CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-164/S-057

Name: Lovenox (Enoxaparin Sodium) Injection

Sponsor: Aventis Pharmaceuticals, Inc.

Approval Date: May 18, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-057

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-164/S-057

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-164/S-057

Aventis Pharmaceuticals, Inc.
Attention: Steve Caffé, M.D.
Head, U.S. Regulatory Affairs
200 Crossing Blvd
Bridgewater, NJ 08807

Dear Dr. Caffé:

Please refer to your supplemental new drug application dated November 17, 2003, received November 18, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (fondaparinux sodium, injection).

We acknowledge receipt of your submission dated May 5, 2004.

This "Changes Being Effected" supplemental new drug application provides for changes in the **ADVERSE REACTIONS** section, *Ongoing Safety Surveillance* subsection of the Lovenox package insert (PI) to include rare cases of hypersensitivity cutaneous vasculitis.

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 the revisions listed below.

1. Incorporate the revisions to the PI approved in S-048 on December 18, 2003.

2. Delete the reference and associated superscript to "Riffitts, M., "Enoxaparin and Vasculitis" Reasoned Statement, by Global Pharmacovigilance, March 6, 2003.

The final printed labeling (FPL) must be identical, and include the revisions indicated, to the submitted labeling (package insert submitted November 17, 2003). These revisions are 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 15 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-057." 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
5/18/04 04:06:33 PM
for Dr. Robert Justice

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-057

APPROVED LABELING

LOVENOX®
(enoxaparin sodium injection)™

Rx only
Rev. April 2004

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 aqueous solution containing enoxaparin sodium, a low molecular weight heparin.

Lovenox Injection is available in two concentrations:

1. 100 mg per mL

-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
-Multiple-Dose Vials	300 mg / 3.0 mL

Lovenox Injection 100 mg/mL Concentration contains 10 mg enoxaparin sodium (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

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

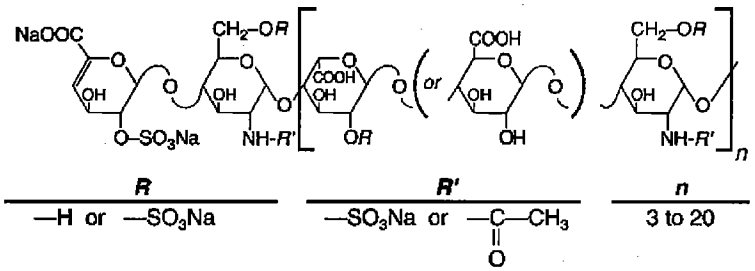
Lovenox Injection 150 mg/mL Concentration contains 15 mg enoxaparin sodium (approximate anti-Factor Xa activity of 1500 IU [with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard]) per 0.1 mL Water for Injection.

The Lovenox prefilled syringes and graduated prefilled syringes are preservative-free and intended for use only as a single-dose injection. The multiple-dose vial contains 15 mg / 1.0 mL benzyl alcohol as a preservative. (See **DOSAGE AND ADMINISTRATION** and **HOW SUPPLIED** for dosage unit descriptions.) The pH of the injection is 5.5 to 7.5.

Enoxaparin sodium 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 drug 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).

Pharmacokinetics (conducted using 100 mg / mL concentration):

Absorption. 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 1 mg/kg SC every 12 hours for 14 days. Mean absolute bioavailability of enoxaparin, after 1.5 mg/kg given SC, based on anti-Factor Xa activity is approximately 100% in healthy volunteers.

Enoxaparin pharmacokinetics appear to be linear over the recommended dosage ranges (see **Dosage and Administration**). After repeated subcutaneous administration of 40 mg once daily and 1.5 mg/kg once-daily regimens in healthy volunteers, the steady state is reached on day 2 with an average exposure ratio about 15% higher than after a single dose. Steady-state enoxaparin activity levels are well predicted by single-dose pharmacokinetics. After repeated subcutaneous administration of the 1 mg/kg twice daily regimen, the steady state is reached from day 4 with mean exposure about 65% higher than after a single dose and mean peak and trough levels of about 1.2 and 0.52 IU/mL, respectively. Based on enoxaparin sodium pharmacokinetics, this difference in steady state is expected and within the therapeutic range.

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)

Distribution. The volume of distribution of anti-Factor Xa activity is about 4.3 L.

Elimination. 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 a single SC dose to about 7 hours after repeated dosing. 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.

Metabolism. Enoxaparin sodium is primarily metabolized in the liver by desulfation and/or depolymerization to lower molecular weight species with much reduced biological potency.

Renal clearance of active fragments represents about 10% of the administered dose and total renal excretion of active and non-active fragments 40% of the dose.

