CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-164/S-055

Name: Lovenox (Enoxaparin Sodium) Injection

Sponsor: Aventis Pharmaceuticals, Inc.

Approval Date: July 23, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-055

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-164/S-055

Aventis Pharmaceuticals Inc.
Attention: Dhiren N. Shah, Ph.D.
Director, Regulatory CMC
200 Crossing Boulevard
P.O. Box 6890
Bridgewater, NJ 08807-0890

Dear Dr. Shah:

Please refer to your supplemental new drug application dated July 11, 2003, received July 14, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium, injection).

We acknowledge receipt of your submissions dated October 10, 2003, March 22 and July 6 and 8, 2004. Your submission of March 22, 2004, constituted a complete response to our November 13, 2003, action letter.

This supplemental new drug application provides for additional characterization and new structural information on the active ingredient of the drug product, enoxaparin sodium.

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.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and/or submitted labeling (package insert submitted July 8, 2004).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-164/S-055." Approval of this submission by FDA is not required before the labeling is used.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999) and *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004). The guidances specify that labeling to be submitted in *pdf* format. To assist in our review, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper.

Please submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Gastrointestinal and Coagulation Drug Products (HFD-180) and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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 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

Enclosure

LOVENOX®
(enoxaparin sodium injection)™

Rx only
Rev. XXXX

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

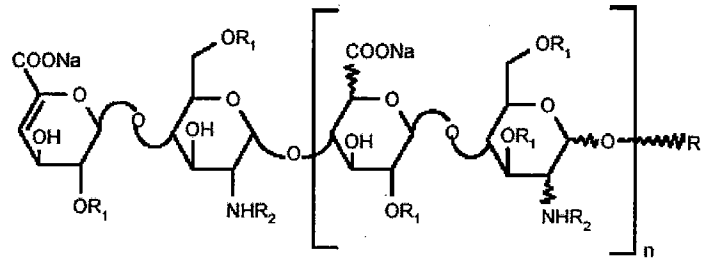
Lovenox Injection 150 mg/mL Concentration contains 15 mg enoxaparin sodium (approximate anti-Factor Xa activity of 1500 IU [with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard]) per 0.1 mL Water for Injection.

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.

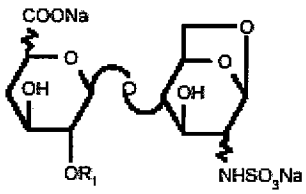
Enoxaparin sodium is obtained by alkaline depolymerization of heparin benzyl ester derived from porcine intestinal mucosa. Its structure is characterized by a 2-O-sulfo-4-enepyranosuronic acid group at the non-reducing end and a 2-N,6-O-disulfo-D-glucosamine at the reducing end of the chain. About 20% (ranging between 15% and 25%) of the enoxaparin structure contains an 1,6 anhydro derivative on the reducing end of the polysaccharide 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



R_1 = H or SO_3Na and R_2 = SO_3Na or $COCH_3$

R	**X*= 15 to 25%**		**n= 0 to 20**
	100 - X	**H**	**n =1 to 21**

*X = Percent of polysaccharide chain containing 1,6 anhydro derivative on the reducing end.

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

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

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

Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction: In a multicenter, double-blind, parallel group study, patients who recently experienced unstable angina or non-Q-wave myocardial infarction were randomized to either Lovenox Injection 1 mg/kg every 12 hours SC or heparin i.v. bolus (5000 U) followed by a continuous infusion (adjusted to achieve an aPTT of 55 to 85 seconds). A total of 3171 patients were enrolled in the study, and 3107 patients were treated. Patients ranged in age from 25-94 years (median age 64 years), with 33.4% of patients female and 66.6% male. Race was distributed as follows: 89.8% Caucasian, 4.8% Black, 2.0% Oriental, and 3.5% other. **All** patients were also treated with aspirin 100 to 325 mg per day. Treatment was initiated within 24 hours of the event and continued until clinical stabilization, revascularization procedures, or hospital discharge, with a maximal duration of 8 days of therapy. The combined incidence of the triple endpoint of death, myocardial infarction, or recurrent angina was lower for Lovenox Injection compared with heparin therapy at 14 days after initiation of treatment. The lower incidence of the triple endpoint was sustained up to 30 days after initiation of treatment. These results were observed in an analysis of both all-randomized and all-treated patients. The efficacy data are provided below.

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

Indication	Dosing Regimen[1] Lovenox Inj. 1mg/kg q12h SC n (%)	Dosing Regimen[1] Heparin aPTT Adjusted i.v. Therapy n (%)	Reduction (%)	p Value
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)

Indication	Dosing Regimen[1] Lovenox Inj. 1 mg/kg q12h SC n (%)	Dosing Regimen[1] Heparin aPTT Adjusted i.v. Therapy n (%)	Reduction (%)	p Value
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	n = 560
	23 (4%)	16 (3%)
Colorectal Surgery	n = 673	n = 674
	28 (4%)	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]

Indications	Dosing Regimen Lovenox Inj. 40 mg q.d. SC	Dosing Regimen Lovenox Inj. 30 mg q12h SC	Dosing Regimen Heparin 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]

Indications	Dosing Regimen Lovenox Inj.[2] 20 mg q.d. SC	Dosing Regimen Lovenox Inj.[2] 40 mg q.d. SC	Dosing Regimen Placebo[2]
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

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

[1] The rates represent major bleeding on study medication up to 12 hours after dose.

[2] Aspirin therapy was administered concurrently (100 to 325 mg per day).

[3] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease by ≥ 3 g/dL or transfusion of 2 or more units of blood products. Intraocular, retroperitoneal, and intracranial hemorrhages were always considered major.

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

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

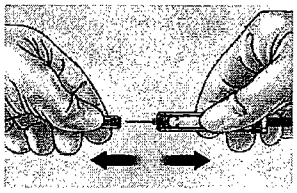
Lovenox Injection is administered by SC injection. It must not be administered by intramuscular injection. Lovenox Injection is intended for use under the guidance of a physician. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up, as necessary.

Proper training in subcutaneous injection technique (with or without the assistance of an injection device) should be provided.

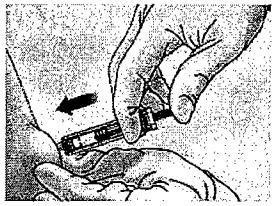
Subcutaneous Injection Technique: Patients should be lying down and Lovenox Injection administered by deep SC injection. To avoid the loss of drug when using the 30 and 40 mg prefilled syringes, do not expel the air bubble from the syringe before the injection. Administration should be alternated between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

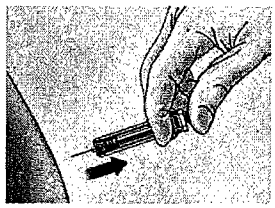
- Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.



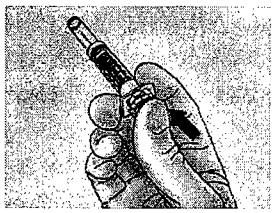
- Inject using standard technique, pushing the plunger to the bottom of the syringe.



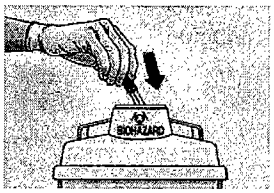
- Remove the syringe from the injection site keeping your finger on the plunger rod.



- 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. XXXX

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/s/

Joyce Korvick
7/23/04 05:32:25 PM
for Dr. Robert Justice

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-055

APPROVABLE LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-164/S-055

Aventis Pharmaceuticals, Inc.
Attention: Dhiren N. Shah, Ph.D.
Director, Regulatory CMC
10236 Marion Park Drive
P.O. Box 9720
Kansas City, MO 64134-0720

Dear Dr. Shah:

Please refer to your supplemental new drug application dated July 11, 2003, received July 14, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium injection).

We acknowledge receipt of your submission dated October 10, 2003.

This supplemental new drug application, submitted as "Changes Being Effected" provides for additional characterization and structural information on the active ingredient of the drug product, enoxaparin sodium. However, as we notified you in our July 30, 2003 letter, an approved supplement is required for this proposed change before distributing the drug product with this change. Therefore, this supplement was reviewed as a prior approval supplement.

We completed our review of this supplemental application, and it is approvable. Before this supplement may be approved, however, you must provide the following information:

1. Patent information for the proposed change as per 21 CFR 314.70 (e) and (f).

2. Data/information (e.g., pharmacological activities, strength and potency) to support that this new identity (1,6 anhydro compounds) of the drug substance is a part of the active moieties. If this is a by-product, then these proposed structures can be considered as product-related substance/impurities and can be used to update the specifications. Accordingly, no labeling changes are needed based on the information you provided.

