CENTER FOR DRUG EVALUATION AND RESEARCH

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-051

CONTENTS

Reviews / Information Included in this Review	
Approval Letter	X
Approvable Letter	
Labeling	X
Labeling Review	X
Medical Review	
Chemistry Review	
Pharmacology / Toxicology Review	
Statistical Review	
Microbiology Review	
Clinical Pharmacology / Biopharmaceutics Review	
Administrative and Correspondence Documents	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-051

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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:

Please refer to your supplemental new drug application dated December 19, 2002, received December 20, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium injection).

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

This "Changes Being Effected" 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/

Joyce Korvick
6/20/03 02:21:13 PM
for Dr. Robert Justice

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-051

APPROVED DRAFT LABELING

S-051

LOVENOX® (enoxaparin sodium injection)™

Aventis

Lovenox®
(enoxaparin sodium injection)

Rx only
Rev. September 2002

SPINAL / EPIDURAL HEMATOMAS

When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

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

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

DESCRIPTION

Lovenox Injection is a sterile solution containing enoxaparin sodium, a low molecular weight heparin.

Lovenox Injection is available in two concentrations:
1 100 mg per mL of Water for Injection

-Prefilled Syringes	30 mg / 0.3 mL, 40 mg / 0.4 mL
-Graduated Prefilled Syringes	60 mg / 0.6 mL, 80 mg / 0.8 mL, 100 mg / 1 mL
-Ampules	30 mg / 0.3 mL

Lovenox Injection 100 mg/mL Concentration contains 10 mg enoxaparin sodium (or approximate anti-Factor Xa activity of 1000 IU [with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard]) per 0.1 mL Water for Injection.

2 150 mg per mL of Water for Injection

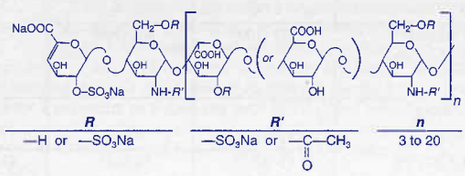
-Graduated Prefilled Syringes	120 mg / 0.8 mL, 150 mg / 1 mL

Lovenox Injection 150 mg/mL Concentration contains 15 mg enoxaparin sodium (or appropriate anti-Factor Xa activity of 1500 IU [with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard]) per 0.1 mL Water for Injection.

The solutions are preservative-free and intended for use only as a single-dose injection. (See **DOSAGE AND ADMINISTRATION** and **HOW SUPPLIED** for dosage unit descriptions.) The pH of the injection is 5.5 to 7.5. Nitrogen is used in the headspace to inhibit oxidation. Enoxaparin is obtained by alkaline degradation of heparin benzyl ester derived from porcine intestinal mucosa. Its structure is characterized by a 2-O-sulfo-4-enepyranosuronic acid group at the non-reducing end and a 2-N,6-O-disulfo-D-glucosamine at the reducing end of the chain. The substance is the sodium salt. The average molecular weight is about 4500 daltons. The molecular weight distribution is:

<2000 daltons	≤20%
2000 to 8000 daltons	≥68%
>8000 daltons	≤18%

STRUCTURAL FORMULA



CLINICAL PHARMACOLOGY

Enoxaparin is a low molecular weight heparin which has antithrombotic properties. In humans, enoxaparin given at a dose of 1.5 mg/kg subcutaneously (SC) is characterized by a higher ratio of anti-Factor Xa to anti-Factor IIa activity (mean±SD, 14.0±3.1) (based on areas under anti-Factor activity versus time curves) compared to the ratios observed for heparin (mean±SD, 1.22±0.13). Increases of up to 1.8 times the control values were seen in the thrombin time (TT) and the activated partial thromboplastin time (aPTT). Enoxaparin at a 1 mg/kg dose (100 mg / mL concentration), administered SC every 12 hours to patients in a large clinical trial resulted in aPTT values of 45 seconds or less in the majority of patients (n = 1607).

Pharmacodynamics (conducted using 100 mg / mL concentration): Maximum anti-Factor Xa and anti-thrombin (anti-Factor IIa) activities occur 3 to 5 hours after SC injection of enoxaparin. Mean peak anti-Factor Xa activity was 0.16 IU/mL (1.58 µg/mL) and 0.38 IU/mL (3.83 µg/mL) after the 20 mg and the 40 mg clinically tested SC doses, respectively. Mean (n = 46) peak anti-Factor Xa activity was 1.1 IU/mL at steady state in patients with unstable angina receiving 1mg/kg SC every 12 hours for 14 days. Mean absolute bioavailability of enoxaparin, given SC, based on anti-Factor Xa activity is 92% in healthy volunteers. The volume of distribution of anti-Factor Xa activity is about 6 L. Following intravenous (i.v.) dosing, the total body clearance of enoxaparin is 26 mL/min. After i.v. dosing of enoxaparin labeled with the gamma-emitter, ^{99m}Tc, 40% of radioactivity and 8 to 20% of anti-Factor Xa activity were recovered in urine in 24 hours. Elimination half-life based on anti-Factor Xa activity was 4.5 hours after SC administration. Following a 40 mg SC once a day dose, significant anti-Factor Xa activity persists in plasma for about 12 hours.

Following SC dosing, the apparent clearance (CL/F) of enoxaparin is approximately 15 mL/min. Apparent clearance and A_{max} derived from anti-Factor Xa values following single SC dosing (40 mg and 60 mg) were slightly higher in males than in females. The source of the gender difference in these parameters has not been conclusively identified, however, body weight may be a contributing factor.

Apparent clearance and A_{max} derived from anti-Factor Xa values following single and multiple SC dosing in elderly subjects were close to those observed in young subjects. Following once a day SC dosing of 40 mg enoxaparin, the Day 10 mean area under anti-

Factor Xa activity versus time curve (AUC) was approximately 15% greater than the mean Day 1 AUC value. In subjects with moderate renal impairment (creatinine 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 (creatinine clearance <30 mL/min), were approximately 30% lower than the mean CL/F value of control group subjects. (See **PRECAUTIONS.**)

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 below):

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

	Concentration	Anti-Xa	Anti-IIa	Heptest	aPTT
Amax (IU/mL or Δ sec)	100 mg/mL	1.37 (±0.23)	0.23 (±0.05)	104.5 (±16.6)	19.3 (±4.7)
	200 mg/mL	1.45 (±0.22)	0.26 (±0.05)	110.9 (±17.1)	22 (±6.7)
	90% CI	102-110%		102-111%	
tmax** (h)	100 mg/mL	3 (2-6)	4 (2-5)	2.5 (2-4.5)	3 (2-4.5)
	200 mg/mL	3.5 (2-6)	4.5 (2.5-6)	3.3 (2-5)	3 (2-5)
AUC (ss) (h*IU/mL or h* Δ sec)	100 mg/mL	14.26 (±2.93)	1.54 (±0.61)	1321 (±219)	
	200 mg/mL	15.43 (±2 96)	1.77 (±0.67)	1401 (±227)	
	90% CI	105-112%		103-109%	

* Means ± 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) with 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 SC, 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 U 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

	Dosing Regimen	
	Lovenox Inj. 40 mg q.d. SC	**Heparin** 5000 U q8h SC
Indication	n (%)	n (%)
All Treated Abdominal Surgery Patients	555 (100)	560 (100)
Treatment Failures		
Total VTE[1] (%)	56 (10.1) (95% CI[2]: 8 to 13)	63 (11.3) (95% CI: 9 to 14)
DVT Only (%)	54 (9.7) (95% CI: 7 to 12)	61 (10.9) (95% CI: 8 to 13)

[1] VTE = Venous thromboembolic events which included DVT, PE, and death considered to be thromboembolic in origin.
[2] CI = Confidence Interval

In a second double-blind, parallel group study, Lovenox Injection 40 mg SC once a day was compared to heparin 5000 U every 8 hours SC in 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 50.1 years) with 54.2% men and 45.8% women. Treatment was initiated approximately 2 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

	Dosing Regimen	
	Lovenox Inj. 40 mg q.d. SC	**Heparin** 5000 U q8h SC
Indication	n (%)	n (%)
All Treated Colorectal Surgery Patients	673 (100)	674 (100)
Treatment Failures		
Total VTE[1] (%)	48 (7.1) (95% CI[2]: 5 to 9)	45 (6.7) (95% CI: 5 to 9)
DVT Only (%)	47 (7.0) (95% CI: 5 to 9)	44 (6.5) (95% CI: 5 to 8)

[1] VTE = Venous thromboembolic events which included DVT, PE, and death considered to be thromboembolic in origin.
[2] CI = Confidence Interval

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 study, Lovenox Injection 30 mg every 12 hours SC was compared to placebo in patients with hip replacement. A total of 100 patients were randomized in the study and all patients were treated. Patients ranged in age from 41 to 84 years (mean age 67.1 years) with 45% men and 55% women. After hemostasis was established, treatment was initiated 12 to 24 hours after surgery and was continued for 10 to 14 days after surgery. The efficacy data are provided below.