Special Populations

Gender: 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.

Geriatric: 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. (See **PRECAUTIONS.)**

Renal Impairment: A linear relationship between anti-Factor Xa plasma clearance and creatinine clearance at steady-state has been observed, which indicates decreased clearance of enoxaparin sodium in patients with reduced renal function. Anti-Factor Xa exposure represented by AUC, at steady-state, is marginally increased in mild (creatinine clearance 50 –80 mL/min) and moderate (creatinine clearance 30-50 mL/min) renal impairment after repeated subcutaneous 40 mg once daily doses. In patients with severe renal impairment (creatinine clearance <30 mL/min), the AUC at steady state is significantly increased on average by 65% after repeated subcutaneous 40-mg once-daily doses (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Weight: After repeated subcutaneous 1.5 mg/kg once daily dosing, mean AUC of anti-Factor Xa activity is marginally higher at steady-state in obese healthy volunteers (BMI 30-48 kg/m^2) compared to non-obese control subjects, while Amax is not increased.

When non-weight adjusted dosing was administered, it was found after a single-subcutaneous 40-mg dose, that anti-Factor Xa exposure is 52% higher in low-weight women (<45 kg) and 27% higher in low-weight men (<57 kg) when compared to normal weight control subjects (see **PRECAUTIONS**).

Hemodialysis: In a single study, elimination rate appeared similar but AUC was two-fold higher than control population, after a single 0.25 or 0.50 mg/kg intravenous dose.

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		
Indication	**Lovenox Inj.** 20 mg q.d. SC n (%)	**Lovenox Inj.** 40 mg q.d. SC n (%)	**Placebo** 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. 1mg/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-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 or any of its constituents.

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.

Pregnant Women with Mechanical Prosthetic Heart Valves: The use of Lovenox Injection for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been

adequately studied. In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. Although a causal relationship has not been established these deaths may have been due to therapeutic failure or inadequate anticoagulation. No patients in the heparin/warfarin group (0 of 4 women) died. There also have been isolated postmarketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. Women with mechanical prosthetic heart valves may be at higher risk for thromboembolism during pregnancy, and, when pregnant, have a higher rate of fetal loss from stillbirth, spontaneous abortion and premature delivery. Therefore, frequent monitoring of peak and trough anti-Factor Xa levels, and adjusting of dosage may be needed.

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**).

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. Lovenox Injection should be used with care in elderly patients who may show delayed elimination of enoxaparin.

If thromboembolic events occur despite Lovenox Injection prophylaxis, appropriate therapy should be initiated.

Mechanical Prosthetic Heart Valves: The use of Lovenox Injection has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves and has not been adequately studied for long-term use in this patient population. Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received enoxaparin for thromboprophylaxis. Some of these cases were pregnant women in whom thrombosis led to maternal and fetal deaths. Insufficient data, the underlying disease and the possibility of inadequate anticoagulation complicate the evaluation of these cases. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism (see **WARNINGS, Pregnant Women with Mechanical Prosthetic Heart Valves**).

Renal Impairment: In patients with renal impairment, there is an increase in exposure of enoxaparin sodium. All such patients should be observed carefully for signs and symptoms of bleeding. Because exposure of enoxaparin sodium is significantly increased in patients with severe renal impairment (creatinine clearance <30 mL/min), a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges. No dosage adjustment is recommended in patients with moderate (creatinine clearance 30-50 mL/min) and mild (creatinine clearance 50-80 mL/min) renal impairment. (see **DOSAGE AND ADMINISTRATION** and **CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations**).

Low-Weight Patients: An increase in exposure of enoxaparin sodium with prophylactic dosages (non-weight adjusted) has been observed in low-weight women (<45 kg) and low-weight men

(<57 kg). All such patients should be observed carefully for signs and symptoms of bleeding (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations**).

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: Pharmacokinetics**).

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: Pregnancy Category B:

All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes Lovenox's potential to increase the risk of developmental abnormalities above background risk.

Fetal Risk Summary

Lovenox is not predicted to increase the risk of developmental abnormalities. Lovenox does not cross the placenta, based on human and animal studies, and shows no evidence of teratogenic effects or fetotoxicity.

Clinical Considerations

It is not known if dose adjustment or monitoring of anti-Xa activity of enoxaparin are necessary during pregnancy.