3. Supportive preclinical and clinical information demonstrating that the proposed structures contribute to the product potency and relate to the safety or effectiveness of the product.

4. Provide ^{1}H and ^{13}C NMR spectroscopic test data including 1D and 2D for each of the above compounds/isomers (di, tetra, hexa, octa and decasaccharides) including specific chemical shifts assignments with coupling constants (e.g. expanded region of the spectra). Provide these data in tabulated format including structural elucidation of the anomeric proton with and without the 1,6-anyhdro bridge.

5. A description of NMR assignments for all the oligosaccharides showing sequence and linkage between various sugar rings.

6. All literature references as cited in the supplement.

7. Mass spectroscopic test data for each compound of the 1,6-anhdro compounds (di, tetra, hexa, octa and decasaccharides).

8. Manufacturing date and site(s) for the 35 batches described in the supplement.

9. The percentage ratio of various individual 1,6-anhydro oligosaccharides (disaccharides, tetrasaccharides, etc.).

10. [redacted]

11. The proposed skip test for the new 1,6-anhydro compounds is not acceptable. All batches should be tested at release and during stability studies as part of the identity test. Provide a revised Stability Protocol.

12. In addition, obtain the revised chemical structure under the current established name from the USAN Council to support the proposed labeling change.

Within 10 days after the date of this letter, you are required to amend this supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

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/

Robert Justice
11/13/03 06:40:09 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-055

LABELING REVIEW(S)

Division of Gastrointestinal and Coagulation Drug Products
(DGICDP)

REGULATORY PROJECT MANAGER LABELING REVIEW

Application Number: NDA 20-164/SCS-055

Name of Drug: Lovenox® (enoxaparin sodium) Injection

Sponsor: Aventis Pharmaceuticals Inc.

Materials Reviewed: Package Insert (PI) submitted July 8, 2004 (received July 9, 2004).

Submission Date: July 11, 2003
Receipt Date: July 14, 2003
Resubmission Date: March 22, 2004
Receipt Date: March 23, 2004
Amendment Date: July 8, 2004
Receipt Date: July 9, 2004

Background and Summary

Background: Lovenox, a low molecular weight heparin (LMWH), 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.

Aventis Pharmaceuticals, Inc. (Aventis) submitted [redacted] on [redacted] (received [redacted]) as a "Changes Being Effected" (CBE)-0 to provide for [redacted] On [redacted], DGCDP acknowledged receipt of [redacted] and notified Aventis that [redacted] did not qualify for a "CBE" application and that [redacted] would be reviewed as a prior approval application.

Aventis submitted SCS-055 (S-055) on July 11, 2003 (received July 14, 2003; amended October 10, 2003 received October 14, 2003) which provides for additional characterization and

structural information on the active ingredient of the drug product, enoxaparin sodium. The information in S-055 supports the information proposed for inclusion in the PI in ——. The chemistry reviewer, Dr. Ali Al-Hakim, completed his review of S-055 on November 7, 2003. In the review for S-055, the chemist recommended that the supplement be issued an "Approvable" action and requested the sponsor submit additional information before the supplement could be approved. Because the information in S-055 supports the labeling revisions requested in ——, S-055 must be approved before the—— can be approved. On November 13, 2003, the Agency sent the sponsor an approvable letter for S-055. On —— the Agency sent the sponsor an approvable letter for ——. On March 22, 2004 (received March 23, 2004), the sponsor submitted a response to the Agency November 13, 2003, approvable letter to S-055. The Medical Officer and Pharmacology reviewer are also reviewing the information submitted to S-055 on March 22, 2004. On ——— (received ———), the sponsor submitted a response to the Agency ———, approvable letter to ——.

On July 8, 2004 (received July 9, 2004), the sponsor submitted revised labeling as an amendment to S-055. This labeling included the revisions proposed in —— and revised labeling from Supplements S-048, S-056, S-057 and S-058. On ——— (received———), Aventis requested—— be withdrawn

Recent supplements containing revised labeling for the PI:

Labeling supplement SLR-048 (S-048) was submitted August 9, 2002, received August 12, 2002, amended August 12, 2003, received August 13, 2003, and approved on draft labeling December 18, 2003. S-048 provided for revisions to 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).

Labeling supplement SLR-056 (S-056) (submitted October 10, 2003, received October 14, 1003, approved on draft labeling on April 13, 2004) provides for revisions to update the information in the **OVERDOSAGE** section, **Symptoms/Treatment** subsection of the PI.

Labeling Supplement SLR-057 (S-057) was submitted November 17, 2003 (received November 18, 2003), to provide 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. S-057 was approved on draft labeling May 18, 2004.

On November 14, 2003 (received November 17, 2003, approved on draft labeling April 21, 2004), 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.

Review

Package Insert

The PI submitted in S-055 on July 8, 2004 (received July 9, 2004) (no identifier)] was compared to the PI from Supplement S-057 (submitted November 17, 2003; received November 18, 2003; approved on draft May 18, 2004), pdf. version "Rev. September 2003a" (Le Trait version "50070788") and (DSM Pharmaceuticals version "50070791"). The PIs were identical except for the following:

I. **DESCRIPTION** section

A. In the seventh paragraph, first sentence that begins "Enoxaparin sodium is obtained . . ." the sponsor revised the term "degradation" to read "depolymerization" so that the sentence reads "Enoxaparin sodium is obtained by alkaline depolymerization of heparin benzyl ester derived from porcine intestinal mucosa."

The chemistry reviewer finds the revision acceptable (per Dr. Al Al-Hakim, Ph. D. to Diane Moore, RPM in verbal communication on July 9, 2004).

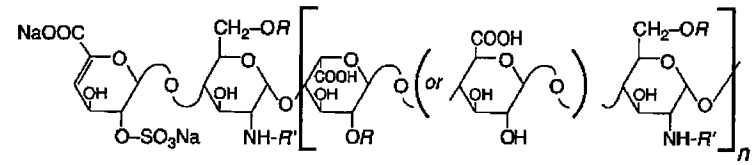
B. In the seventh paragraph, following the second sentence that begins, "Its structure is characterized by . . ." the sponsor proposes to add a new sentence that reads as follows:

"About 20% (ranging between 15% and 25%) of the enoxaparin structure contains an 1,6 anhydro derivative on the reducing end of the polysaccharide chain."

The chemist finds this revision acceptable. "The applicant provided the necessary information regarding the patent information (amendment) which includes the new structural information of 1,6-anhydro derivatives." (See CMC review by Dr. Ali Al-Hakim dated July 9, 2004).

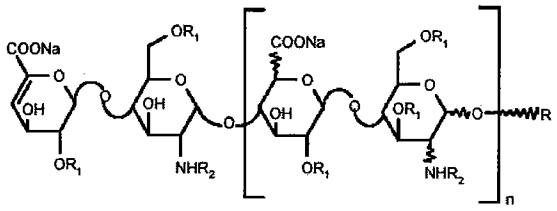
C. **DESCRIPTION** section, **STRUCTURAL FORMULA** subsection

The sponsor revised the structural formula from:



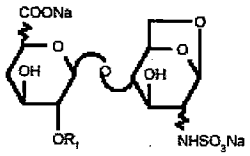
R	R'	n
—H or —SO_3Na	—SO_3Na or —C(=O)—CH_3	3 to 20

to:



R_1 = H or SO_3Na and R_2 = SO_3Na or $COCH_3$

and added the following additional information following the structural information:

R	X*= 15 to 25%		n= 0 to 20
	100 - X	H	n =1 to 21

The combined chemistry review — and S-055 by Dr. Ali Al-Hakim dated November 7, 2003 recommended an approvable action for both supplemental applications. The review states "Based on the information provided in SCS-055, it appears that the newly discovered 1,6-anhydro compounds are by-products during the manufacturing process of the drug substance. If this is the case, then new structures are for information only. This proposed change can be added to the specifications as an additional identity test. Therefore, it is not necessary to reflect the change in the labeling. However, if the new structures are shown to be part of the active moieties (e.g., contributing to the overall potency and biological activities), then supportive information should be provided to demonstrate that they may relate to the safety or effectiveness of the product." Information was requested in a letter to the sponsor regarding S-055 on July 30, 2003. Additional information was requested in the action letter to S-055 dated November 13, 2003. (see CMC review by Dr. Ali Al-Hakim dated November 7, 2003).

The Agency requested the following information in the July 30, 2003 letter:

"Provide test data and any related information to support the proposed changes for the following items described in your supplemental application:

1. **The proposed modified structural formula for Lovenox®.**

2. **The proposed percentage ratio of the 1,6 anhydro ring (15-25%)."**

The Agency requested the following information in the November 13, 2003 agency letter:

"1. Patent information for the proposed change as per 21 CFR 314.70 (e) and (f).