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

	Dosing Regimen	
	Lovenox Inj. 30 mg q12h SC	**Placebo** q12h SC
Indication	n (%)	n (%)
All Treated Hip Replacement Patients	50 (100)	50 (100)
Treatment Failures		
Total DVT (%)	5 (10)[1]	23 (46)
Proximal DVT (%)	1 (2)[2]	11 (22)

[1] p value versus placebo = 0.0002
[2] p value versus placebo = 0.0134

A double-blind, multicenter study compared three dosing regimens of Lovenox Injection in patients with hip replacement. A total of 572 patients were randomized in the study and 568 patients were treated. Patients ranged in age from 31 to 88 years (mean age 64.7 years) with 63% men and 37% women. Patients were 93% Caucasian, 6% Black, <1% Oriental, and 1% others. Treatment was initiated within two days after surgery and was continued for 7 to 11 days after surgery. The efficacy data are provided below.

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

	Dosing Regimen		
	10 mg q.d. SC	**30 mg q12h SC**	**40 mg q.d. SC**
Indication	n (%)	n (%)	n (%)
All Treated Hip Replacement Patients	161 (100)	208 (100)	199 (100)
Treatment Failures			
Total DVT (%)	40 (25)	22 (11)[1]	27 (14)
Proximal DVT (%)	17 (11)	8 (4)[2]	9 (5)

[1] p value versus Lovenox 10 mg once a day = 0.0008
[2] p value versus Lovenox 10 mg once a day = 0.0168

There was no significant difference between the 30 mg every 12 hours and 40 mg once a day regimens. In a double-blind study, Lovenox Injection 30 mg every 12 hours SC was compared to placebo in patients undergoing knee replacement surgery. A total of 132 patients were randomized in the study and 131 patients were treated, of which 99 had total knee replacement and 32 had either unicompartmental knee replacement or tibial osteotomy. The 99 patients with total knee replacement ranged in age from 42 to 85 years (mean age 70.2 years) with 36.4% men and 63.6% women. After hemostasis was established, treatment was initiated 12 to 24 hours after surgery and was continued up to 15 days after surgery. The incidence of proximal and total DVT after surgery was significantly lower for Lovenox Injection compared to placebo. The efficacy data are provided below.

Efficacy of Lovenox Injection in the Prophylaxis of Deep Vein Thrombosis Following Total Knee Replacement Surgery

	Dosing Regimen	
	Lovenox Inj. 30 mg q12h SC	**Placebo** q12h SC
Indication	n (%)	n (%)
All Treated Total Knee Replacement Patients	47 (100)	52 (100)
Treatment Failures		
Total DVT (%)	5 (11)[1] (95% CI[2]: 1 to 21)	32 (62) (95% CI: 47 to 76)
Proximal DVT (%)	0 (0)[3] (95% Upper CL[4]: 5)	7 (13) (95% CI: 3 to 24)

[1] p value versus placebo = 0.0001
[2] CI = Confidence Interval
[3] p value versus placebo = 0.013
[4] CL = Confidence Limit

Additionally, in an open-label, parallel group, randomized clinical study, Lovenox Injection 30 mg every 12 hours SC in patients undergoing elective knee replacement surgery was compared to heparin 5000 U every 8 hours SC. A total of 453 patients were randomized in the study and all were treated. Patients ranged in age from 38 to 90 years (mean age 68.5 years) with 43.7% men and 56.3% women. Patients were 92.5% Caucasian, 5.3% Black, 0.2% Oriental, and 0.4% others. Treatment was initiated after surgery and continued up to 14 days. The incidence of deep vein thrombosis was significantly lower for Lovenox Injection compared to heparin.

Extended Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery: In a study of extended prophylaxis for patients undergoing hip replacement surgery, patients were treated, while hospitalized, with Lovenox Injection 40 mg SC, initiated up to 12 hours prior to surgery for the prophylaxis of post-operative DVT. At the end of the peri-operative period, all patients underwent bilateral venography. In a double-blind design, those patients with no venous thromboembolic disease were randomized to a post-discharge regimen of either Lovenox Injection 40 mg (n = 90) once a day SC or to placebo (n = 89) for 3 weeks. A total of 179 patients were randomized in the double-blind phase of the

study and all patients were treated. Patients ranged in age from 47 to 87 years (mean age 69.4 years) with 57% men and 43% women. In this population of patients, the incidence of DVT during extended prophylaxis was significantly lower for Lovenox Injection compared to placebo. The efficacy data are provided below.

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

	Post-Discharge Dosing Regimen	
	Lovenox Inj. 40 mg q.d. SC	**Placebo** q.d. SC
Indication (Post-Discharge)	n (%)	n (%)
All Treated Extended Prophylaxis Patients	90 (100)	89 (100)
Treatment Failures		
Total DVT (%)	6 (7)[1] (95% CI[2]: 3 to 14)	18 (20) (95% CI: 12 to 30)
Proximal DVT (%)	5 (6)[3] (95% CI: 2 to 13)	7 (8) (95% CI: 3 to 16)

[1] p value versus placebo = 0.008
[2] CI– Confidence Interval
[3] p value versus placebo = 0.537

In a second study, patients undergoing hip replacement surgery were treated, while hospitalized, with Lovenox Injection 40 mg SC, initiated up to 12 hours prior to surgery. All patients were examined for clinical signs and symptoms of venous thromboembolic (VTE) disease. In a double-blind design, patients without clinical signs and symptoms of VTE disease were randomized to a post-discharge regimen of either Lovenox Injection 40 mg (n = 131) once a day SC or to placebo (n = 131) for 3 weeks. A total of 262 patients were randomized in the study double-blind phase and all patients were treated. Patients ranged in age from 44 to 87 years (mean age 68.5 years) with 43.1% men and 56.9% women. Similar to the first study the incidence of DVT during extended prophylaxis was significantly lower for Lovenox Injection compared to placebo, with a statistically significant difference in both total DVT (Lovenox Injection 21 [16%] versus placebo 45 [34%]; p = 0.001) and proximal DVT (Lovenox Injection 8 [6%] versus placebo 28 [21%]; p = <0.001).

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 of <10 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 rheumatic disorder [acute lumbar or sciatic pain, vertebral compression (due to osteoporosis or tumor), acute arthritic 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 97 years (mean age 73 years) with equal proportions of men and women. 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.

Efficacy of Lovenox Injection in the Prophylaxis of Deep Vein Thrombosis in Medical Patients With Severely Restricted Mobility During Acute Illness

	Dosing Regimen		
	Lovenox Inj. 20 mg q.d. SC	**Lovenox Inj.** 40 mg q.d. SC	**Placebo**
Indication	n (%)	n (%)	n (%)
All Treated Medical Patients During Acute Illness	351 (100)	360 (100)	362 (100)
Treatment Failure[1]			
Total VTE[2] (%)	43 (12.3)	16 (4.4)	43 (11.9)
Total DVT (%)	43 (12.3) (95% CI[3] 8.8 to 15.7)	16 (4.4) (95% CI[3] 2.3 to 6.6)	41 (11.3) (95% CI[3] 8.1 to 14.6)
Proximal DVT (%)	13 (3.7)	5 (1.4)	14 (3.9)

[1] Treatment failures during therapy, between Days 1 and 14.
[2] VTE = Venous thromboembolic events which included DVT, PE, and death considered to be thromboembolic in origin.
[3] CI = Confidence Interval

At approximately 3 months following enrollment, the incidence of venous thromboembolism remained significantly lower in the Lovenox Injection 40 mg treatment group versus the placebo treatment group.

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 3171 patients were enrolled in the study, and 3107 patients were treated. Patients ranged in age from 25-94 years (median age 64 years), with 33.4% of patients female and 66.6% male. Race was distributed as follows: 89.8% Caucasian, 4.8% Black, 2.0% Oriental, and 3.5% other. **All** patients were also treated with aspirin 100 to 325 mg per day. Treatment was initiated within 24 hours of the event and continued until clinical stabilization, revascularization procedures, or hospital discharge, with a maximal duration of 8 days of therapy. The combined incidence of the triple endpoint of death, myocardial infarction, or recurrent angina was lower for Lovenox Injection compared with heparin therapy at 14 days after initiation of treatment. The lower incidence of the triple endpoint was sustained up to 30 days after initiation of treatment. These results were observed in an analysis of both all-randomized and all-treated patients. The efficacy data are provided below.