Pregnancy alone confers an increased risk for thromboembolism, that is even higher for women with thromboembolic disease and certain high risk pregnancy conditions. While not adequately studied, pregnant women with mechanical prosthetic heart valves may be at even higher risk for thrombosis (See **WARNINGS, Pregnant Women with Mechanical Prosthetic Heart Valves** and **PRECAUTIONS, Mechanical Prosthetic Heart Valves.**) Pregnant women with thromboembolic disease, including those with mechanical prosthetic heart valves, and those with inherited or acquired thrombophilias, also have an increased risk of other maternal complications and fetal loss regardless of the type of anticoagulant used.

All patients receiving anticoagulants such as enoxaparin, including pregnant women, are at risk for bleeding. Pregnant women receiving enoxaparin should be carefully monitored for evidence

of bleeding or excessive anticoagulation. Consideration for use of a shorter acting anticoagulant should be specifically addressed as delivery approaches (see **BOXED WARNING, SPINAL/EPIDURAL HEMATOMAS**). Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.

Data

- Human Data - There are no adequate and well-controlled studies in pregnant women.
  A retrospective study reviewed the records of 604 women who used enoxaparin during pregnancy. A total of 624 pregnancies resulted in 693 live births. There were 72 hemorrhagic events (11 serious) in 63 women. There were 14 cases of neonatal hemorrhage. Major congenital anomalies in live births occurred at rates (2.5%) similar to background rates.[1]
  There have been postmarketing reports of fetal death when pregnant women received Lovenox Injection. Causality for these cases has not been determined. Insufficient data, the underlying disease, and the possibility of inadequate anticoagulation complicate the evaluation of these cases.
  See **WARNINGS: Pregnant Women with Mechanical Prosthetic Heart Valves** for a clinical study of pregnant women with mechanical prosthetic heart valves.
- Animal Data - 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. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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**).

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]
	1 mg/kg q12h SC	aPTT Adjusted
Indication		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
	1.5 mg/kg q.d. SC	1 mg/kg q12h SC	aPTT Adjusted
Indication			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, rare cases of hypersensitivity cutaneous vasculitis, 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, if enoxaparin sodium was administered in the previous 8 hours. An infusion of 0.5 mg protamine per 1 mg of enoxaparin sodium may be administered if enoxaparin sodium was administered greater than 8 hours previous to the protamine administration, or if it has been determined that a second dose of protamine is required. The 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.

After 12 hours of the enoxaparin sodium injection, protamine administration may not be required. 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 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.
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.

Renal Impairment: Although no dose adjustment is recommended in patients with moderate (creatinine clearance 30-50 mL/min) and mild (creatinine clearance 50-80 mL/min) renal impairment, all such patients should be observed carefully for signs and symptoms of bleeding.

The recommended prophylaxis and treatment dosage regimens for patients with severe renal impairment (creatinine clearance <30 mL/min) are described in the following table (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations** and **PRECAUTIONS, Renal Impairment**).

Dosage Regimens for Patients with Severe Renal Impairment (creatinine clearance <30mL/minute)	
Indication	**Dosage Regimen**
Prophylaxis in abdominal surgery	30 mg administered SC once daily
Prophylaxis in hip or knee replacement surgery	30 mg administered SC once daily
Prophylaxis in medical patients during acute illness	30 mg administered SC once daily
Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin	1 mg/kg administered SC once daily
Inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin sodium	1 mg/kg administered SC once daily
Outpatient treatment of acute deep vein thrombosis without pulmonary embolism, when administered in conjunction with warfarin sodium	1 mg/kg administered SC once daily

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.

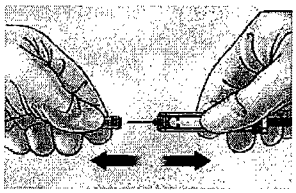
The use of a tuberculin syringe or equivalent is recommended when using Lovenox multiple-dose vials to assure withdrawal of the appropriate volume of drug.

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.

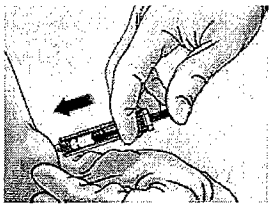
Subcutaneous Injection Technique: Patients should be lying down and Lovenox Injection administered by deep SC injection. To avoid the loss of drug when using the 30 and 40 mg prefilled syringes, do not expel the air bubble from the syringe before the injection. Administration should be alternated between 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.

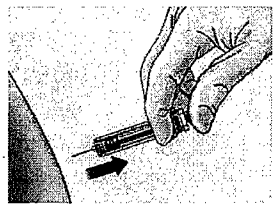
- Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.



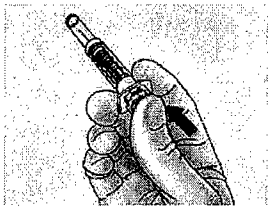
- Inject using standard technique, pushing the plunger to the bottom of the syringe.