2. **Data/information (e.g., pharmacological activities, strength and potency) to support that this new identity (1,6 anhydro compounds) of the drug substance is a part of the active moieties. If this is a by-product, then these proposed structures can be considered as product-related substance/impurities and can be used to update the specifications. Accordingly, no labeling changes are needed based on the information you provided.**

3. **Supportive preclinical and clinical information demonstrating that the proposed structures contribute to the product potency and relate to the safety or effectiveness of the product.**

4. **Provide ^{1}H and ^{13}C NMR spectroscopic test data including 1D and 2D for each of the above compounds/isomers (di, tetra, hexa, octa and decasaccharides) including specific chemical shifts assignments with coupling constants (e.g. expanded region of the spectra). Provide these data in tabulated format including structural elucidation of the anomeric proton with and without the 1,6-anyhdro bridge.**

5. **A description of NMR assignments for all the oligosaccharides showing sequence and linkage between various sugar rings.**

6. **All literature references as cited in the supplement.**

7. **Mass spectroscopic test data for each compound of the 1,6-anhdro compounds (di, tetra, hexa, octa and decasaccharides).**

8. **Manufacturing date and site(s) for the 35 batches described in the supplement.**

9. **The percentage ratio of various individual 1,6-anhydro oligosaccharides (disaccharides, tetrasaccharides, etc.).**

10. 

11. **The proposed skip test for the new 1,6-anhydro compounds is not acceptable. All batches should be tested at release and during stability studies as part of the identity test. Provide a revised Stability Protocol.**

12. **In addition, obtain the revised chemical structure under the current established name from the USAN Council to support the proposed labeling change."**

The sponsor responded to the above requests for information in the resubmission to S-055 on March 22, 2004 (received March 23, 2004). The sponsor had included both the original structure and the new proposed structure in the labeling submitted in the March 22, 2004, submission. The sponsor revised the PI in the July 8, 2004 amendment to S-055 (received July 9, 2004) to propose only the new proposed structure (the original structure was deleted from the PI). The chemistry reviewer finds the new proposed structure acceptable. (See CMC review by Dr. Ali Al-Hakim, Ph.D., dated July 9, 2004). The review states "The applicant provided the necessary information regarding the patent information (amendment) which includes the new structural information of 1,6 anhydro derivatives." "Structure should be revised as per the new proposed structural formula." The sponsor revised the structural formula in the July 8, 2004, submission to conform to the new proposed structural formula. The Proposed revision is acceptable.

II. **CLINICAL PHARMACOLOGY** section

The revisions made in S-048 (submitted August 9, 2002, received August 12, 2002, amended August 12, 2003, received August 13, 2003, and approved on draft labeling December 18, 2003) were incorporated into the revised PI in S-055, as requested in the approval letter to S-057 dated May 18, 2004. (See RPM labeling review to S-048 by Ms. Diane Moore dated September 25, 2003, and the Medical Officer review to S-048 by Dr. Ruyi He dated October 15, 2003, and the Biopharmaceutics review to S-048 dated February 10, 2003).

The section is acceptable.

III. **PRECAUTIONS** section

The revisions made to the **PRECAUTIONS** section of S-048 (submitted August 9, 2002, received August 12, 2002, amended August 12, 2003, received August 13, 2003, approved on draft labeling December 18, 2003) were incorporated into the revised PI submitted in S-055 on July 8, 2004 (received July 9, 2004). (See RPM labeling review to S-048 by

Ms. Diane Moore dated September 25, 2003, and the Medical Officer review by Dr. Ruyi He dated October 15, 2003, and the Biopharmaceutics review to S-048 dated February 10, 2003).

The section is acceptable.

IV. **ADVERSE EVENTS** section

The sponsor included the revisions made in S-057 (submitted November 17, 2003, received November 18, 2003, approved on draft labeling May 18, 2004) into the revised PI submitted in S-055 on July 8, 2004 (received July 9, 2004). (See RPM labeling review to S-057 by Diane Moore dated March 23, 2004, and the Medical Officer review by Dr. Ruyi He dated May 5, 2004).

The section is acceptable.

V. **OVERDOSAGE** section

The revisions approved in S-056 (submitted October 10, 2003, received October 14, 2003, approved on draft labeling April 13, 2004) were incorporated into the PI submitted in S-055 on July 8, 2004 (received July 9, 2004). (See RPM review to S-056 by Ms. Diane Moore dated February 19, 2004 and the Medical Officer review by Dr. Ruyi He dated April 1, 2004).

The section is acceptable.

VI. **DOSAGE AND ADMINISTRATION** section:

A. The sponsor has added the "Renal Impairment" subsection that was added in S-048 (submitted August 9, 2002, received August 12, 2002, approved on draft labeling December 18, 2003), to the PI submitted in S-055 on July 8, 2004 (received July 9, 2004) as requested in the approval letter to S-057 dated May 18, 2004. (See RPM labeling review to S-048 dated September 25, 2003).

The section is acceptable.

B. The sponsor has included the revisions to the **DOSAGE AND ADMINISTRATION** section of the PI approved in S-058 (submitted November 14, 2003, received November 17, 2003, approved on draft labeling April 21, 2004) in the PI submitted in S-055 on July 8, 2004 (received July 9, 2004). (See RPM review to S-058 by Diane Moore dated March 22, 2004).

The section is acceptable.

VII. **HOW SUPPLIED** section

A. The sponsor has included the revisions to the **HOW SUPPLIED** section of the PI approved in S-058 (submitted November 14, 2003, received November 17, 2003, approved on draft labeling April 21, 2004) in the PI submitted in S-055 on July 8, 2004 (received July 9, 2004). (See RPM review to S-058 by Diane Moore dated March 22, 2004).

The section is acceptable.

B. Following the line that reads "Manufactured for: Aventis Pharmaceuticals Inc. Bridgewater, NJ 088007" the sponsor revised the line that reads "©2002 Aventis Pharmaceuticals Inc. Rev.XXXX" to read "©2004 Aventis Pharmaceuticals Inc. Rev. XXXX."

The revision is editorial and acceptable.

Conclusions

1. Items I. A., B. and C. are acceptable per the chemistry reviewer.
2. Items II., III., IV., V., VI. and VII. are acceptable.
3. Item VII.B. is editorial and acceptable.
4. Supplement SLR-055 should be approved pending review by the Medical Officer and Pharmacology reviewer.

Diane Moore, B.S.
Regulatory Health Project Manager

Ali Al-Hakim, Ph.D.
Chemist

Liang Zhou, Ph.D.
Chemistry Team Leader

cc:
Archival NDA 20-164/S-055
HFD-180/Div. Files
HFD-180/D.Moore
Drafted by: dm/7/14/04
Initialed by: A.Al-Hakim, L.Zhou 7.19.04
Final: July 19, 2004
Filename:N20164S55Lblrev.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
7/19/04 04:53:25 PM
CSO

Ali Al-Hakim
7/19/04 05:15:26 PM
CHEMIST

Liang Zhou
7/19/04 05:19:32 PM
CHEMIST

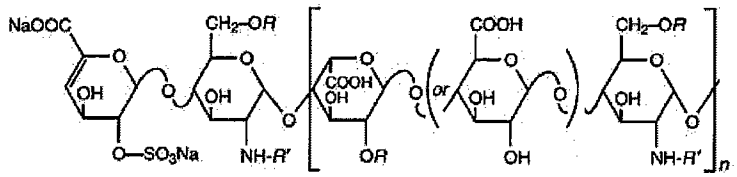
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-055

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW # 1	1. Organization: HFD-180	2. NDA number: 20-164	
3. Name and Address of Applicant (City & State):		4. AF Number:	
Aventis Pharmaceuticals 200 Crossing Boulevard Bridgewater, NJ 08807-0800		5. Supplement(s)	
6. Name of Drug: Lovenox® injection	7. Nonproprietary Name: Enoxaparin Sodium	Numbers SCS-055 [redacted]	Dates 07-11-03 07-11-03
8. Supplement Provides for: Additional characterization and structural information on the active ingredient of the drug product, enoxaparin sodium.		9. Amendments & Other (Reports, etc.) Dates: Amendment dated October 10, 2003.	
10. Pharmacological Category: Anticoagulant	11.How Dispensed: RX X OTC	12. Related DMF(s):	
13.Dosage Form: Solution for Injection	14. Potency: 30/40/60/80/100/120/150/300 mg		
15. Structure and Chemical Name:		16. Records and Reports: Teleconference dated July 17, 2003 Letter dated July 17, 2003 Teleconference dated July 30, 2003 Letter dated October 30, 2003	
		Current Yes X No	
		Reviewed Yes X No	



R	R'	n
– H or – SO_3Na	– SO_3Na or – C–CH_3 (O)	3 to 20

2-O-sulfo-4-enepyranosuronic acid group at the non-reducing end and a 2-N, 6-O-disulfo-D-glucosamine at the reducing end of the chain. The substance is the sodium salt. The average molecular weight is about 4500 daltons.
Molecular weight distribution:
<2000 daltons < 20%; 2000 to 8000 daltons > 68%; > 8000 daltons < 18%

17. Comments:
See review and information request at the end of the review.

CC: NDA 20-164
HFD-180/Div File/NDA 20-164/S055
HFD-181/CSO/D. Moore
HFD-180/B.Justice
HFD-180/J.Choudary
HFD-180/A.Al-Hakim
HFD-180/L.Zhou
HFD-820/E.Duffy
HFD-820/D.Wu
11-06-03 /Wordfiles\S\20164/S055

18. Conclusions and Recommendations:
Recommend that the regulatory Health Project Manager issue An-Approvable letter for this supplement. See information request letter at the end of the review.

