. An approval letter should be drafted.**

---

Diane Moore, B.S.
Regulatory Health Project Manager

Ruiyi He, M.D.
Medical Officer

Kathy Robie-Suh, M.D., Ph.D.
Hematology Team Leader

Julieann Du Beau, MSN, RN
Chief, Project Management Staff

Cc:
Archival NDA 20-164/S-043
HFD-180/Div. Files
HFD-180/D.Moore
HFD-180/R.He/K.Robie-Suh/L.Zhou/A.Al-Hakim
HFD-180/RJustice/J.Korvick
Drafted by: dm/1/17/03
Initialed by: J.DuBeau 1.21.03/R.He, K.Robie-Suh 1.22.03
APPEARS THIS WAY
ON ORIGINAL
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
-------------------------
Diane V. Moore
6/19/03 03:32:59 PM
CSO

Ruyi He
6/19/03 03:34:31 PM
MEDICAL OFFICER

Ruyi He
6/19/03 03:35:48 PM
MEDICAL OFFICER
For Dr. Kathy Robie-Suh, Medical Team Leader.

Julieann DuBeau
6/19/03 03:44:36 PM
CSO
APPLICATION NUMBER:
NDA 20-164/S-051

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
December 19, 2002

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

NDA 20-164
Lovonox® (enoxaparin sodium injection)
SPECIAL SUPPLEMENT: CHANGES BEING EFFECTED
Labeling and Chemistry, Manufacturing and Controls
Automatic Safety Device

Dear Dr. Justice:

Reference is made to NDA 20-164, Lovonox® (enoxaparin sodium injection), to the November 6, 2000 Needlestick Safety and Prevention Act (Public Law 106-430), and to final rule by Occupational Safety and Health Administration (OSHA) amending the Blood Borne Pathogen (BBP) standard published in the January 18, 2001 Federal Register.

Aventis Pharmaceuticals Inc. hereby submits, in triplicate, a SPECIAL SUPPLEMENT: CHANGES BEING EFFECTED for an automatic safety device for all presentations of Lovonox pre-filled syringes. The addition of an automatic safety device to all Lovonox® syringes is predicated on the enactment of the federal Needlestick Safety and Prevention, the revised BBP standards, and numerous state laws, based on both the federal Needlestick Safety and Prevention and the revised BBP standards, which are to be enacted starting in 2003 and which will require an integrated safety device on all syringes.

This SPECIAL SUPPLEMENT: CHANGES BEING EFFECTED has been discussed with Ms. Diane Moore, Regulatory Health Project Manager, to determine the regulatory process for this type of application. At a teleconference with the Division, held on August 27, 2002, this supplement was again discussed with Drs. K. Robic-Suh and R. He and Ms. Moore, and it was determined, after consultation with Dr. L. Zhou, Chemistry Team Leader, that it could be filed as a SPECIAL SUPPLEMENT: CHANGES BEING EFFECTED. A copy of the Division’s meeting minutes, which outline this decision, is attached for your information.
The safety device, which is manufactured by Becton Dickinson, is subject to the BD Hypak™ Type III Drug Master File 501. A letter of cross-reference can be found in Appendix 3 of the Chemistry, Manufacturing and Controls section. Both the safety device and its labeling, including the Directions For Use, have been reviewed and approved by the Center for Devices and Radiological Health (CDRH).

In support of this SPECIAL SUPPLEMENT: CHANGES BEING EFFECTED, the following are provided: 1) Final Printed Labeling (FPL); 2) updated Lovenox® cartons, blister foil and syringe (device) labels; and 3) Chemistry, Manufacturing and Controls information. The salient aspects of these elements supporting this SPECIAL SUPPLEMENT: CHANGES BEING EFFECTED are described below.

**Final Printed Labeling (FPL)**

- The currently approved Lovenox® FPL (November 2001) is the basis for the revised FPL contained in this SPECIAL SUPPLEMENT: CHANGES BEING EFFECTED.

- The generic name has been changed from “(enoxaparin sodium)” to “(enoxaparin sodium injection)”. This change is based on the FDA’s request in the approvable letter for Supplement 043.

- The “Dosage and Administration” section has been revised to include directions on how to use the automatic safety system. These revisions are based on Becton Dickinson’s approved safety device labeling.

- Printed labeling is provided in Running Text, Annotated, Maison-Alfort FPL, and Dagenham FPL.