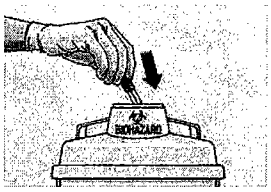
- Remove the syringe from the injection site keeping your finger on the plunger rod.



- 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.

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)	Label Color	NDC # 0075-
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
Multiple-Dose Vial[4]				
300 mg / 3.0 mL	30,000 IU	1 vial	Red	0626-03

[1] Strength represents the number of milligrams of enoxaparin sodium in Water for Injection. **Lovenox Injection** 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.

[4] Each Lovenox multiple-dose vial contains 15 mg / 1.0 mL of benzyl alcohol as a preservative.

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 / 1 mL	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 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Keep out of the reach of children.

[1] Lepercq J, Conard J, Borel-Derlon A, et al. Venous thromboembolism during pregnancy: a retrospective study of enoxaparin safety in 624 pregnancies. *Br J Obstet Gynec* 2001; 108 (11): 1134-40.

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 multiple-dose vials manufactured by:
DSM Pharmaceuticals, Inc.
Greenville, NC 27835

Manufactured for:
Aventis Pharmaceuticals Inc.
Bridgewater, NJ 08807

Rev. April 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-057

LABELING REVIEW(S)

Division of Gastrointestinal and Coagulation Drug Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application Number: NDA 20-164/SLR-057

Name of Drug: Lovenox® (enoxaparin sodium) Injection

Sponsor: Aventis Pharmaceuticals, Inc.

Materials Reviewed: package insert (PI).

Submission Date: November 17, 2003
Receipt Date: November 18, 2003

Background and Summary

BACKGROUND

On August 9, 2002 (received August 12, 2002), Aventis submitted SLR-048 (S-048) to revise the current Lovenox prescribing information based on the findings provided in the final study reports for the Weight-Dependent Effect protocol (Study RP54563Q-150) and the Renal Impairment protocol (Study RP54563Q-146). DGCDP sent the sponsor an approvable letter on February 13, 2003. The sponsor responded to the approvable letter on August 12, 2003 (received August 12, 2003). The S-048 was approved on draft labeling on December 18, 2003.

On November 14, 2003 (received November 17, 2003), Aventis submitted SLR-058 (S-058) providing for changes in the labeling section of the approved New Drug Application for Lovenox. Specifically, to delete the one point ampule from the **DESCRIPTION, DOSAGE AND ADMINISTRATION** and **HOW SUPPLIED** sections of the approved labeling.

On November 17, 2003 (received November 18, 2003), Aventis submitted SLR-057 (S-057) providing for revisions to the **ADVERSE REACTIONS** section, **Ongoing Safety Surveillance** subsection of the PI. Supplement S-048 was approved one month after S-057 was submitted. Therefore, the labeling submitted to S-057 did not incorporate the revisions approved in S-048.

Review

PACKAGE INSERT

The package insert proposed for S-057, dated November 17, 2003 (received November 18, 2003), identification number 50070791 (DSM Pharmaceuticals) and identification number 50070788 (Le Trait) were compared to approved labeling from Supplement S-048 dated August 12, 2003 (no identifier number). The submitted package inserts are identical to the approved package insert except for the following:

I. The sponsor has not incorporated the revisions to the **DESCRIPTION, PRECAUTIONS** and **DOSAGE AND ADMINISTRATION** sections of the PI approved in S-048 (submitted August 9, 2002, received August 12, 2002, approved on draft labeling December 18, 2003) (see RPM review by Diane Moore dated February 4, 2003).

II. The sponsor has incorporated revisions to the **DECRIPTION, DOSAGE AND ADMINISTRATION** and **HOW SUPPLIED** sections of the PI proposed in S-058 (see RPM review by Diane Moore dated March 22, 2004).

III. **ADVERSE REACTIONS** section

In the **Other Ongoing Safety Surveillance Reports** sub-section, in the first sentence that begins, "local reactions at the injection site . . ." the sponsor proposes to add the phrase "rare cases of hypersensitivity cutaneous vasculitis" to that the sentence reads as follows:

> "Local reactions at the injection site (i.e., skin necrosis, nodules, inflammation, oozing), systemic allergic reactions (i.e., pruritus, urticaria, anaphylactoid reactions), vesiculobullous rash, rare cases of hypersensitivity cutaneous vasculitis[1], purpura, thrombocytosis, and thrombocytopenia with thrombosis (see **WARNINGS, Thrombocytopenia**)."

The Medical Officer should comment on the addition of this phrase.