19.Reviewer Name: Ali Al-Hakim, Ph.D.	Date Completed: 11-06-03

Background

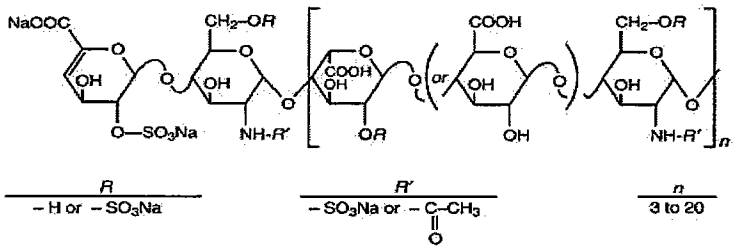
This supplement was submitted originally as a change being effected (CBE-0 submission date: July 11, 2003), however, after examining its content, we recommended that the submission should be change to a prior approval supplement (PAS) due to its impact on the drug product specifications (teleconference/letter dated July 17, 2003)

During the reviewing process of the supplement, contacted (teleconference/letter dated July 30, 2003) and was asked to provide additional supporting Chemistry, Manufacturing and Controls (CMC) information. Consequently, the sponsor submitted amendment to supplement dated October 10, 2003.

Review Notes

The sponsor reported that the purpose of the submission is to provide additional characterization and structural information on the active ingredient of the drug product, enoxaparin sodium. The applicant reported that this new information was obtained due to the improved and advanced analytical techniques during the continual examination of the structure of enoxaparin. This work led to the discovery of structural fingerprints for the presence of oligosaccharides bearing 6-O-sulfo groups on the glucosamine moiety. Below are the approved chemical structure and the proposed chemical structure of Enoxaparin Sodium.

Chemical structure of the currently approved Lovenox

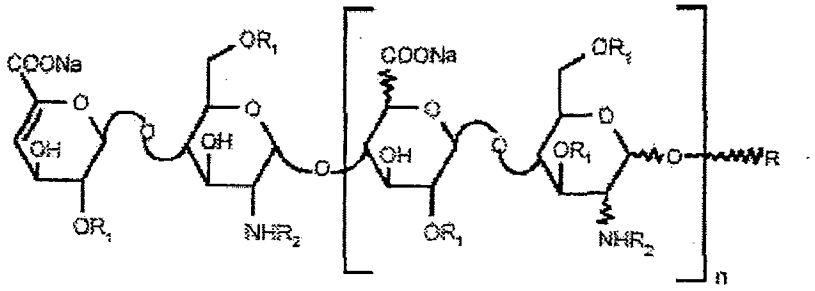


Average molecular weight is about 4500 Dalton

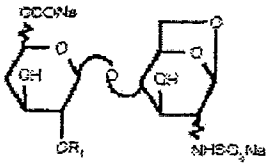
Molecular weight distribution

NMT 20%	< 2,000
At least 68%	between 2,000 and 8,000
NMT < 18%	> 8.000

Chemical structure of the proposed Lovenox



R_1 = H or SO_3Na and R_2 = SO_3Na or $COCH_3$

R	X*= 15 to 25%		n= 0 to 20
	100 - X	H	n =1 to 21

*X = Percent of polysaccharide chain containing 1,6 anhydro derivative on the reducing end

Aventis reported that formation of the 1,6-anhudro ring occurs during the ——— deploymerization process. The cyclization takes place by intramolecuar nucleophilic substitution and the in the enoxaparin process, the yield for these 1,6-anhydro groups is between 15-25%.

Evaluation

The new proposed structure provided additional structural features, in addition to the previously approved structure. Chemical structures of heparin and low molecular weight heparins drug products are usually represented by the major repeating units and the modified structure of the non-reducing end. However, Aventis presented additional structural characterization which improved the identity of these complex and poorly identified compounds.

The applicant did not provide the complete information related exclusivity issues and regulatory requirements. This also includes information about if the new discovered compounds are part of the active ingredients so that labeling changes can be justified. Therefore, the applicant needs to provide the following additional information.

According to CFR 314.70 (c)(1), the proposed change complies with the current regulatory requirement that provides increases assurances that the drug product will have the characteristics of identity, strength, quality and purity which it purports.
According to CFR 314.70 (e) and (f), patent information should be submitted. Also refer to 314.50(j) which outlines that certain information should be submitted if claiming exclusivity.

Based on the current information provided in the supplement, it appears that the newly discovered 1,6-anhydro compounds are by-products during the manufacturing process of the drug substance. If this is the case, then new structures are for information only. This proposed change can be added to the specifications as additional identity test. Therefore, it is not necessary to reflect the change in the labeling.

However, if the new structures are shown to be part of the active moieties (e.g. contributing to the overall potency and biological activities), then supportive information should be provided to demonstrate that they may relate to the safety or effectiveness of the product.

Information Request

1. Provide patent information for the proposed change as per 21 CFR 314.70 (e) and (f) and 314.50(j).

2. a) Provide data/information (e.g., pharmacological activities, strength and potency) to support this new identity (1,6 anhydro compounds) of the drug substance is a part of the active moieties. If this is by-product, then these proposed structures can be considered as product related substance/impurities and can be used to update the specifications. Accordingly, no labeling changes are needed based on the information you provided.
   b) Provide supportive preclinical and clinical information if the proposed structures contribute to potency to demonstrate that they may relate to the safety or effectiveness of the product.
   c) Obtain revised chemical structure and current established name from USAN Council to support the proposed labeling change

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information from

CHEMISTRY REVIEW #1

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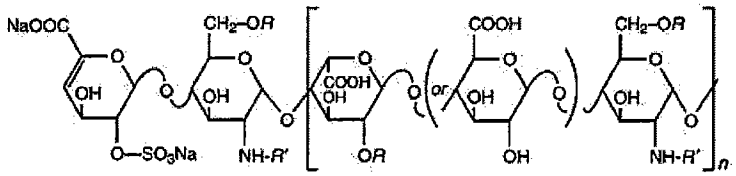
/s/

Ali Al-Hakim
11/7/03 02:31:37 PM
CHEMIST

Liang Zhou
11/7/03 02:50:40 PM
CHEMIST
1. Issues were discussed with review team at 10/31/03 NDA review team meeting. 2. The review division will decide whether these two supplements should be acted on together. 3. Ali's special leave and sign off this review based on the policy (Mapp)

CHEMIST'S REVIEW # 2	1. Organization: HFD-180	2. NDA number: 20-164	
3. Name and Address of Applicant (City & State):		4. AF Number:	
Aventis Pharmaceuticals 200 Crossing Boulevard Bridgewater, NJ 08807-0800		5. Supplement(s)	
6. Name of Drug: Lovenox® injection	7. Nonproprietary Name: Enoxaparin Sodium	Numbers SCS-055	Dates 07-11-03
8. Supplement Provides for: Additional characterization and structural information on the active ingredient of the drug product, enoxaparin sodium.		9. Amendments & Other (Reports, etc.) Dates: Amendment dated October 10, 2003. Amendment dated March 22, 2004	
10. Pharmacological Category: Anticoagulant	11.How Dispensed: RX X OTC	12. Related DMF(s):	
13.Dosage Form: Solution for Injection	14. Potency: 30/40/60/80/100/120/150/300 mg		

15. Structure and Chemical Name:



R	R'	n
– H or – SO_3Na	– SO_3Na or – C–CH_3 (O)	3 to 20

2-O-sulfo-4-enepyranosuronic acid group at the non-reducing end and a 2-N, 6-O-disulfo-D-glucosamine at the reducing end of the chain. The substance is the sodium salt. The average molecular weight is about 4500 daltons.
Molecular weight distribution:
<2000 daltons < 20%; 2000 to 8000 daltons > 68%; > 8000 daltons < 18%

16. Records and Reports:
Teleconference dated July 17, 2003
Letter dated July 17, 2003
Teleconference dated July 30, 2003
Letter dated October 30, 2003
Agency letter dated November 13, 2003.