Efficacy of Lovenox Injection in the Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction (Combined Endpoint of Death, Myocardial Infarction, or Recurrent Angina)

	Dosing Regimen[1]			
	Lovenox Inj. 1 mg/kg q12h SC	Heparin aPTT Adjusted i.v. Therapy	Reduction (%)	p Value
Indication	n (%)	n (%)		
All Treated Unstable Angina and Non-Q-Wave MI Patients	1578 (100)	1529 (100)		
Timepoint[2]				
48 Hours	96 (6.1)	112 (7.3)	1.2	0.120
14 Days	261 (16.5)	303 (19.8)	3.3	0.017
30 Days	313 (19.8)	358 (23.4)	3.6	0.014

[1] All patients were also treated with aspirin 100 to 325 mg per day.
[2] Evaluation timepoints are after initiation of treatment. Therapy continued for up to 8 days (median duration of 2.6 days).

The combined incidence of death or myocardial infarction at all time points was lower for Lovenox Injection compared to standard heparin therapy, but did not achieve statistical significance. The efficacy data are provided below.

Efficacy of Lovenox Injection in the Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction (Combined Endpoint of Death or Myocardial Infarction)

	Dosing Regimen[1]			
	Lovenox Inj. 1 mg/kg q12h SC	Heparin aPTT Adjusted i.v. Therapy	Reduction (%)	p Value
Indication	n (%)	n (%)		
All Treated Unstable Angina and Non-Q-Wave MI Patients	1578 (100)	1529 (100)		
Timepoint[2]				
48 Hours	16 (1.0)	20 (1.3)	0.3	0.126
14 Days	76 (4.8)	93 (6.1)	1.3	0.115
30 Days	96 (6.1)	118 (7.7)	1.6	0.069

[1] All patients were also treated with aspirin 100 to 325 mg per day.
[2] Evaluation timepoints are after initiation of treatment. Therapy continued for up to 8 days (median duration of 2.6 days).

In a survey one year following treatment, with information available for 92% of enrolled patients, the combined incidence of death, myocardial infarction, or recurrent angina remained lower for Lovenox Injection versus heparin (32.0% vs 35.7%).
Urgent revascularization procedures were performed less frequently in the Lovenox Injection group as compared to the heparin group, 6.3% compared to 8.2% at 30 days ($p = 0.047$)

Treatment of Deep Vein Thrombosis (DVT) with or without Pulmonary Embolism (PE):
In a multicenter, parallel group study, 900 patients with acute lower extremity DVT with or without PE were randomized to an inpatient (hospital) treatment of either (i) Lovenox Injection 1.5 mg/kg once a day SC, (ii) Lovenox Injection 1 mg/kg every 12 hours SC, or (iii) heparin i.v. bolus (5000 IU) followed by a continuous infusion (administered to achieve an aPTT of 55 to 85 seconds). A total of 900 patients were randomized in the study and all patients were treated. Patients ranged in age from 18 to 92 years (mean age 60.7 years) with 54.7% men and 45.3% women. All patients also received warfarin sodium (dose adjusted according to PT to achieve an International Normalization Ratio [INR] of 2.0 to 3.0), commencing within 72 hours of initiation of Lovenox Injection or standard heparin therapy, and continuing for 90 days. Lovenox Injection or standard heparin therapy was administered for a minimum of 5 days and until the targeted warfarin sodium INR was achieved. Both Lovenox Injection regimens were equivalent to standard heparin therapy in reducing the risk of recurrent venous thromboembolism (DVT and/or PE). The efficacy data are provided below.

Efficacy of Lovenox Injection in Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism

	Dosing Regimen[1]		
	Lovenox Inj. 1.5 mg/kg q.d. SC	Lovenox Inj. 1 mg/kg q12h SC	Heparin aPTT Adjusted i.v. Therapy
Indication	n (%)	n (%)	n (%)
All Treated DVT Patients with or without PE	298 (100)	312 (100)	290 (100)
Patient Outcome			
Total VTE[2] (%)	13 (4.4)[3]	9 (2.9)[3]	12 (4.1)
DVT Only (%)	11 (3.7)	7 (2.2)	8 (2.8)
Proximal DVT (%)	9 (3.0)	6 (1.9)	7 (2.4)
PE (%)	2 (0.7)	2 (0.6)	4 (1.4)

[1] All patients were also treated with warfarin sodium commencing within 72 hours of Lovenox Injection or standard heparin therapy.
[2] VTE – venous thromboembolic event (DVT and/or PE).
[3] The 95% Confidence Intervals for the treatment differences for total VTE were:
Lovenox Injection once a day versus heparin (-3.0 to 3.5)
Lovenox Injection every 12 hours versus heparin (-4.2 to 1.7).

Similarly, in a multicenter, open-label, parallel group study, patients with acute proximal DVT were randomized to Lovenox Injection or heparin. Patients who could not receive outpatient therapy were excluded from entering the study. Outpatient exclusion criteria included the following: inability to receive outpatient heparin therapy because of associated co-morbid conditions or potential for non-compliance and inability to attend follow-

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up visits as an outpatient because of geographic inaccessibility. Eligible patients could be treated in the hospital, but ONLY Lovenox Injection patients were permitted to go home on therapy (72%). A total of 501 patients were randomized in the study and all patients were treated. Patients ranged in age from 19 to 96 years (mean age 57.8 years) with 60.5% men and 39.5% women. Patients were randomized to either Lovenox Injection 1 mg/kg every 12 hours SC or heparin i.v. bolus (5000 IU) followed by a continuous infusion administered to achieve an aPTT of 60 to 85 seconds (in-patient treatment). All patients also received warfarin sodium as described in the previous study. Lovenox Injection or standard heparin therapy was administered for a minimum of 5 days. Lovenox Injection was equivalent to standard heparin therapy in reducing the risk of recurrent venous thromboembolism. The efficacy data are provided below.

Efficacy of Lovenox Injection in Treatment of Deep Vein Thrombosis

	Dosing Regimen[1]	
	Lovenox Inj. 1 mg/kg q12h SC	Heparin aPTT Adjusted i.v. Therapy
Indication	n (%)	n (%)
All Treated DVT Patients	247 (100)	254 (100)
Patient Outcome		
Total VTE[2] (%)	13 (5.3)[3]	17 (6.7)
DVT Only (%)	11 (4.5)	14 (5.5)
Proximal DVT (%)	10 (4.0)	12 (4.7)
PE (%)	2 (0.8)	3 (1.2)

[1] All patients were also treated with warfarin sodium commencing on the evening of the second day of Lovenox Injection or standard heparin therapy.
[2] VTE = venous thromboembolic event (deep vein thrombosis [DVT] and/or pulmonary embolism [PE]).
[3] The 95% Confidence Intervals for the treatment difference for total VTE was: Lovenox Injection versus heparin (-5.6 to 2.7).

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.
- Lovenox Injection is indicated for the prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin.
- Lovenox Injection is indicated for:
  - the **inpatient treatment** of acute deep vein thrombosis **with or without pulmonary embolism,** when administered in conjunction with warfarin sodium;
  - the **outpatient treatment** of acute deep vein thrombosis **without pulmonary embolism** when administered in conjunction with warfarin sodium.

See **DOSAGE AND ADMINISTRATION: Adult Dosage** for appropriate dosage regimens

CONTRAINDICATIONS

Lovenox Injection is contraindicated in patients with active major bleeding, in patients with thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of enoxaparin sodium, or in patients with hypersensitivity to enoxaparin sodium. Patients with known hypersensitivity to heparin or pork products should not be treated with Lovenox Injection.