IV. **HOW SUPPLIED** section

A. Following the **HOW SUPPLIED** section, in the seventh sentence that reads "©2002 Aventis Pharmaceuticals Inc. Rev. July 2003," the sponsor revised the date to "September 2003a" so that the sentence reads "©2002 Aventis Pharmaceuticals Inc. Rev. September 2003a."

The revision is editorial and acceptable.

B. Following the date of the document, the sponsor proposes to add the following footnote:

> "1 *Reasoned Statement* Riffitts, M. "Enoxaparin and vasculitis," Reasoned Statement, by Global Pharmacovigilance. March 6, 2003."

The revision cites the reference for the addition in the ADVERSE REACTIONS section. The Medical Officer should comment on the addition.

CONCLUSIONS

1. **The following revision is editorial and acceptable: IV.A.**

2. **The Medical Officer should comment on Items III and IV.B.**

3. **The sponsor should incorporate the revisions approved in S-048 on December 18, 2003, into the labeling for S-057 (See Item I. above).**

4. **Supplement S-058 should be approved before incorporating the proposed revisions to S-058 into S-057 (See Item II above).**

5. **Pending the approval of the proposed revisions to S-057 by the Medical Officer, and the approval of the labeling for S-058, S-057 could be approved on draft with the revisions approved in S-048 and S-058 incorporated into the final printed labeling to S-057.**

Diane Moore, B.S.
Regulatory Health Project Manager

Julieann DuBeau, MSN, RN
Chief, Project Management Staff

Drafted by: dm/March 16, 2004
Initialed by: J.DuBeau 3.17.04
Final: March 22, 2004
Filename: N20164S57Lblrev.doc
RPM LABELING REVIEW

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Diane V. Moore
3/22/04 09:54:16 AM
CSO

Julieann DuBeau
3/23/04 09:01:37 AM
CSO

Division of Gastrointestinal and Coagulation Drug Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application Number: NDA 20-164/SLR-057 Final Printed Labeling (FPL)

Name of Drug: Lovenox® (enoxaparin sodium) Injection

Sponsor: Aventis Pharmaceuticals, Inc.

Materials Reviewed: Package Insert (PI).

Submission Date: July 30, 2004
Receipt Date: July 30, 2004

Background and Summary

BACKGROUND

Background: Lovenox was approved March 29, 1993. It is approved 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.

On August 9, 2002 (received August 12, 2002), Aventis submitted SLR-048 (S-048) to revise the current Lovenox prescribing information based on the findings provided in the final study reports for the Weight-Dependent Effect protocol (Study RP54563Q-150) and the Renal Impairment protocol (Study RP54563Q-146). DGCDP sent the sponsor an approvable letter on February 13, 2003. The sponsor responded to the approvable letter on August 12, 2003 (received August 12, 2003). The S-048 was approved on draft labeling on December 18, 2003.

SLR-056 (S-056) was submitted on October 10, 2003 (received October 14, 2003), to provide for revisions to update the information in the **OVERDOSAGE** section, **Symptoms/Treatment** subsection of the PI. S-056 was approved on draft labeling on April 13, 2004.

On November 14, 2003 (received November 17, 2003), Aventis submitted SLR-058 (S-058) providing for the deletion of the one point ampule from the **DESCRIPTION, DOSAGE AND ADMINISTRATION** and **HOW SUPPLIED** sections of the PI. S-058 was approved on draft on April 21, 2004.

On November 17, 2003 (received November 18, 2003), Aventis submitted SLR-057 (S-057) providing for revisions to the **ADVERSE REACTIONS** section, **Ongoing Safety Surveillance** subsection of the PI. Supplement S-048 was approved one month after S-057 was submitted. Therefore, the labeling submitted to S-057 did not incorporate the revisions approved in S-048. S-057 was approved on draft on May 18, 2004.

On March 8, 2004 (received March 9, 2004), Aventis submitted FPL to S-048. The FPL in S-048 incorporated the proposed revisions in S-057 and S-058. Because neither S-057 nor S-058 were approved on March 8, 2004, the FPL submitted to S-048 could not include the proposed revisions in those PIs. Therefore, the FPL submitted to S-048 could not supersede S-057 or S-058 and the FPL in S-048 was not acceptable (See RPM review by Diane Moore dated March 24, 2004).

Review

PACKAGE INSERT

The PI FPL for S-057, dated July 30, 2004 (received July 30, 2004), identification number 50070791 (DSM Pharmaceuticals) and identification number 50070788 (Le Trait) were compared to approved labeling for S-057. The FPL submitted in S-057 are identical to the approved PI in S-057 except for the following:

I. The sponsor incorporated the revisions to the **DESCRIPTION, PRECAUTIONS** and **DOSAGE AND ADMINISTRATION** sections of the PI approved in S-048 (submitted August 9, 2002, received August 12, 2002, approved on draft labeling December 18, 2003) (see RPM review to S-048 by Diane Moore dated September 25, 2003).