The updated Prescribing Information is being provided as an Electronic Regulatory Submission for Archive and has been checked for viruses by ——— using McAfee VirusScan v4.5.1SP1, created on December 18, 2002. The size of the contents is approximately 3MB and is contained on three diskettes.

**Updated Lovenox Cartons, Blister Foil and Syringe (Device) Labels**

- All Lovenox® container cartons for pre-filled syringes have been revised to include directions on how to use the automatic safety device. These revisions are based on Becton Dickinson’s device labeling which has been reviewed and approved by CDRH.

- Based on the FDA’s request in the approvable letter for Supplement 043, the generic name has been changed from “(enoxaparin sodium)” to “(enoxaparin sodium injection)” on all carton containers, blister foils and syringe (device) labels.

- All graduated syringes (60 mg, 80 mg, 100 mg, 120 mg, and 150 mg) contain a graduation statement on the container carton and blister foil.
Updated Lovenox Cartons, Blister Foil and Syringe (Device) Labels (continued)

- A concentration statement is contained on the 30 mg, 40 mg, 60 mg, 80 mg, and 120 mg container cartons. The former four strengths are based on a 100-mg/ml concentration and the latter is based on a 150-mg/ml concentration, respectively. Concentration statements are not on the container cartons for the 100-mg/ml and 150-mg/ml syringes as these are the actual concentrations and volumes per syringe, respectively. A concentration statement for these two strengths would result in redundant labeling.

Chemistry, Manufacturing and Controls Section

- The automatic safety device will never be in contact with the drug product and, therefore, has no impact on manufacturing, filling and stability of the drug product.

- The manufacturing sites will remain the same as for the currently marketed Lovenox pre-filled syringes.

- The manufacturing processes for all presentations of Lovenox pre-filled syringes are the same as those used to manufacture the approved pre-filled syringes.

- The container/closure system integrity is not affected by the change, as the process of placing an automatic safety device on the pre-filled syringe does not involve an additional process that could have a potential impact on the integrity of the pre-filled syringe.

- The packaging process is slightly modified to introduce the safety device and syringe automatic assembly and the safety device labeling.

- The plunger rod length is modified (slightly extended) to allow proper activation of the safety device during actual use.

- Secondary packaging components, i.e., blister foil, container cartons and shipping cases, are modified to account for the addition of the automatic safety device.

- Specifications and methods for the Lovenox drug product remain unchanged except that a "description" of the complete drug packaging (including automatic safety device) will be added to the existing pre-filled syringes specifications.

- Pursuant to 21 CFR Part 25.31(b), Aventis is requesting a categorical exclusion from environmental assessment for this proposed change since its implementation will not result in the Expected Introduction Concentration (EIC) to exceed one parts per billion of the active ingredient, enoxaparin sodium.
Pursuant to 21 CFR 314.71(b), we hereby provide an exact copy of this correspondence to the Kansas City FDA District Office.

If you should have any questions or comments, please do not hesitate to contact the undersigned at 908-231-3103 or Steve Caffè, M.D. at 908-231-5863. Should you have any question or comment on the Chemistry, Manufacturing and Controls section of this supplement, please contact Dhiren Shah, Ph.D. at 816-966-7104.

Sincerely,

[Signature]

Joseph A. Carrado, M.Sc., R.Ph.
Director and Regulatory Liaison
Global Drug Regulatory Affairs

APPEARS THIS WAY ON ORIGINAL
Aventis Pharmaceuticals  
Attention: Joseph A. Carrado, M.Sc., R.Ph.  
Director and Regulatory Liaison  
Global Drug Regulatory Affairs  
200 Crossing Boulevard P.O. Box 6890  
Bridgewater, NJ 08807-0890

Dear Mr. Carrado:

We have received your supplemental drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Lovenox® (enoxaparin sodium) Injection, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, 120 mg and 150 mg

NDA Number: 20-164

Supplement number: S-051

Date of supplement: December 19, 2002

Date of receipt: December 20, 2002

This supplemental application, submitted as “Supplement - Changes Being Effected” proposes the following change: the addition of an automatic safety device to all presentations of Lovenox® pre-filled syringes.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 18, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 20, 2003.
All communications concerning these supplements should be addressed as follows:

**U.S. Postal Service:**
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

**Courier/Overnight Mail:**
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Document Room 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7476.