WARNINGS

Lovenox Injection is not intended for intramuscular administration.
Lovenox Injection cannot be used interchangeably (unit for unit) with heparin or other low molecular weight heparins as they differ in manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units, and dosage. Each of these medicines has its own instructions for use.
Lovenox Injection should be used with extreme caution in patients with a history of heparin-induced thrombocytopenia.
Hemorrhage: Lovenox Injection, like other anticoagulants, should be used with extreme caution in conditions 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 in patients treated concomitantly with platelet inhibitors.
Cases of epidural or spinal 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 post-operative 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 hemorrhages including retroperitoneal 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/mm^3 and 50,000/mm^3) occurred at a rate of 1.3% in 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/mm^3 occurred at a rate of 0.1% in patients given Lovenox Injection, in 0.2% of patients given heparin, and 0.4% of patients given placebo in the same trials.
Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm^3, Lovenox Injection should be discontinued. Cases of heparin-induced thrombocytopenia with thrombosis have also been observed in clinical practice. Some of these cases were complicated by organ infarction, limb ischemia, or death.
Prosthetic Heart Valves: The use of Lovenox Injection is not recommended for thromboprophylaxis in patients with prosthetic heart valves. Cases of prosthetic heart valve thrombosis have been reported in patients with prosthetic valves who have received enoxaparin for thromboprophylaxis. Some of these cases were pregnant women in whom thrombosis led to maternal deaths and fetal deaths. Pregnant women with prosthetic heart valves may be at higher risk for thromboembolism **(see PRECAUTIONS: Pregnancy).**

PRECAUTIONS

General: Lovenox Injection should not be mixed with other injections or infusions.
Lovenox Injection should be used with care in patients with a bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration, diabetic retinopathy, and hemorrhage. Elderly patients and patients with renal insufficiency may show delayed elimination of enoxaparin. Lovenox Injection should be used with care in these patients. Adjustment of enoxaparin sodium dose may be considered for low weight (<45 kg) patients and/or for patients with severe renal impairment (creatinine clearance <30 mL/min).
If thromboembolic events occur despite Lovenox Injection prophylaxis, appropriate therapy should be initiated.

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 prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of Lovenox Injection activity and, therefore, unsuitable for monitoring. Anti-Factor Xa may be used to monitor the anticoagulant effect of Lovenox Injection in patients with significant renal impairment. If during Lovenox Injection therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa levels may be used to monitor the anticoagulant effects of Lovenox Injection (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 acetylsalicylic acid, salicylates, NSAIDs (including ketorolac tromethamine), dipyridamole, or sulfinpyrazone. If co-administration is essential, conduct close clinical and laboratory monitoring (see **PRECAUTIONS: Laboratory Tests**).

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* rat 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 up to 20 mg/kg/day or 141 mg/m^2/day. The maximum human dose in clinical trials was 2.0 mg/kg/day or 78 mg/m^2/day (for an average body weight of 70 kg, height of 170 cm, and body surface area of 1.8 m^2).

Pregnancy: *Teratogenic Effects:* Pregnancy Category B: Teratology studies have been conducted in pregnant rats and rabbits at SC doses of enoxaparin up to 30 mg/kg/day or 211 mg/m^2/day and 410 mg/m^2/day, respectively. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
There have been reports of congenital anomalies in infants born to women who received enoxaparin during pregnancy including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia, and cardiac defect. A cause and effect relationship has not been established nor has the incidence been shown to be higher than in the general population.
Non-teratogenic Effects: There have been post-marketing reports of fetal death when pregnant women received Lovenox Injection. Causality for these cases has not been determined. Pregnant women receiving anti-coagulants, including enoxaparin, are at increased risk for bleeding. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women receiving enoxaparin should be carefully monitored. Pregnant women and women of child-bearing potential should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.
In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 7 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. There are postmarketing reports of prosthetic valve thrombosis in pregnant women with prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. These events resulted in maternal death or surgical interventions. The use of Lovenox Injection is not recommended for thromboprophylaxis in pregnant women with prosthetic heart valves (see **WARNINGS: Prosthetic Heart Valves).**

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Lovenox Injection is administered to nursing women.

Pediatric Use: Safety and effectiveness of Lovenox Injection in pediatric patients have not been established.

Geriatric Use: Over 2800 patients, 65 years and older, have received Lovenox Injection in pivotal clinical trials. The efficacy of Lovenox Injection in the elderly (≥65 years) was similar to that seen in younger patients (<65 years). The incidence of bleeding complications was similar between elderly and younger patients when 30 mg every 12 hours or 40 mg once a day doses of Lovenox Injection were employed. The incidence of bleeding complications was higher in elderly patients as compared to younger patients when Lovenox Injection was administered at doses of 1.5 mg/kg once a day or 1 mg/kg every 12 hours. The risk of Lovenox Injection-associated bleeding increased with age. Serious adverse events increased with age for patients receiving Lovenox Injection. Other clinical experience (including postmarketing surveillance and literature reports) has not revealed additional differences in the safety of Lovenox Injection between elderly and younger patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised. Monitoring of geriatric patients with low body weight (<45 kg) and those predisposed to decreased renal function should be considered. (see **CLINICAL PHARMACOLOGY** 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 rates of major bleeding events have been reported during clinical trials with Lovenox Injection.

Major Bleeding Episodes Following Abdominal and Colorectal Surgery[1]

	Dosing Regimen	
	Lovenox Inj.	**Heparin**
Indications	40 mg q.d. SC	5000 U q8h SC
Abdominal Surgery	n = 555 23 (4%)	n = 560 16 (3%)
Colorectal Surgery	n = 673 28 (4%)	n = 674 21 (3%)

[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. Retroperitoneal, intraocular, and intracranial hemorrhages were always considered major.

Major Bleeding Episodes Following Hip or Knee Replacement Surgery[1]

	Dosing Regimen		
	Lovenox Inj.	**Lovenox Inj.**	**Heparin**
Indications	40 mg q.d. SC	30 mg q12h SC	15,000 U/24h SC
Hip Replacement Surgery Without Extended Prophylaxis[2]		n = 786 31 (4%)	n = 541 32 (6%)
Hip Replacement Surgery With Extended Prophylaxis			
Peri-operative Period[3]	n = 288 4 (2%)		
Extended Prophylaxis Period[4]	n = 221 0 (0%)		
Knee Replacement Surgery Without Extended Prophylaxis[2]		n = 294 3 (1%)	n = 225 3 (1%)

[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. Retroperitoneal and intracranial hemorrhages were always considered major. In the knee replacement surgery trials, intraocular 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.
NOTE: At no time point were the 40 mg once a day pre operative and the 30 mg every 12 hours post-operative hip replacement surgery prophylactic regimens compared in clinical trials.
Injection site hematomas 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 Medical Patients With Severely Restricted Mobility During Acute Illness[1]

	Dosing Regimen		
	Lovenox Inj.[2]	**Lovenox Inj.**[2]	**Placebo**[2]
Indications	20 mg q.d. SC	40 mg q.d. SC	
Medical Patients During Acute Illness	n = 351 1 (<1%)	n = 360 3 (<1%)	n = 362 2 (<1%)

[1] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, (2) if the hemorrhage caused a decrease in hemoglobin of ≥2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal 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.

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

	Dosing Regimen	
	Lovenox Inj.[1]	**Heparin**[1]
Indication	1 mg/kg q12h SC	aPTT Adjusted i.v. Therapy
Unstable Angina and Non-Q-Wave MI[2,3]	n = 1578 17 (1%)	n = 1529 18 (1%)

[1] The rates represent major bleeding on study medication up to 12 hours after dose.
[2] Aspirin therapy was administered concurrently (100 to 325 mg per day).
[3] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease by ≥3 g/dL or transfusion of 2 or more units of blood products. Intraocular, retroperitoneal, and intracranial hemorrhages were always considered major.

Major Bleeding Episodes in Deep Vein Thrombosis With or Without Pulmonary Embolism Treatment [1]

	Dosing Regimen[2]		
	Lovenox Inj.	**Lovenox Inj.**	**Heparin**
Indication	1.5 mg/kg q.d SC	1 mg/kg q12h SC	aPTT Adjusted i.v. Therapy
Treatment of DVT and PE	n = 298 5 (2%)	n = 559 9 (2%)	n = 554 9 (2%)

[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. Retroperitoneal, intraocular, and intracranial hemorrhages were always considered major.
[2] All patients also received warfarin sodium (dose-adjusted according to PT to achieve an INR of 2.0 to 3.0) commencing within 72 hours of Lovenox Injection or standard heparin therapy and continuing for up to 90 days.

Thrombocytopenia: see **WARNINGS: Thrombocytopenia**.

Elevations of Serum Aminotransferases: Asymptomatic increases in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels greater than three times the upper limit of normal of the laboratory reference range have been reported in up to 6.1% and 5.9% of patients, respectively, during treatment with Lovenox Injection. Similar significant increases in aminotransferase levels have also been observed in patients and healthy volunteers treated with heparin and other low molecular weight heparins. Such elevations are fully reversible and are rarely associated with increases in bilirubin.
Since aminotransferase determinations are important 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.

Local Reactions: Mild local irritation, pain, hematoma, ecchymosis, and erythema may follow SC injection of Lovenox Injection.

Other: Other adverse effects that were thought to be possibly or probably related to treatment with Lovenox Injection, heparin, or placebo in clinical trials with patients undergoing hip or knee replacement surgery, abdominal or colorectal surgery, or treatment for DVT and that occurred at a rate of at least 2% in the Lovenox Injection group, are provided below.

Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Patients[1] Undergoing Abdominal or Colorectal Surgery

	Dosing Regimen			
	Lovenox Inj. 40 mg q.d. SC n = 1228		Heparin 5000 U q8h SC n = 1234	
Adverse Event	**Severe**	**Total**	**Severe**	**Total**
Hemorrhage	<1%	7%	<1%	6%
Anemia	<1%	3%	<1%	3%
Ecchymosis	0%	3%	0%	3%

[1] Excluding unrelated adverse events.

Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Patients[1] Undergoing Hip or Knee Replacement Surgery

	Dosing Regimen									
	Lovenox Inj. 40 mg q.d. SC				Lovenox Inj. 30 mg q12h SC		Heparin 15,000 U/24h SC		Placebo q12h SC	
	Peri-operative Period n = 288[2]		Extended Prophylaxis Period n = 131[3]		n = 1080		n = 766		n = 115	
Adverse Event	**Severe**	**Total**	**Severe**	**Total**	**Severe**	**Total**	**Severe**	**Total**	**Severe**	**Total**
Fever	0%	8%	0%	0%	<1%	5%	<1%	4%	0%	3%
Hemorrhage	<1%	13%	0%	5%	<1%	4%	1%	4%	0%	3%
Nausea					<1%	3%	<1%	2%	0%	2%
Anemia	0%	16%	0%	<2%	<1%	2%	2%	5%	<1%	7%
Edema					<1%	2%	<1%	2%	0%	2%
Peripheral edema	0%	6%	0%	0%	<1%	3%	<1%	4%	0%	3%

[1] Excluding unrelated adverse events.
[2] Data represents Lovenox Injection 40 mg SC once a day initiated up to 12 hours prior to surgery in 288 hip replacement surgery patients who received Lovenox Injection peri-operatively in an unblinded fashion in one clinical trial.
[3] Data represents Lovenox Injection 40 mg SC once a day given in a blinded fashion as extended prophylaxis at the end of the peri-operative period in 131 of the original 288 hip replacement surgery patients for up to 21 days in one clinical trial.

Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Medical Patients[1] With Severely Restricted Mobility During Acute Illness

	Dosing Regimen	
	Lovenox Inj. 40 mg q.d. SC n = 360	Placebo q.d. SC n = 362
Adverse Event	%	%
Dyspnea	3.3	5.2
Thrombocytopenia	2.8	2.8
Confusion	2.2	1.1
Diarrhea	2.2	1.7
Nausea	2.5	1.7

[1]Excluding unrelated and unlikely adverse events.

Adverse Events in Lovenox Injection Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction: Non-hemorrhagic clinical events reported to be related to Lovenox Injection therapy occurred at an incidence of ≤1%.
Non-major hemorrhagic episodes, primarily injection site ecchymoses and hematomas, were more frequently reported in patients treated with SC Lovenox Injection than in patients treated with i.v. heparin.
Serious adverse events with Lovenox Injection or heparin in a clinical trial in patients with unstable angina or non-Q-wave myocardial infarction that occurred at a rate of at least 0.5% in the Lovenox Injection group, are provided below (irrespective of relationship to drug therapy).

Serious Adverse Events Occurring at ≥0.5% Incidence in Lovenox Injection Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction

	Dosing Regimen	
	Lovenox Inj. 1 mg/kg q12h SC n = 1578	Heparin aPTT Adjusted i.v. Therapy n = 1529
Adverse Event	n (%)	n (%)
Atrial fibrillation	11 (0.70)	3 (0.20)
Heart failure	15 (0.95)	11 (0.72)
Lung edema	11 (0.70)	11 (0.72)
Pneumonia	13 (0.82)	9 (0.59)

Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Patients[1] Undergoing Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism

	Dosing Regimen					
	Lovenox Inj. 1.5 mg/kg q.d. SC n = 298		Lovenox Inj. 1 mg/kg q12h SC n = 559		Heparin aPTT Adjusted i.v. Therapy n = 544	
Adverse Event	**Severe**	**Total**	**Severe**	**Total**	**Severe**	**Total**
Injection Site Hemorrhage	0%	5%	0%	3%	<1%	<1%
Injection Site Pain	0%	2%	0%	2%	0%	0%
Hematuria	0%	2%	0%	<1%	<1%	2%

[1] Excluding unrelated adverse events.

Ongoing Safety Surveillance: Since 1993, there have been over 80 reports of epidural or spinal hematoma formation with 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.
Other Ongoing Safety Surveillance Reports: local reactions at the injection site (i.e., skin necrosis, nodules, inflammation, oozing), systemic allergic reactions (i.e., pruritus, urticaria, anaphylactoid reactions), vesiculobullous rash, purpura, thrombocytosis, and thrombocytopenia with thrombosis (see **WARNINGS, Thrombocytopenia**). Very rare cases of hyperlipidemia have been reported, with one case of hyperlipidemia, with marked hypertriglyceridemia, reported in a diabetic pregnant woman; causality has not been determined

OVERDOSAGE

Symptoms/Treatment: Accidental overdosage following administration of Lovenox Injection may lead to hemorrhagic complications. Injected Lovenox Injection may be largely neutralized by the slow i.v. injection of protamine sulfate (1% 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 1 mg of Lovenox Injection may be administered if the aPTT measured 2 to 4 hours after the first infusion remains prolonged. However, even with higher doses of protamine, the aPTT may remain more prolonged than under normal conditions found following administration of heparin. In all cases, the anti-Factor Xa activity is never completely neutralized (maximum about 60%). Particular care should be taken to avoid overdosage with protamine sulfate. Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulfate, it should be given only when resuscitation techniques and treatment of anaphylactic shock are readily available. For additional information consult the labeling of Protamine Sulfate Injection, USP, products.
A single SC dose of 46.4 mg/kg enoxaparin was lethal to rats. The symptoms of acute toxicity were ataxia, decreased motility, dyspnea, cyanosis, and coma.

DOSAGE AND ADMINISTRATION

All patients should be evaluated for a bleeding disorder before administration of Lovenox Injection, unless the medication is needed urgently. Since coagulation parameters are unsuitable for monitoring Lovenox Injection activity, routine monitoring of coagulation parameters is not required (see **PRECAUTIONS, Laboratory Tests**).

Note: Lovenox Injection is available in two concentrations:

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

Adult Dosage:
Abdominal Surgery: In patients undergoing abdominal surgery who are at risk for thromboembolic complications, the recommended dose of Lovenox Injection is **40 mg once a day** administered by SC injection with the initial dose given 2 hours prior to surgery. The usual duration of administration is 7 to 10 days; up to 12 days administration has been well tolerated in clinical trials.
Hip or Knee Replacement Surgery: In patients undergoing hip or knee replacement surgery, the recommended dose of Lovenox Injection is **30 mg every 12 hours** administered by SC injection. Provided that hemostasis has been established, the initial dose should be given 12 to 24 hours after surgery. For hip replacement surgery, a dose of **40 mg once a day** SC, given initially 12 (±3) hours prior to surgery, may be considered. Following the initial phase of thromboprophylaxis in hip replacement surgery patients, continued prophylaxis with Lovenox Injection 40 mg once a day administered by SC injection for 3 weeks is recommended. The usual duration of administration is 7 to 10 days; up to 14 days administration has been well tolerated in clinical trials.
Medical Patients During Acute Illness: In medical patients at risk for thromboembolic complications due to severely restricted mobility during acute illness, the recommended dose of Lovenox Injection is **40 mg once a day** 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 the controlled clinical trial.
Unstable Angina and Non-Q-Wave Myocardial Infarction: In patients with unstable angina or non-Q-wave myocardial infarction, the recommended dose of Lovenox Injection is **1 mg/kg** administered SC **every 12 hours** in conjunction with oral aspirin therapy (100 to 325 mg once daily). Treatment with Lovenox Injection should be prescribed for a minimum of 2 days and continued until clinical stabilization. To minimize the risk of bleeding following vascular instrumentation during the treatment of unstable angina, adhere precisely to the intervals recommended between Lovenox Injection doses. The vascular access sheath for instrumentation should remain in place for 6 to 8 hours following a dose of Lovenox Injection. The next scheduled dose should be given no sooner than 6 to 8 hours after sheath removal. The site of the procedure should be observed for signs of bleeding or hematoma formation. The usual duration of treatment is 2 to 8 days; up to 12.5 days of Lovenox Injection has been well tolerated in clinical trials.

Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism: In **outpatient treatment**, patients with acute deep vein thrombosis 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 pulmonary embolism or patients with acute deep vein thrombosis without pulmonary embolism (who are not candidates for outpatient treatment), the recommended dose of Lovenox Injection is **1 mg/kg every 12 hours** administered SC **or 1.5 mg/kg once a day** administered SC at the same time every day. In both outpatient and inpatient (hospital) treatments, 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.

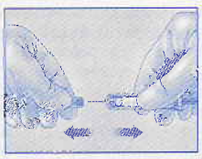
Administration: Lovenox Injection is a clear, colorless to pale yellow sterile solution, and as with other parenteral drug products, should be inspected visually for particulate matter and discoloration prior to administration.

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. 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.

- 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.

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

100 mg/mL Concentration

Dosage Unit / Strength[1]	Anti-Xa Activity[2]	Package Size (per carton)	Syringe Label Color	NDC # 0075-
Ampules				
30 mg / 0.3 mL	3000 IU	10 ampules	Medium Blue	0624-03
Prefilled Syringes[3]				
30 mg / 0.3 mL	3000 IU	10 syringes	Medium Blue	0624-30
40 mg / 0.4 mL	4000 IU	10 syringes	Yellow	0620-40
Graduated Prefilled Syringes[3]				
60 mg / 0.6 mL	6000 IU	10 syringes	Orange	0621-60
80 mg / 0.8 mL	8000 IU	10 syringes	Brown	0622-80
100 mg / 1 mL	10,000 IU	10 syringes	Black	0623-00

[1] Strength represents the number of milligrams of enoxaparin sodium in Water for Injection. **Lovenox Injection** ampules, 30 and 40 mg prefilled syringes, and 60, 80, and 100 mg graduated prefilled syringes each contain **10 mg enoxaparin sodium per 0.1 mL Water for Injection.**
[2] Approximate anti-Factor Xa activity based on reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard.
[3] Each **Lovenox Injection** syringe is affixed with a 27 gauge x 1/2 inch needle.

150 mg/mL Concentration

Dosage Unit / Strength[1]	Anti-Xa Activity[2]	Package Size (per carton)	Syringe Label Color	NDC # 0075-
Graduated Prefilled Syringes[3]				
120 mg / 0.8 mL	12,000 IU	10 syringes	Purple	2912-01
150 mg / 1mL	15,000 IU	10 syringes	Navy Blue	2915-01

[1] Strength represents the number of milligrams of enoxaparin sodium in Water for Injection. **Lovenox Injection** 120 and 150 mg graduated prefilled syringes contain **15 mg enoxaparin sodium per 0.1 mL** Water for Injection.
[2] Approximate anti-Factor Xa activity based on reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard.
[3] Each **Lovenox Injection** graduated prefilled syringe is affixed 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
94700 Maisons-Alfort
France.
And
Aventis Pharma
Boulevard Industriel
76580 Le Trait
France
Lovenox Injection ampules manufactured by:
Aventis Pharma LTD
Dagenham Essex RM10 7XS
United Kingdom.

Aventis Pharmaceuticals Inc.
Bridgewater, NJ 08807

Prescribing information as of September 2002

50066809

Lovenox 30 mg
Carton

512112A

NDC 0075-0624-30

LOVENOX®
(enoxaparin sodium injection)™

30mg/0.3mL
[100mg/mL]

Rx ONLY

SINGLE DOSE SYRINGES WITH
AUTOMATIC SAFETY DEVICE
FOR SUBCUTANEOUS INJECTION

Ten 0.3mL Syringes

Aventis

NDC 0075-0624-30

LOVENOX®
(enoxaparin sodium injection)™

30mg/0.3mL
[100mg/mL]

Rx ONLY

SINGLE DOSE SYRINGES WITH AUTOMATIC SAFETY DEVICE
FOR SUBCUTANEOUS INJECTION

Ten 0.3mL Syringes

Aventis

3 0075-0624-30 4

III

NDC 0075-0624-30

LOVENOX®
(enoxaparin sodium injection)

30mg/**0.3**mL
[**100**mg/mL]

Rx ONLY

SINGLE DOSE SYRINGES WITH AUTOMATIC SAFETY DEVICE
FOR SUBCUTANEOUS INJECTION

Ten 0.3mL Syringes

Aventis

Lovenox®
(enoxaparin sodium injection)

℞ 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].

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France

and

Aventis Pharma
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France

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50062559

1

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.

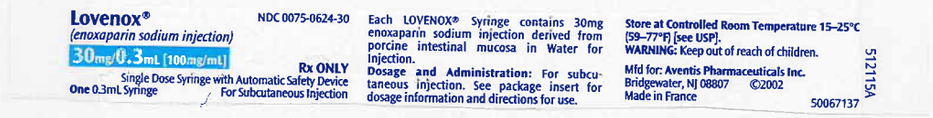
5. Immediately dispose of the syringe in the nearest sharps container.

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 40 mg
Carton

512113A

NDC 0075-0620-40

LOVENOX®
(enoxaparin sodium injection)™

40mg/0.4mL
[100mg/mL]

Rx ONLY

SINGLE DOSE SYRINGES WITH
AUTOMATIC SAFETY DEVICE
FOR SUBCUTANEOUS INJECTION

Ten 0.4mL Syringes

Aventis

NDC 0075-0620-40

LOVENOX®
(enoxaparin sodium injection)™

40mg/0.4mL
[100mg/mL]

Rx ONLY

SINGLE DOSE SYRINGES WITH AUTOMATIC SAFETY DEVICE
FOR SUBCUTANEOUS INJECTION

Ten 0.4mL Syringes

Aventis

3 0075-0620-40 5

NDC 0075-0620-40

LOVENOX®
(enoxaparin sodium injection)
TM

40 mg/**0.4** mL
[**100** mg/mL]

Rx ONLY

SINGLE DOSE SYRINGES WITH AUTOMATIC SAFETY DEVICE
FOR SUBCUTANEOUS INJECTION

Ten 0.4mL 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].

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94700 Maisons-Alfort
France

and

Aventis Pharma
Boulevard Industriel
76580 Le Trait
France

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50062611

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®
(enoxaparin sodium injection)

NDC 0075-0620-40

40mg/0.4mL [100mg/mL]

Rx ONLY

Single Dose Syringe with Automatic Safety Device
One 0.4mL Syringe — For Subcutaneous Injection

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

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)

NDC 0075-0620-40

40mg/0.4mL [100mg/mL]

Rx ONLY

Single Dose Syringe with Automatic Safety Device
One 0.4mL Syringe — For Subcutaneous Injection

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.

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)* **℞ ONLY**

40mg/0.4mL [100mg/mL]

Lot Exp

Mfd for: **Aventis Pharmaceuticals Inc.**

Lovenox 60 mg
Carton

512136A

NDC 0075-0621-60

LOVENOX®
(enoxaparin sodium injection)™

60mg/**0.6**mL
[**100**mg/mL]

Rx ONLY

SINGLE DOSE SYRINGES WITH
AUTOMATIC SAFETY DEVICE
FOR SUBCUTANEOUS INJECTION

Ten 0.6mL Syringes

Aventis

NDC 0075-0621-60

LOVENOX®
(enoxaparin sodium injection)™

60mg/0.6mL
[100mg/mL]

Rx ONLY

SINGLE DOSE SYRINGES WITH AUTOMATIC SAFETY DEVICE
FOR SUBCUTANEOUS INJECTION

Ten 0.6mL Syringes

Aventis

3 0075-0621-60 0

NDC 0075-0621-60

LOVENOX®
(enoxaparin sodium injection)™

60mg/**0.6**mL
[**100**mg/mL]

Rx ONLY

SINGLE DOSE SYRINGES WITH AUTOMATIC SAFETY DEVICE
FOR SUBCUTANEOUS INJECTION

Ten 0.6mL Syringes

Aventis

Lovenox®
(enoxaparin sodium injection)

℞ 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
76580 Le Trait
F
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I

nc.

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.

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Lovenox® NDC 0075-0621-60
(enoxaparin sodium injection)
60mg/0.6mL [100mg/mL]
Rx ONLY
Single Dose Syringe with Automatic Safety Device
One 0.6mL Syringe For Subcutaneous Injection

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.