The sponsor was requested to incorporate these revisions in the labeling for S-058 in the Approval letter to S-058 dated May 18, 2040. The revisions are acceptable.

II. The sponsor has incorporated revisions to the **DECRIPTION, DOSAGE AND ADMINISTRATION** and **HOW SUPPLIED** sections of the PI approved in S-058 (see RPM review to S-058 by Diane Moore dated March 22, 2004).

Since S-057 was approved after S-058 was approved, it is appropriate to include the revisions made in S-058 into the FPL for S-057.

III. The sponsor incorporated revisions to the **OVERDOSAGE** section, **Symptoms/Treatment** subsection of the PI approved in S-056 (see RPM review to S-056 by Diane Moore dated February 19, 2004).

Since S-057 was approved after S-056 was approved, it is appropriate to include the revisions made in S-056 into the FPL for S-057.

IV. **HOW SUPPLIED** section

A. Following the **HOW SUPPLIED** section, in the seventh sentence that reads "©2003 Aventis Pharmaceuticals Inc. Rev. September 2003a," the sponsor revised the date to "April 2004" so that the sentence reads "©2004 Aventis Pharmaceuticals Inc. Rev. April 2004."

The revision is editorial and acceptable.

B. The sponsor deleted the following footnote from after the date of the document: "1 *Reasoned Statement* Riffitts, M. "Enoxaparin and vasculitis," Reasoned Statement, by Global Pharmacovigilance. March 6, 2003."

The sponsor was requested to delete the sentence in the approval letter to S-057 dated May 18, 2004. The deletion is acceptable.

C. The sponsor moved the following footnote from the **PRECAUTIONS** section to after the storage statement and the "Keep out of the reach of children" notice:

"[1]Lepercq J. Conard J. Borel-Derlon A. et al. Venous thromboembolism during pregnancy: a retrospective study of enoxaparin safety in 624 pregnancies. Br. J. Obstet Gynec 2001; 108 (11): 1134-40."

The revision is editorial and acceptable.

CONCLUSIONS

1. **The FPL in S-057 is identical to the PI in S-057 with the revisions approved in S-048, S-056 and S-058.**

2. **The FPL for S-057 is acceptable. An acknowledgement and retain letter should be sent to the sponsor accepting the labeling in the FPL to S-057. Since S-057 was approved after S-048, S-056 and S-058, and because S-057 incorporates the revisions approved in S-048, S-056 and S-057, the FPL in S-057 supersedes the labeling in S-048, S-056 and S-058. A letter should notify the sponsor that these PIs are superseded.**

Diane Moore, B.S.
Regulatory Health Project Manager

Drafted by: dm/January 13, 2004
Final: January 14, 2005
Filename: N20164S57FPLLblrev.doc
RPM LABELING REVIEW

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Diane V. Moore
1/14/05 03:49:16 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164 / S-057

MEDICAL REVIEW(S)

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

NDA:	NDA 20-164/SLR-057
Sponsor:	Aventis Pharmaceuticals Inc.
Drug name:	Lovenox (enoxaparin sodium) Injection
Subject:	Labeling supplement
Date submitted:	November 17, 2003
Date received:	November 19, 2003
Review completed:	May 3, 2004
Reviewer:	Ruyi He, M.D.

Lovenox was approved March 29, 1993. It is currently approved 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.

In the current submission, the sponsor proposed to include "rare cases of hypersensitivity cutaneous vasculitis" under the section of ADVERSE REACTION, Ongoing Safety Surveillance subsection of the label.

By 3-Feb-2003, 23 cases of vasculitis were identified during enoxaparin administration by a cumulative search of the Aventis Pharmacovigilance data base. According to the sponsor, an estimated 108 million patients have received enoxaparin in cumulative experience during that period.

Although insufficient information, concomitant medications and/or underlying disease(s) confound the analysis of many of the cases, the timing of event onset in relation to enoxaparin administration suggests enoxaparin was the cause in at least 2 cases. The positive rechallenge in one case indicates enoxaparin might have played a role in causing the leukocytoclastic vasculitis.

COMMENTS

The proposed changes "including rare cases of hypersensitivity cutaneous vasculitis" under the section of ADVERSE REACTION, Ongoing Safety Surveillance subsection of the label is acceptable and will provide useful information for both patients and physicians.