Current
Yes X No

Reviewed
Yes X No

17. Comments:
See review notes
CC: NDA 20-164
HFD-180/Div File/NDA 20-164/S055
HFD-181/CSO/D. Moore
HFD-180/B.Justice
HFD-180/K.Robie-Suh
HFD-180/J.Choudary
HFD-180/A.Al-Hakim
HFD-180/L.Zhou
HFD-820/E.Duffy
07-10-04 /Wordfiles\S\20164/S055

18. Conclusions and Recommendations:
Recommend that the Regulatory Health Project Manager issue An-Approved letter for this supplement. See review notes and recommendation.

19.Reviewer Name: Ali Al-Hakim, Ph.D.	Date Completed: 07-10-04

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CHEMISTRY REV #2

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/s/

Ali Al-Hakim
7/9/04 12:09:26 PM
CHEMIST

Liang Zhou
7/9/04 12:19:11 PM
CHEMIST
Bob or Joyce signature May be rquired .

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-055

PHARMACOLOGY REVIEW(S)

SUPERVISORY PHARMACOLOGIST'S REVIEW OF NDA 20-164
(Supplement # S–055 Dated March 22, 2004)

Sponsor and Address: Aventis Pharmaceuticals, Inc.
Kansas City, MO 64134

Reviewer: Jasti B. Choudary, B.V.Sc., Ph.D.
Supervisory Pharmacologist, HFD-180

Date of Submission: March 22, 2004

Date of HFD-180 Receipt: March 23, 2004

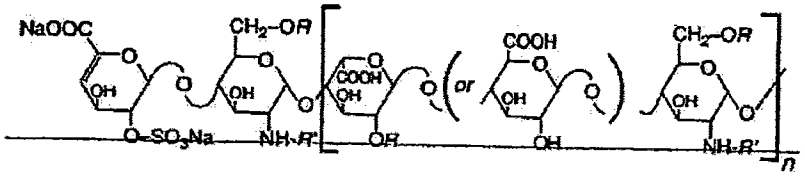
Date of Review: July 22, 2004. This review is based on a draft provided by Pharmacologist Dr. S. Chakder.

Drug:

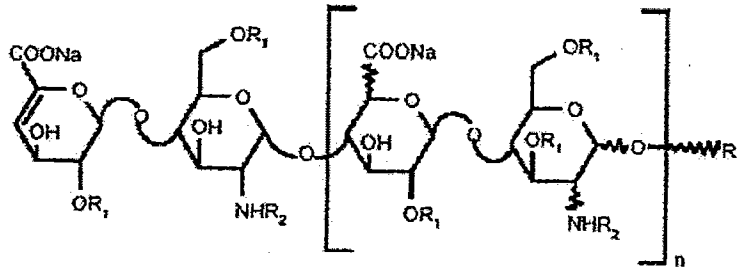
Trade Name: Lovenox Injection

Generic Name: Enoxaparin sodium

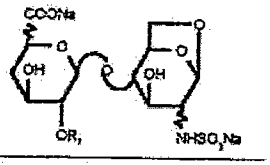
Chemical Name and Structure: Enoxaparin sodium is a low molecular weight heparin obtained by alkaline polymerization of heparin benzyl ester obtained from porcine intestinal mucosa. Its structure is characterized by a 2-O-sulfo-4-enepyranosuric acid group at the non-reducing end and a 2-N,6-O-sulfo-D-glucosamine at the reducing end of the chain. About 20% (ranging between 15% and 25%) of the enoxaparin structure contains a 1,6 anhydro derivative on the reducing end of the polysaccharide chain. The average molecular weight distribution is: <2000 daltons $\leq$ 20%, 2000 to 8000 daltons $\geq$68%, >8000 daltons $\leq$ 18%.



R	R'	n
—H or —SO_3Na	—SO_3Na or —C(=O)—CH_3	3 to 20



R_1 = H or SO_3Na and R_2 = SO_3Na or $COCH_3$

R	X*= 15 to 25%		n= 0 to 20
	100 - X	H	n =1 to 21

*X = Percent of polysaccharide chain containing 1,6 anhydro derivative on the reducing end

Category: Antithrombotic agent/Low Molecular Weight Heparin.

SUBMISSION CONTENTS:

In vitro pharmacology studies with 1,6-anhydro fractions of enoxaparin with different saccharide chains.

Enoxaparin sodium is currently approved for the prevention of deep vein thrombosis in hip, knee and abdominal surgery, and the prevention of ischemic complications of unstable angina, and non-Q-wave myocardial infarction, when concurrently administered with aspirin. In NDA Supplement #055, the sponsor has disclosed the presence of a 1, 6 anhydro derivative at the reducing end of the enoxaparin molecule. The following pharmacology studies were conducted with different oligosaccharides containing either <7% (DIA 2044) or 15-25% (WSD 3093) of the 1,6 anhydro structure.

***In Vitro* Evaluation of Anticoagulant Activity of Enoxaparin Fractions.**

The study was conducted to compare the anti-factor Xa and anti-factor IIa activities of six 1, 6-anhydro fractions of enoxaparin with different saccharide chains (hexasaccharides, octasaccharides, decasaccharides, dodecasaccharides, < 16-mer, ≥16-mer) with their corresponding non-anhydro counterparts. In addition, the anticoagulant effect of both sets of different fractions was assessed by thromboelastography. The following fractions of enoxaparin were used in the study:

Standard Enoxaparin Fractions (15-25% anhydro structure)	**Enoxaparin Fractions (<7% anhydro structure)**
WSD3093-Hexasaccharides	DIA2844-Hexasaccharides
WSD3093-Octasaccharides	DIA2844-Octasaccharides
WSD3093-Decasaccharides	DIA2844-Decasaccharides
WSD3093-Dodecasaccharides	DIA2844-Dodecasaccharides
WSD3093 < Hexadecasaccharides	DIA2844 < Hexadecasaccharides
WSD3093 ≥Hexadecasaccharides	DIA2844 ≥Hexadecasaccharides

The anti-factor IIa activity was determined by the microtiter-plate method using a chromogenic substrate. Anti-factor Xa activity was determined with an automated coagulation instrument using Heparin-kit containing ATIII, FXa and the chromogenic substrate S-2765. Anti-Xa/IIa activities of the compounds were determined using a standard calibration curve constructed with enoxaparin.

Significant differences in anti-FXa and anti-FIIa activities were observed between hexasaccharides with Anhydro and Non-Anhydro fractions and >16-mers with Anhydro and Non-Anhydro fractions. In both cases, the Non-Anhydro (DIA) fraction had higher specific anti-FXA and anti-FIIa activities than the Anhydro (WSD) fraction. The anti-FXA and anti-FIIa activities of different enoxaparin fractions are summarized in the Table below.

Table 1 – Effect of Enoxaparin fractions on anti-factor Xa activity (U/mg)

	WSD 3093	SEM	DIA 2844	SEM	
Hexasaccharide	9,8	0,7	13,9	0,6	*P<0.05*
Octasaccharide	42,9	4,0	47,6	5,2	*NS*
Decasaccharide	69,3	3,4	67,0	7,5	*NS*
Dodecasaccharide	78,4	6,1	95,1	4,8	*NS*
< Hexadecasaccharide	51,3	5,5	56,9	0,7	*NS*
>= Hexadecasaccharide	140,0	8,0	164,6	8,8	*P<0.05*

Table 2 – Effect of Enoxaparin fractions on anti-factor IIa activity (U/mg)

	WSD 3093	SEM	DIA 2844	SEM	
Hexasaccharide	0,0	0,01	0,1	0,01	*P<0.05*
Octasaccharide	0,1	0,01	0,2	0,01	*NS*
Decasaccharide	0,2	0,01	0,2	0,01	*NS*
Dodecasaccharide	0,2	0,01	0,2	0,01	*NS*
< Hexadecasaccharide	0,1	0,01	0,2	0,01	*NS*
>= Hexadecasaccharide	44,5	2,18	60,3	2,80	*P<0.05*

Thromboelastography showed that at the same anti-FXa concentration, the Non-Anhydro ≥ 16-mer caused a significant prolongation of reaction time and a reduction of clot strength when compared with the Anhydro >16-mer fraction. Thus, at the same anti-FXa concentration, the >16-mer Non-Anhydro (DIA) had higher anti-coagulant potency than the >16-mer Anhydro (WSD). The effects of enoxaparin fractions on the thromboelastography parameters (reaction time, maximum amplitude) are shown in the sponsor's Table below.