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® NDC 0075-0621-60
(enoxaparin sodium injection)
60mg/0.6mL [100mg/mL]
Rx ONLY
Single Dose Syringe with Automatic Safety Device
One 0.6mL Syringe For Subcutaneous Injection

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

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.
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Made in France

Lovenox® *(enoxaparin sodium injection)* **℞ ONLY**
60mg/0.6mL [100mg/mL]
Lot Exp Mfd for: **Aventis Pharmaceuticals Inc.**

Lovenox 80 mg
Carton

512137A

NDC 0075-0622-80

LOVENOX®
(enoxaparin sodium injection)™

80mg/**0.8**mL
[**100**mg/mL]

Rx ONLY

SINGLE DOSE SYRINGES WITH
AUTOMATIC SAFETY DEVICE
FOR SUBCUTANEOUS INJECTION

Ten 0.8mL Syringes

Aventis

NDC 0075-0622-80

LOVENOX®
(enoxaparin sodium injection)™

80mg/**0.8**mL
[**100**mg/mL]

Rx ONLY

SINGLE DOSE SYRINGES WITH AUTOMATIC SAFETY DEVICE
FOR SUBCUTANEOUS INJECTION

Ten 0.8mL Syringes

Aventis

3 0075-0622-80 5

NDC 0075-0622-80

LOVENOX®
(enoxaparin sodium injection)

80mg/0.8mL
[100mg/mL]

Rx ONLY

SINGLE DOSE SYRINGES WITH AUTOMATIC SAFETY DEVICE
FOR SUBCUTANEOUS INJECTION

Ten 0.8mL Syringes

Aventis

Lovenox®
(enoxaparin sodium injection)

℞ 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].

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Aventis Pharma
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76580 Le Trait
France

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50062754

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.

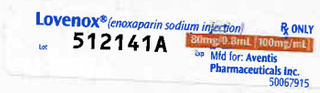
4. Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm shield activation.

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

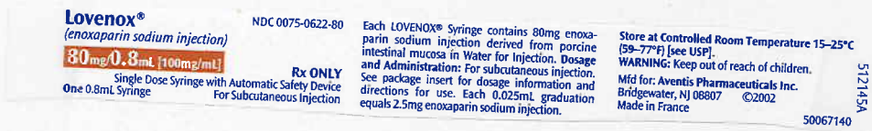
NOTE:

- 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 80 mg Device Label

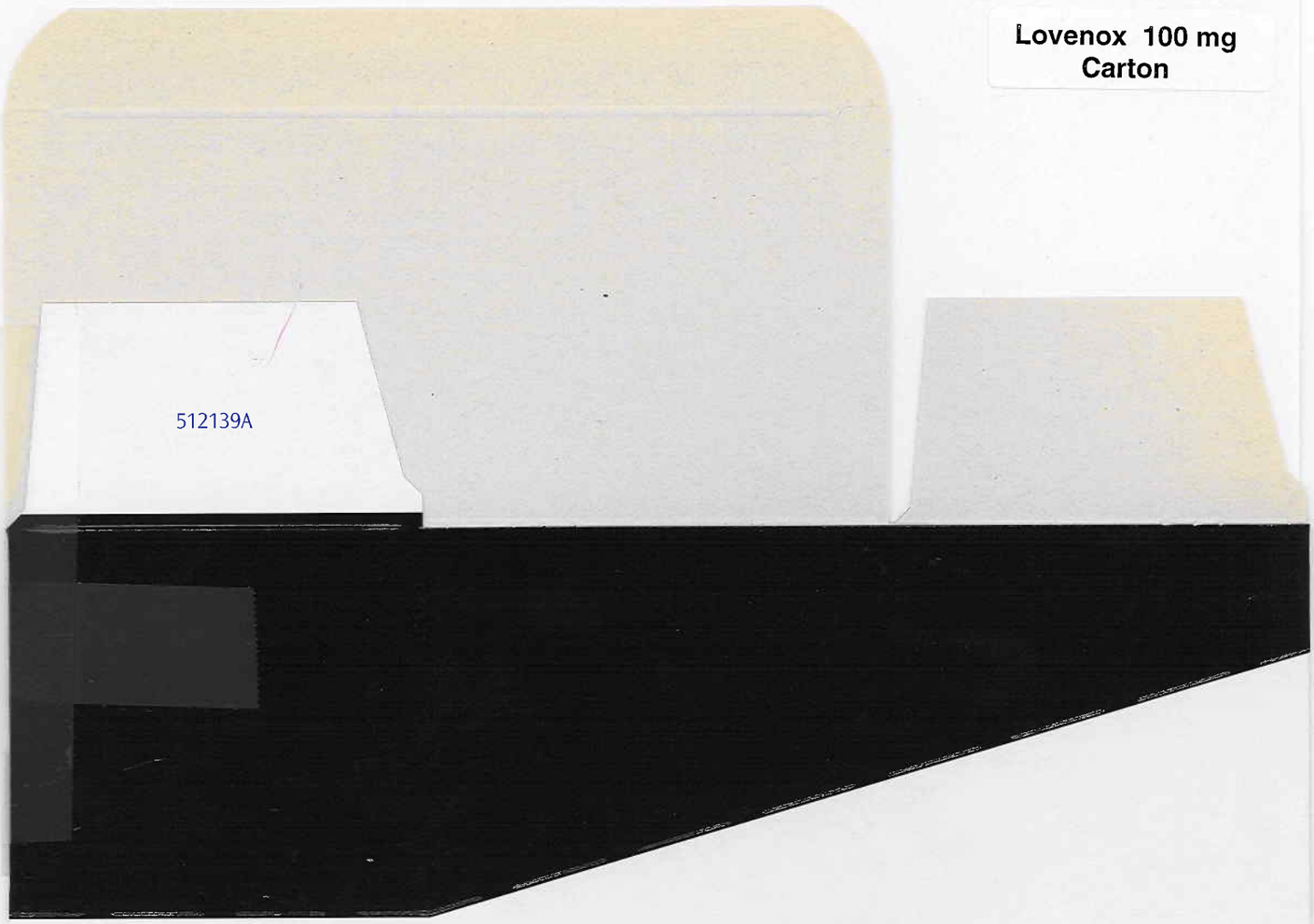


Lovenox 80 mg Blisterfoil



Lovenox 100 mg
Carton

512139A



NDC 0075-0623-00

LOVENOX®
(enoxaparin sodium injection)™

100mg/**1**mL

Rx ONLY

SINGLE DOSE SYRINGES WITH
AUTOMATIC SAFETY DEVICE
FOR SUBCUTANEOUS INJECTION

Ten 1mL Syringes

Aventis

NDC 0075-0623-00

LOVENOX®
(enoxaparin sodium injection)™

100mg/**1**mL

Rx ONLY

SINGLE DOSE SYRINGES WITH AUTOMATIC SAFETY DEVICE
FOR SUBCUTANEOUS INJECTION

Ten 1mL Syringes

Aventis

3 0075-0623-00 0

Aventis

Ten 1mL Syringes

SINGLE DOSE SYRINGES WITH AUTOMATIC SAFETY DEVICE
FOR SUBCUTANEOUS INJECTION

Rx ONLY

100mg/**1**mL

LOVENOX®
(enoxaparin sodium injection)
TM

NDC 0075-0623-00

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].

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94700 Maisons-Alfort
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and

Aventis Pharma
Boulevard Industriel
76580 Le Trait
France

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50062614

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.

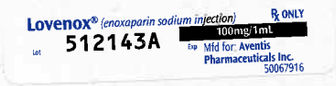
4. Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm shield activation.

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

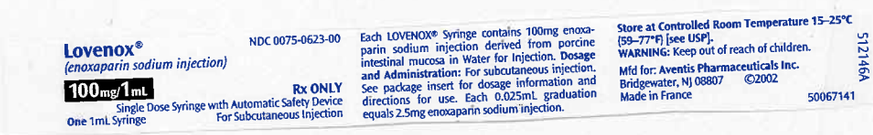
NOTE:

- 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 100 mg Blisterfoil



Lovenox 120 mg
Carton

512192A

NDC 0075-2912-01

LOVENOX®
(enoxaparin sodium injection)™

120mg/0.8mL
[150mg/mL]

Rx ONLY

SINGLE DOSE SYRINGES WITH
AUTOMATIC SAFETY DEVICE
FOR SUBCUTANEOUS INJECTION

Ten 0.8mL Syringes

Aventis

NDC 0075-2912-01

LOVENOX®
(enoxaparin sodium injection)™

120mg/0.8mL
[150mg/mL]

Rx ONLY

SINGLE DOSE SYRINGES WITH AUTOMATIC SAFETY DEVICE
FOR SUBCUTANEOUS INJECTION

Ten 0.8mL Syringes

Aventis

3 0075-2912-01 0

NDC 0075-2912-01

LOVENOX®
(enoxaparin sodium injection)

120mg/0.8mL
[150mg/mL]

Rx ONLY

SINGLE DOSE SYRINGES WITH AUTOMATIC SAFETY DEVICE
FOR SUBCUTANEOUS INJECTION

Ten 0.8mL Syringes

Aventis

Lovenox®
(enoxaparin sodium injection)

℞ ONLY

Each LOVENOX® Syringe contains 120mg 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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94700 Maisons-Alfort
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76580 Le Trait
France

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50062618

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.