CONCLUSION

The proposed change is acceptable and I recommend that the labeling supplement be approved.

cc:
NDA 20-164/SLR057
HFD-180/RJustice
HFD-180/ JKorvick
HFD-180/RHe
HFD-180/KRobie-Suh
HFD-180/DMoore
HFD-180/JChoudary
HFD-180/SDoddapaneni
HFD-180/Lzhou
FT05/3/04RH

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ruyi He
5/3/04 05:03:25 PM
MEDICAL OFFICER

Kathy Robie-Suh
5/5/04 04:47:46 PM
MEDICAL OFFICER
Sponsor confirmed (fax 5/5/04) that the reference and footnotes shown in the electronic labeling submitted on 11/17/03 will not appear on the final printed label.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-057

CORRESPONDENCE

Aventis Pharmaceuticals

November 17, 2003

Robert Justice, MD, Director
Food and Drug Administration
Central Document Room (HFD-180)
12229 Wilkins Avenue
Rockville, Maryland 20852-1833

NDA 20-164
Lovenox® (Enoxaparin Sodium) Injection
SUPPLEMENTAL NEW DRUG APPLICATION
Changes Being Effected: Labeling Supplement
Addition of Adverse Event: Vasculitis

Dear Dr. Justice:

Pursuant to Section 505(b) of the Food, Drug and Cosmetic Act and in accordance with 506A(d)(3)(B)(i) of the Food and Drug Administration Modernization Act, we submit for the Agency's review and approval a supplement to NDA 20-164.

As indicated on the attached Form FDA356H, this supplemental application provides for changes in the labeling section of the approved New Drug Application for LOVENOX®. The **ADVERSE REACTION**, *Ongoing Safety Surveillance* section of the package insert has been revised to include rare cases of hypersensivity cutaneous vasculitis.

With this letter, Aventis is providing the following documentation to support the safety update to the **ADVERSE REACTION** section of the Lovenox® US package insert (PI):

Labeling
I. Labeling History
II. Labeling Text
  a) Proposed labeling text
  b) Currently used labeling text
  c) Last approved labeling text
III. Final Printed Package Insert

Summary
I. Annotated package circular
II. Supportive documentation
  a) Published Literature
  b) Other
    Reference: Riffitts, M. "Enoxaparin and Vasculitis," Reasoned Statement, by Global Pharmacovigilance. March 6, 2003.

The revised labeling will be available on the Aventis intranet. in December 2003. It may not be available for use in all packages sold or distributed from the Company's manufacturing facilities until third quarter 2004.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Aventis Pharmaceuticals is providing one Compact Disk (CD) that contains the complete submission and is not greater than 10MB. All documents requiring signatures for certification are included as paper for archival purposes Aventis certifies that we have taken precautions to ensure that all electronic media are free from computer viruses (Norton Anti-Virus 7.50.846, Scan Engine Version 4.1.0.6, Virus Definition File Version 51002h with an updated date of October 2, 2003).

A list of reviewers from the Division of Gastrointestinal and Coagulation Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Robert Justice, MD, Director, Division of Gastrointestinal and Coagulation Drug Products.

In accordance with the Prescription Drug User Fee Act of 1992 (PDUFA) and reauthorized in the Food and Drug Administration Modernization Act of 1997 (FDAMA), as indicated on the attached Form FDA3397, no user fee is required for this supplemental application.

Aventis Pharmaceuticals considers the information contained in this submission private and confidential in accordance with provisions established in 21 CFR §312.130 and §314.430 and requests that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Aventis.

If you should have any questions or comments, please do not hesitate of contact me at 908- 304-6278 or, in my absence, Steve Caffé, MD at 908-231-5863.

Sincerely,

Christine Chansky, MD, JD
Director, Regulatory Liaison
Global Drug Regulatory Affairs

Attachment: CD (1)

Desk Copy (Letter Only): Robert Justice, M. D., Director
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research (HFD-180)
Document Control Room #6B-24

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-164/S-057

CBE-0 SUPPLEMENT

Aventis Pharmaceuticals, Inc.
Attention: Christine Chansky, M.D., J.D.
200 Crossing Blvd.
Bridgewater, NJ 08807

Dear Dr. Chansky:

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

Name of Drug Product:	Lovenox® (enoxaparin sodium, injection)
NDA Number:	20-164
Supplement number:	S-057
Date of supplement:	November 17, 2003
Date of receipt:	November 18, 2003

This supplemental application, submitted as "Supplement - Changes Being Effected" proposes the following changes: Revisions to the **ADVERSE REACTIONS** section, *Ongoing Safety Surveillance* subsection of the package insert to include rare cases of hypersensitivity cutaneous vasculitis.