Table 3 - Effect of Enoxaparin fractions on thromboelastography (parameters reaction time [min], maximum amplitude [mm])

		WSD3093				DIA2844			
	anti-fXa activity	Reaction Time	SEM	Maximum amplitude	SEM	Reaction Time	SEM	Maximum amplitude	SEM
Hexasaccharide	0.1U/ml	56,5	5,2	14,5	4,0	79,1	12,8	14,5	5,3
	0.075U/ml	35,7	3,7	20,0	0,5	34,2	2,4	25,2	1,0
	0.05U/ml	30,8	2,3	28,0	3,4	22,6	0,2	24,0	0,0
Octasaccharide	0.1U/ml	40,8	7,6	14,8	1,4	78,8	25,0	20,2	5,5
	0.075U/ml	32,6	0,3	20,8	0,1	31,1	4,0	24,3	1,8
	0.05U/ml	30,6	2,4	21,8	1,2	24,9	3,8	20,0	0,3
Decasaccharide	0.1U/ml	60,1	9,0	17,0	4,2	50,6	8,6	20,3	0,9
	0.075U/ml	31,1	1,1	20,3	0,3	42,8	6,4	21,0	3,1
	0.05U/ml	81,2	28,5	23,3	1,3	25,0	2,3	21,5	0,2
Dodecasaccharide	0.1U/ml	32,6	6,0	22,5	0,7	39,0	3,1	27,7	2,8
	0.075U/ml	23,2	3,2	20,2	0,1	27,2	2,6	27,3	2,7
	0.05U/ml	32,0	5,8	25,3	2,6	33,5	1,6	21,0	0,2
< Hexadecasaccharide	0.1U/ml	42,4	5,6	20,7	1,7	52,3	12,3	24,2	3,9
	0.075U/ml	35,9	4,4	19,7	0,9	49,0	15,6	24,2	3,0
	0.05U/ml	52,4	6,7	24,0	1,2	28,0	3,2	20,3	0,4
>= Hexadecasaccharide	0.1U/ml	53,3	2,0	19,3	0,3	146,5	10,4	7,5	1,6*
	0.075U/ml	48,5	5,8	19,0	0,3	101,3	11,9	14,8	2,5
	0.05U/ml	36,0	3,7	20,3	1,1	36,5	2,9	19,7	0,3

*P<0.05 (WSD vs. DIA)

Thus, significant differences in the anti-FXa and anti-FIIa activities were observed between the anhydro and non-anhydro derivatives, the non-anhydro derivative being more potent than the anhydro derivative.

Evaluation of the Influence of 12 Heparinoid Derivatives on Thrombin Generation;

The study was conducted to compare the anticoagulant effect of the heparinoid derivatives with that of enoxaparin. The anticoagulant effect was evaluated as an inhibition of thrombin generation by the compounds. Thrombin generation was measured with the Thrombogram-Thrombinoscope assay using fresh platelet rich human plasma. The following parameters were calculated from the thrombogram.

Lag time – Time required for a deviation superior to two standard deviations of the fluorescent signal from the baseline.

Endogenous thrombin potential (ETP) – It is the area under the curve, and represents the complete kinetics of thrombin generation in time.

Time to peak - It is the time for the maximal generation of thrombin.

Time to peak-lag time – This parameter estimates the time to reach the peak once the reaction has started.

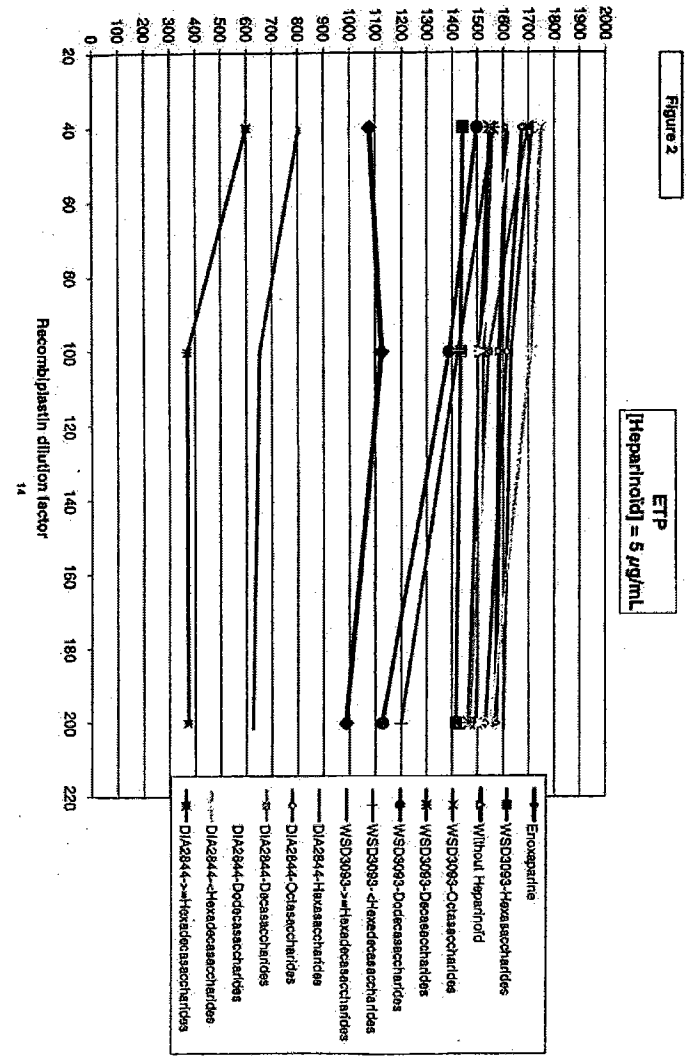
Start tail – It is the time required for the thrombin concentration to return to zero.

The following heparin fractions were used in the study:

WSD3093-Hexasaccharide	DIA2844-Hexasaccharide
WSD3093-Octasaccharide	DIA2844-Octasaccharide
WSD3093-Decasaccharide	DIA2844-Decasaccharide
WSD3093-Dodecasaccharide	DIA2844-Dodecasaccharide
WSD3093 < Hexadecasaccharide	DIA2844 < Hexadecasaccharide
WSD3093 ≥Hexadecasaccharide	DIA2844 ≥Hexadecasaccharide

A prolongation of lag time was observed with WSD ≥ hexadecasaccharide and DIA ≥hexadecasaccharide compounds. These two compounds also showed higher inhibition of ETP than enoxaparin and the effect was more pronounced with DIA ≥ hexadecasaccharide than with WSD ≥ hexadecasaccharide. The DIA ≥ hexadecasaccharide compounds also induced more reduction of the peak than the WSD ≥ hexadecasaccharides. No differences in the delay of the time to peak were observed between the DIA and WSP compounds. WSD ≥ hexadecasaccharides induced a prolongation of the time to peak-lag time parameter as compared with the other compounds. It also caused more prolongation of the start-tail than the other compounds. The other polysaccharides used in the study had only minimal effects, observed only at highest concentration. Thus, DIA ≥ Hexadecasaccharides had higher effects than the WSD ≥ Hexadecasaccharides on two important parameters, i.e. ETP and Peak.

Based on these findings, complementary experiments were conducted with DIA ≥ hexadecasaccharide, WSD ≥ hexadecasaccharide and enoxaparin at concentrations of 10, 9.0, 8.0, 6.25, 5.0, 4.0, 2.5, 1.6, 1.0, 0.5 and 0 μg/ml. The results confirmed that WSD ≥ hexadecasaccharide and DIA ≥ hexadecasaccharide had more pronounced effects on ETP and peak, when compared with enoxaparin. For the 5 μg/ml concentration, the ETP was decreased by 58% and 68% for WSD ≥ hexadecasaccharide and DIA ≥ hexadecasaccharide, respectively. The peak for thrombin generation was dose-dependently decreased at ≥2.5 μg/ml concentrations. DIA ≥ hexadecasaccharide had slightly higher effect than WSD ≥ hexadecasaccharide on the peak. For the 5 μg/ml concentration, the peak was decreased by 73% and 79% for WSD ≥ hexadecasaccharide and DIA ≥ hexadecasaccharide, respectively. For the 5 μg/ml concentration, the Time to Peak was prolonged by 66% and 42% for WSD ≥ hexadecasaccharide and DIA ≥ hexadecasaccharide, respectively. Time to peak-lag time was also significantly prolonged by both WSD ≥ hexadecasaccharide and DIA ≥ hexadecasaccharide. The effects of the heparinoid fragments (5 μg/ml) on ETP and Peak are shown in the sponsor's Figure below.