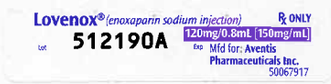
4. Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm shield activation.

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

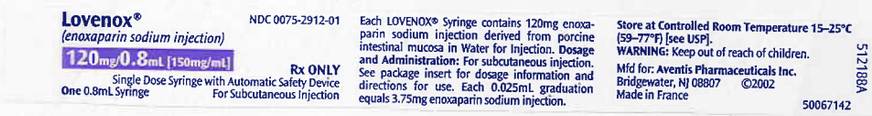
NOTE:

- 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 120 mg Device Label



Lovenox 120 mg Blisterfoil



Lovenox 150 mg
Carton

512193A

NDC 0075-2915-01

LOVENOX®
(enoxaparin sodium injection)™

150mg/1mL

Rx ONLY

SINGLE DOSE SYRINGES WITH
AUTOMATIC SAFETY DEVICE
FOR SUBCUTANEOUS INJECTION

Ten 1mL Syringes

Aventis

NDC 0075-2915-01

LOVENOX®
(enoxaparin sodium injection)™

150mg/1mL

Rx ONLY

SINGLE DOSE SYRINGES WITH AUTOMATIC SAFETY DEVICE
FOR SUBCUTANEOUS INJECTION

Ten 1mL Syringes

Aventis

3 0075-2915-01 1

Aventis

Ten 1mL Syringes

Rx ONLY

SINGLE DOSE SYRINGES WITH AUTOMATIC SAFETY DEVICE
FOR SUBCUTANEOUS INJECTION

LOVENOX® *(enoxaparin sodium injection)* TM

150 mg/ **1** mL

NDC 0075-2915-01

Lovenox®
(enoxaparin sodium injection)

℞ 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].

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
Made in France
www.aventispharma-us.com
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.

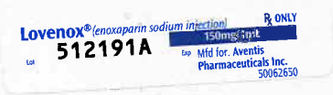
4. Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm shield activation.

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

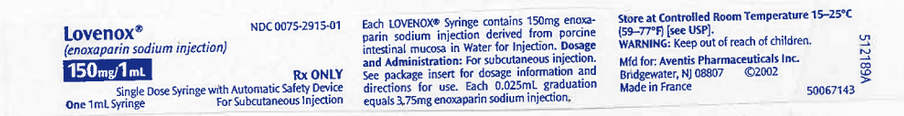
NOTE:

- 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 150 mg Blisterfoil



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-051

LABELING REVIEWS

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).

Supplement S-051 was submitted by Aventis to comply with the Occupational Safety and Health Administrations's (OSHA) Needlestick Safety and Prevention Act (Public Law 106-430) dated November 6, 2000, and the Department of Labor, Occupational Safety and Health Administration (OSHA) regulations (29 CFR Part 1910 [Docket No. H370A] RIN 1218-AB85 Final Rule entitled, "Occupational Exposure to Bloodborne Pathogens; Needlestick and Other Sharps Injuries" dated January 18, 2001.

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 (GHDB), 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

I. 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:

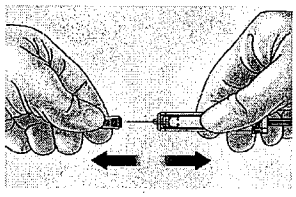
      " An automatic injector, Lovenox EasyInjector™, is available for patients to administer Lovenox Injection packaged in 30 mg and 40 mg prefilled syringes. Please see directions accompanying the Lovenox EasyInjector™ automatic injection device."

Since the sponsor is discontinuing the EasyInjector™ product, the deletion of these two sentences is acceptable.

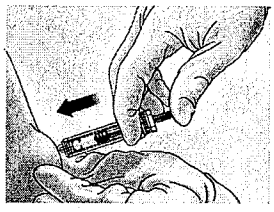
b. In the first paragraph, following the fifth sentence that begins "To minimize bruising, . . ." the sponsor has added the following section to describe the use of the needle safety system to shield needle after injection (based on manufacturer's device labeling):

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

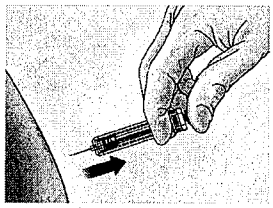
- Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.



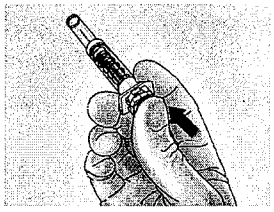
- Inject using standard technique, pushing the plunger to the bottom of the syringe.



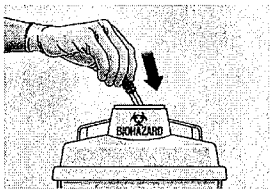
- Remove the syringe from the injection site keeping your finger on the plunger rod.



- 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, "[4] 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 the30 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

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):

IMMEDIATE CONTAINER LABELING CHART

Labeling Item	**SLR-051 identification number**	**SCF-030 Approved labeling identification number**	**Lot number added to SLR-051 labeling**
30mg/0.3 mL Pre-filled Syringe immediate container label	50067912	50062330	512106A
40mg/0.4 mL Pre-filled Syringe immediate	50067913	50057403	512107A

container label			
60mg/0.6 mL Pre-filled Syringe immediate container label	50067914	50057404	512140A
80mg/0.8 mL Pre-filled Syringe immediate container label	50067915	50057405	512145A
100mg/1 mL Pre-filled Syringe immediate container label	50067916	50057406	512143A
120mg/0.8 mL Pre-filled Syringe immediate container label	50067917	50058603	512188A
150mg/1.0 mL Pre-filled Syringe immediate container label	50062650	50062331	512191A

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):

BLISTER LABELING CHART

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

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. Bridewater, 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 [redacted]: is not acceptable. In addition, in the first sentence in the second column, the sponsor moved the term [redacted]' to after [redacted] so that the sentence reads "[redacted] 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 [redacted] 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 [redacted] 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 [redacted] 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 [redacted] 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

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

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:

   "**Lovenox®** (*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:

   "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"

   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

1. **Items I.E.4.a, I.F.4, II.A.1.-5., II.B., II.C.1.-2., II.D.1.-2., II.E., II.F.1.-2., II.G., III.A.1.-12., III.B., III.C.1.-2., III.D.1.-3., III.E.1.-2. III. F.1.-2., III.G.1.-3., III.H.1.-2., IV.A.1.a.-j., IV.A.2.a.-e., IV.B.1.-2., IV.C.1.-2., IV.D., IV.E.1.-9. are acceptable.**

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. Ruyi 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

Ruyi He, M.D.
Medical Officer

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

Julieann DuBeau, 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

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/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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-051

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Aventis Pharmaceuticals

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
Lovenox® (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, Lovenox® (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 Lovenox pre-filled syringes. The addition of an automatic safety device to all Lovenox® 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. Robie-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.

Aventis Pharmaceuticals Inc. · www.aventis.com
200 Crossing Boulevard · PO Box 6890 · Bridgewater, NJ 08807-0890 · Telephone (908) 304-7000

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 [redacted] 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 Caffé, 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,

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

**APPEARS THIS WAY
ON ORIGINAL**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-164/S-051

CBE-0 SUPPLEMENT

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 (HDF-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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

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

FROM: HFD-580 (Division of Gastro-Intestinal and Coagulation Drug Products) Diane Moore 6B-45

DATE:	IND NO.:	NDA NO.:	TYPE OF DOCUMENT :	DATE OF DOCUMENT:
March 18, 2003		20-164/S-051	SLR	December 19, 2002

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
Lovenox® (enoxaparin sodium), Injection	Rush	Low Molecular Weight Heparin	April 18, 2003

NAME OF FIRM: Pharmacia & Upjohn Company

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
TYPE A OR B NDA REVIEW	CHEMISTRY REVIEW
END OF PHASE II MEETING	PHARMACOLOGY
CONTROLLED STUDIES	BIOPHARMACEUTICS
PROTOCOL REVIEW	OTHER:
OTHER:	

III. BIOPHARMACEUTICS

DISSOLUTION	DEFICIENCY LETTER RESPONSE
BIOAVAILABILTY STUDIES	PROTOCOL-BIOPHARMACEUTICS
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

CLINICAL	PRECLINICAL

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:	METHOD OF DELIVERY (Check one):
Diane Moore 3/18/03	MAIL HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

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/s/

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

April 17, 2003

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

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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