Sincerely,

(See appended electronic signature page)

Diane Moore
Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Office of Drug Evaluation III
Center for Drug Evaluation and Research
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/s/

Diane V. Moore
1/7/03 03:42:34 PM
REQUEST FOR CONSULTATION

TO (Division/Office): Center for Devices and Radiological Health
Division (CDRH) Office of Device Evaluation (ODE), DAGID Attention:
Patricia Cincineti, Supervisor Microbiologist
HFZ-480 CORPORATE Room 340D

FROM: HFD-580 (Division of Gastro-Intestinal and Coagulation Drug Products) Diane Moore 68-45

DATE: March 18, 2003

BND NO.: 20-164/S-051

NAME OF DRUG: Lovenox® (enoxaparin sodium), Injection

PRIORITY CONSIDERATION: Rush

CLASSIFICATION OF DRUG: Low Molecular Weight Heparin

NAME OF FIRM: Pharmacia & Upjohn Company

DATE OF DOCUMENT: December 19, 2002

DESIRED COMPLETION DATE: April 18, 2003

REASON FOR REQUEST

I. GENERAL

| NEW PROTOCOL | END OF PHASE II MEETING | RESPONSE TO DEFICIENCY LETTER |
| PROGRESS REPORT | RESUBMISSION | FINAL PRINTED LABELING |
| NEW CORRESPONDENCE | SAFETY/EFFICACY | X-LABELING REVISION |
| DRUG ADVERTISING | PAPER NDA | ORIGINAL NEW CORRESPONDENCE |
| ADVERSE REACTION REPORT | CONTROL SUPPLEMENT | FORMULATIVE REVIEW |
| MANUFACTURING CHANGE/ADDITION | | OTHER (SPECIFY BELOW): |
| MEETING PLANNED BY | | |

II. BIOMETRICS

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III. BIOPHARMACEUTICS

| DISSOLUTION | DEFICIENCY LETTER RESPONSE |
| BIOAVAILABILITY STUDIES | PROTOCOL-BIPHARMACEUTICS |
| PHASE IV STUDIES | IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

| PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | SUMMARY OF ADVERSE EXPERIENCE |
| CASE REPORTS OF SPECIFIC REACTIONS (List below) | POISON RISK ANALYSIS |
| COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

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COMMENTS/SPECIAL INSTRUCTIONS: Sponsor claims that the proposed automatic safety device is approved. Please review DMF for Becton Dickinson and Company Drug Master file 501 on behalf of Aventis Pharma (Section B dated February 15, 2002 and Section C dated May 1, 2001.) Also note any modifications to the device. Please review revised carton labeling regarding instructions for use of needle device. (Similar device has been reviewed for Fragmin (NDA 20-287) and found to be acceptable.)

cc: Original NDA 20-164/S-051
HFD-180/Div. Files
HFD-180/Diane Moore

SIGNATURE OF REQUESTER: Diane Moore

SIGNATURE OF RECEIVER: METHOD OF DELIVERY (Check one): MAIL HAND
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Diane V. Moore
3/18/03 01:24:17 PM
Memorandum

To: The Record
   Patricia Cricenti, Branch Chief, GHDB, DAGID, HFZ-480
   April 17, 2003

Re: Consult review for NDA 20-164 S51 Labeling Changes to Lovenox

This consult is a request by the Division of Gastrointestinal and Coagulation Drug Products to review the sponsors labeling for this Supplement. The sponsor has added a safety feature (sharps injury prevention or anti-needlestick feature) onto the previously approved prefilled syringe(s). The safety feature does not contact the fluid pathway. The safety feature addition to the Hypak system which is manufactured by BD was previously reviewed under the Device Master File MAF 454 which is the same as Drug Master File 501. The Device Master File was previously reviewed by GHDB/CDRH and the information in the Device Master File for the safety feature is consistent with the CDRH Guidance Document for Devices with Sharps Injury Prevention Features. The labeling for the safety feature in this supplement appears to be consistent with the labeling reviewed in the Device Master File.

Therefore, from a CDRH perspective the addition of the safety feature raises no issues of safety and effectiveness and the labeling in this Supplement is consistent with the Device master File.

Patricia Cricenti
Chief GHDB
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/s/

Diane V. Moore
4/17/03 12:39:14 PM
Memo from Pat Cricenti, Chief GHDB