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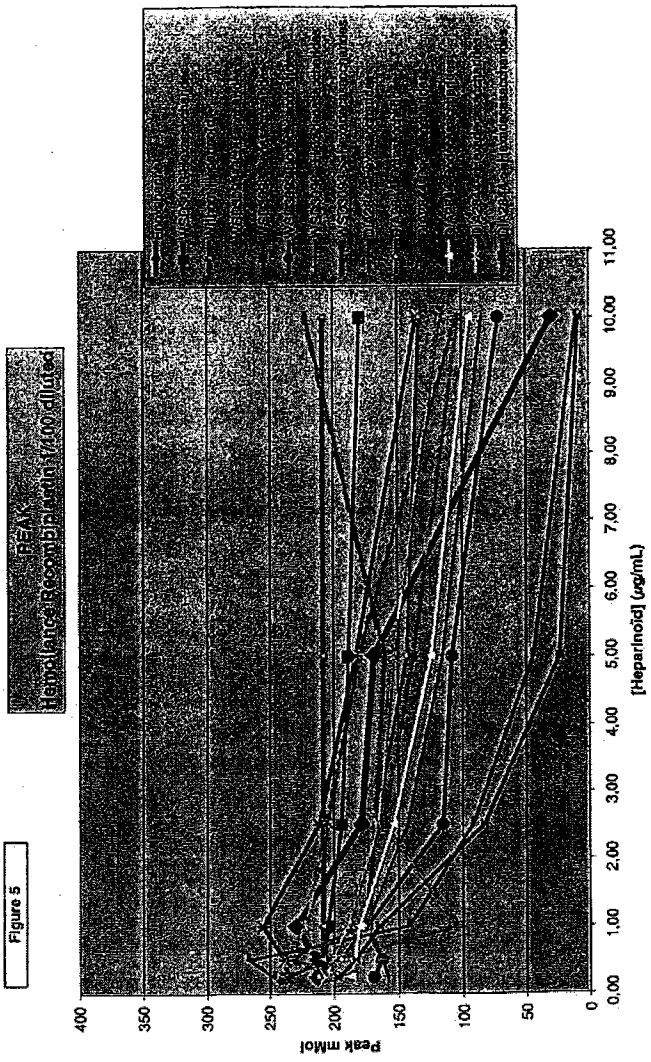


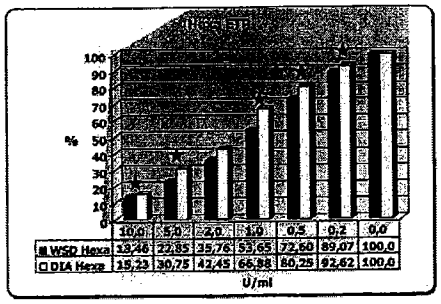
Thus, there was an inhibition of thrombin generation by enoxaparin and the heparin fragments. A difference in the thrombin generation was observed between ≥ hexadecasaccharide and < hexadecasaccharide compounds, ≥ hexadecasaccharides being more active. ≥ hexadecasaccharide fractions were more potent than enoxaparin in inhibiting thrombin generation. The effect was particularly marked for ETP, which is the area under the curve and includes the amount of thrombin formed and the time to form this thrombin. The DIA ≥ hexadecasaccharide fraction induced a more potent inhibition of thrombin generation than the WSD ≥ hexadecasaccharide fraction. The differences observed between these two fractions may be related to the differences in the chemical structure of these fractions.

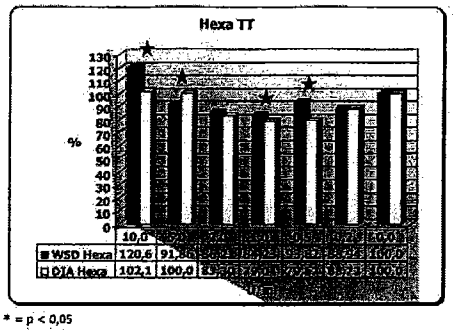
<u>In Vitro Testing the Efficacy of Twelve Heparinoid Agents on Four Hemostatic Parameters</u>.

The study was conducted to determine the efficacy of the twelve heparin fragments (six DIA fragments containing <7% anhydro structure, and six WSD fragments containing 15-25% anhydro structure) on the hemostatic parameters assessing fibrin formation, classical coagulation tests and thrombin activity. The concentrations of all 12 agents used were 0.0, 0.2, 0.5, 1.0, 2.0, 5.0 and 10.0 U/ml. The following parameters were measured using standard methods: thrombin time (TT), partial thromboplastin time (PTT), prothrombin time (Quick, Q) and thrombin generation. TT, PTT and Quick-test were determined using Amelung Amax CS-190 and CS-400 coagulation diagnostic analyzer, and thrombin generation was measured using Hemker's methods.

There were some differences in the hemostatic parameters between the WSD (15-20% anhydro structure) and DIA (<7% anhydro structure) fractions. DIA hexasaccharides were more effective in TT reduction (at 1 and 0.5 U/ml) than the WSD hexasaccharides. WSD decasaccharides (10 U/ml) caused more prolongation of APTT than the DIA fraction. DIA hexadecasaccharides caused more reductions in ETP than the WSD hexadecasaccharides. DIA hexadecasaccharides caused more reduction of the Quick value than WDS at 10, 2 and 1 U/ml concentrations. However, the differences between the two groups were not observed at all concentrations. The effects of the heparin fractions on the hemostatic parameters are shown in the sponsor's Figures below.

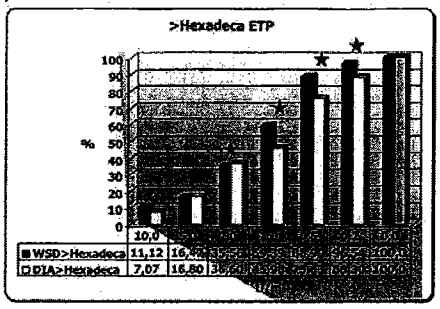
a) Hexasaccharide:



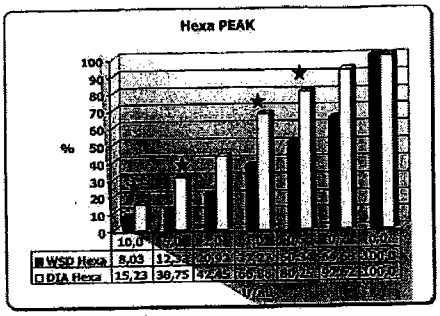


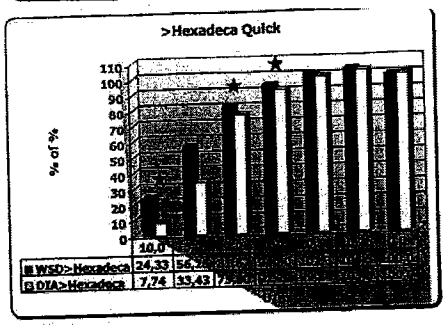
* = p < 0,05

f) > Hexasaccharide:



* = p < 0,05





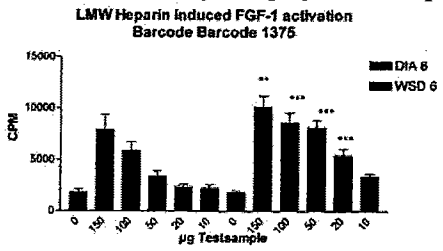
* = p < 0,05

Thus, some differences in the hemostatic parameters were observed between the WSD and the DIA fractions. However these differences were not observed at all concentrations and were not consistent.

Regulation of the Biological Activity of Fibroblast Growth Factor by Enoxaparin *In Vitro*.

The growth promoting effect of the heparin fractions were examined *in vitro* on the fibroblast growth factor (FGF)-induced cell proliferation. The 12 heparin fractions used in previous studies were used in this study. BHK-21 cells (baby hamster kidney cells) were grown in culture and the effects of the heparin fractions on recombinant human acidic fibroblast growth factor-induced growth of the cells were determined. Cell growth was assessed by measuring the incorporation of [methyl-^{3}H]thymidine].

In the first series of experiments, the DIA (<7% anhydro structure) and WSD (15-25% anhydro structure) compounds of the same chain length were compared at 10, 20, 50, 100 and 150 μg doses of the test substances with the fixed dose of FGF (1 ng). The DIA hexasaccharides had significantly higher activity than the WSD compounds on the cell growth in the first assay. However, in four other assays, with higher chain polymers, no significant differences were observed between them. The effects of different heparin fractions on methyl-^{3}H]thymidine uptake is shown in the Figure below.



The assay was repeated with all compounds on one plate with two different cell concentrations ($4X10^4$ and $8X10^4$). In this assay, at the 150 μg dose, significant differences in EGF-induced cell growth were observed between the DIA and WSD compounds. At lower chain length (6-10), the WSD compounds were more active, while at the higher chain length, the DIA compounds were more active. The results are shown in the Figures below.