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 January 17, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be May 18, 2004.

All communications concerning this supplement 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 Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Document Room 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Diane V. Moore
12/8/03 04:45:42 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-164/S-057

Aventis Pharmaceuticals, Inc.
Attention: Steve Caffé, M.D.
Head, U.S. Regulatory Affairs
200 Crossing Blvd
Bridgewater, NJ 08807-0890

Dear Dr. Caffé:

Please refer to your supplemental new drug application dated November 17, 2003, received November 18, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium, injection).

We also refer to our approval letter dated May 18, 2004.

In the May 18, 2004 agency letter, there was a typographical error in the first paragraph, third line. Specifically, the term "fondaparinux sodium" should read "enoxaparin sodium." The rest of the letter should remain unchanged.

We are sorry for any inconvenience this may have caused you. If you have any questions, call Diane Moore, Regulatory Health 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

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/s/

Joyce Korvick
5/27/04 04:33:31 PM
for Dr. Robert Justice

July 30, 2004

Robert Justice, M.D.
Director, Division of Gastrointestinal and Coagulation Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-180)
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705

NDA 20-164/S-057: LOVENOX® (enoxaparin sodium) Injection
FINAL PRINTED LABELING
For Approved Supplement S-057
(AE Term: Vasculitis)

Dear Dr. Justice:

Reference is made to the Supplemental New Drug Application (sNDA) cited above. Reference is also made to the Agency's approval letter of May 18, 2004 requesting Final Printed Labeling identical to the labeling submitted on November 17, 2003. This "Changes Being Effected" sNDA provides for changes in the **ADVERSE REACTIONS** section, *Ongoing Safety Surveillance* subsection of the LOVENOX® INJECTION package insert (PI) to include rare cases of hypersensitivity cutaneous vasculitis.

As indicated on the attached Form FDA 356h, this submission provides the Final Printed Labeling for approved sNDA 057 for enoxaparin sodium injection as follows:

Labeling

II. Labeling text
   a. Proposed labeling text (proposed.pdf) April 2004

III. Final Printed Package Insert
   pi1.pdf (#50072216) for use in packaging at DSM Pharmaceuticals, Inc in North Carolina, April 2004.
   pi2.pdf (#50072241) for use in packaging at Le Trait, France, April 2004

All other labeling revisions previously approved by FDA have also been incorporated into the final printed labeling. These revisions included supplements **S-048**, renal impairment and weight-dependent information; **S-056**, updates to the overdosage section; and **S-058**, deletion of the one-point-cut ampule information.

Please note that the FDA approval letter dated May 18, 2004 incorrectly identified the generic of LOVENOX® INJECTION as "fondaparinux sodium, injection." The correct generic for LOVENOX® INJECTION is enoxaparin sodium injection.

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

The review aid (Microsoft WORD version) of the proposed labeling text is also supplied as PROPOSED.DOC within the labeling folder on the Compact Disk (CD) provided.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Aventis Pharmaceuticals is providing one Compact Disk (CD) that contains the Final Printed Labeling. All documents requiring signatures for certification are included as paper for archival purposes.

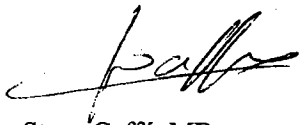
All of the information is contained on one CD and is not more than 100MB. We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus Version 60726b) with an updated date of July 26, 2004.

A list of reviewers from the Division of Gastrointestinal and Coagulation Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Diane Moore, Regulatory Project Manager, Division of Gastrointestinal and Coagulation Drug Products.

Aventis Pharmaceuticals Inc. considers the information contained in this submission private and confidential in accordance with the provisions in 21 CFR §312.130 and §314.430 and requests that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Aventis.

If you should have any questions or comments, please do not hesitate to contact me at 908-231-5863.

Sincerely,



Steve Caffé, MD
Head, US Regulatory Affairs

Fax (301-443-9285) Diane Moore, Regulatory Project Manager (cover letter + 356H only)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-164/S-057

Aventis Pharmaceuticals Inc.
Attention: Steve Caffe, MD
Head, US Regulatory Affairs
200 Crossing Boulevard
PO Box 6890
Bridgewater, NJ 08807-0890

Dear Dr. Caffe:

We acknowledge receipt of your July 30, 2004, submission containing final printed labeling in response to our May 18, 2004, letter approving your supplemental new drug application for Lovenox® (enoxaparin sodium) injection.

We have reviewed the labeling that you submitted in accordance with our May 18, 2004, letter and we find it acceptable.

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

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Acting 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/

Kathy Robie-Suh
1/21/05 11:39:59 AM
for Dr. Joyce Korvick