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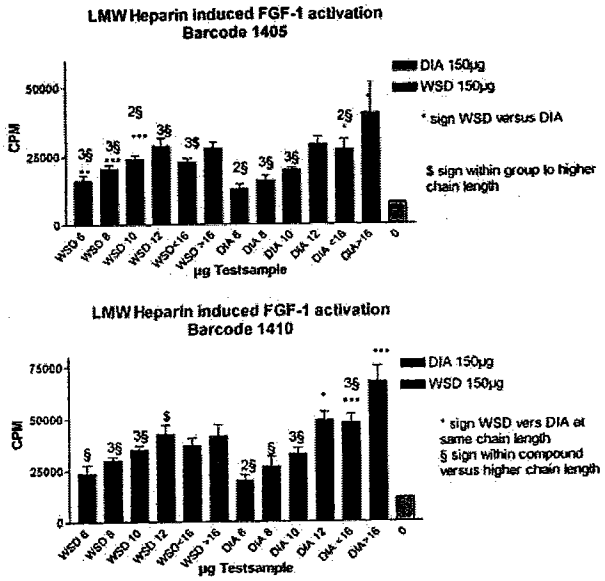

Effect of Enoxaparin and Novel Polysaccharides on Proliferation of Vascular Smooth Muscle Cells.

The vascular smooth muscle cell proliferating effects of enoxaparin and twelve heparin fractions (six WSD3093 compounds with 15-25% anhydro structure, and six DIA2844 compounds with <7% anhydro structure) were determined in cultured human internal mammary artery smooth muscle cells. The total cell number in each culture plate was measured using a Coulter counter. Growth was calculated as the end of the 5% serum treatment (Day 7) minus cell number at the end of 0.1% serum treatment (Day 7). The effect of five concentrations (1, 3, 10, 30, 100 µg/ml) of the test substances on cell growth was examined. The growth inhibition during 3 days of treatment with enoxaparin and the heparin fractions was calculated.

Treatment of the cells with 5% serum caused an average of 4.6 fold increase in the cell growth over that with 1% serum. The cell growth was inhibited by 26% with unfractionated heparin. Similar inhibition was also observed with enoxaparin (100). Most of the 12 heparin fractions examined inhibited cell growth at the 100 µg/ml concentration. The inhibitions ranged from 3% (DIA <hexadecasaccharides) to 28% (DIA hexadecasaccharides). WSD dodecasaccharides and WSD hexadecasaccharides caused similar inhibition of the cell growth (26%). At lower chain length (6-10), the WSD compounds had less effect on cell growth, while at the higher chain length, the DIA compounds had less effect (except hexadecasaccharides). However, a pair wise comparison did not show any significant differences between the WSD and DIA compounds. When the dose-dependence of the effect were examined, WSD octasaccharides, <hexadecasaccharides and ≥hexadecasaccharides, and DIA ≥hexadecasaccharides showed significant dose dependence. The inhibition of cell growth by the DIA and WSD compounds at 100 µg/ml concentration are summarized in the Table below.

Table 1 Growth inhibition at 100 µg/ml concentration of test compound. Percent inhibition of growth in 5% serum.

	WSD3093	DIA2844
Hexasaccharides	9 ± 3*	16 ± 2*
Octasaccharides	18 ± 2*	21 ± 2*
Decasaccharides	11 ± 2*	15 ± 5*
Dodecasaccharides	26 ± 11*	10 ± 6*
<Hexadecasaccharides	19 ± 5*	3 ± 7
Hexadecasaccharides	26 ± 11*	28 ± 4*

* = P < 0.05 for cell number in test compound at 100 µg/ml vs 5% serum control

In a separate study, the dose dependence of the smooth muscle cell growth inhibitory effect was examined for DIA<hexadecasaccharides and WSD hexadecasaccharides fractions. At 1-100 µg/ml concentrations, both compounds had dose-dependent effects. At 100 µg/ml concentration, WSD <hexadecasaccharides caused significantly higher inhibition of cell growth (16±3%) than the DIA <hexadecasaccharides (3±3%).

In Vitro HIT Cross-reactivity of Chemical Synthetic Oligosaccharides.

Heparin-induced thrombocytopenia (HIT) results from the formation of heparin-dependent antiplatelet antibodies whose major target is a macromolecular complex associating heparin and platelet factor 4. The potential in vitro HIT cross reactivity of 12 heparin fragments (six DIA fractions with <7% 1, 6 anhydro structure, and six WSD fractions with 15-25% 1, 6 anhydro structure) were examined using platelet aggregation test (PAT). Platelet rich plasma was prepared by centrifugation to obtain a constant value for PAT analysis. Frozen HIT positive plasmas were used to test the *in vitro* cross reactivity of these compounds.

All the polysaccharides, except the WSD and DIA hexasaccharides showed an in vitro immune cross reactivity similar to enoxaparin. There were no significant differences between the WSD and DIA oligosaccharides regarding their ability to induce an immune cross reactivity with HIT antibodies. The *in vitro* cross reactivity of the heparin fractions in presence of various HIT plasma is shown in the Table below.

Compound	**% Cross Reactivity**
UFH	100
Pentasaccharide	0
Enoxaparin	72
Sodium Denaparoid	7
Enoxaparin Polysaccharides	69
<Hexadecasaccharide	
DIA 2844	64
WSD 3093	67
≥Hexasaccharide	
DIA 2844	68
WSD 3093	65
Hexasaccharide	
DIA 2844	0

WSD 3093	0.5
Octasacchahride	
DIA 2844	70
WSD 3093	68
Decasaccharide	
DIA 2844	70
WSD 3093	65
Dodecasaccharide	
DIA 2844	70
WSD 3093	72

Thus, a minimal chain length (>hexasaccharide) of the polysaccharides is required to have cross reactivity with HIT. The presence of varying amounts of the 1,6 anhydro structure in the polypeptide chain did not alter the cross reactivity.

Effects of Unfractionated Heparin, Low Molecular Weight Heparin, Synthetic Polysaccharides and Pentasaccharides on CD62-Mediated Platelet-Neutrophil Adhesion.

In some pathological conditions, such as inflammation, there is adhesion of activated platelets to leucocytes. This phenomenon is mediated by both P-selectin (CD62) and CD15 on polymorphonuclear leucocytes. Enoxaparin inhibits P-selectin mediated cell adhesion, and this effect is not related to its anti-Xa or anti-IIa ctivities. The in vitro effects of various polysaccharide fragments on P-selection-mediated leucocyte association in normal citrated human blood were examined using flow cytometry. All the polysaccharides were used at 10 and 100 µg/ml concentrations. In addition to unfractionated heparin, pentasaccharide (Arixtra), enoxaparin and 13 other compounds were studied.

A partial inhibition of the P-selectin-mediated platelet-leucocyte complex formation was observed in presence of the oligosaccharides. In the whole blood, both unfractionated heparin (UFH) and enoxaparin caused an inhibition of the complex formation. For enoxaparin, the inhibition was significant at both 10 and 100 µg/ml concentrations, while for UFH, the effect was significant only at 100 µg/ml. The pentasaccharide had no effect on P-selectin-mediated complex formation either in a purified or the whole blood milieus. The other oligosaccharides showed inhibitory effects only at the high concentration, and the effect was more pronounced in the purified milieu than in citrated whole blood. The inhibition caused by different oligosaccharide fractions, was dose-dependent. The inhibitory profiles of the hexadecasaccharide fractions were similar to that of enoxaparin, and no apparent differences were observed between the DIA (<7% 1,6 anhydro) and WSD (15-25% 1,6 anhydro) compounds. The mean inhibition of platelet-leucocyte complex formation (%) in whole citrated blood is summarized in the Table below.

Compound	% Inhibition (10 µg/ml)	% Inhibition (100 µg/ml)
UFH	2	20
Pentasaccharide	-	0
Enoxaparin	15	35
Enoxaparin Polysaccharides	13	28
<Hexadecasaccharide		
DIA 2844	10	36
WSD 3093	4	11

≥Hexasaccharide		
DIA 2844	10	37
WSD 3093	10	41
Hexasaccharide		
DIA 2844	10	34
WSD 3093	2	19
Octasaccharide		
DIA 2844	2	18
WSD 3093	4	13
Decasaccharide		
DIA 2844	7	22
WSD 3093	8	24
Dodecasaccharide		
DIA 2844	8	23
WSD 3093	15	47

SUMMARY AND EVALUATION:

Enoxaparin sodium is a low molecular weight heparin prepared by alkaline depolymerization of heparin benzyl ester obtained from porcine intestinal mucosa. Its structure is characterized by a 2-O-sulfo-4-enepyranosuric acid group at the non-reducing end and a 2-N,6-O-sulfo-D-glucosamine at the reducing end of the chain. In the current submission (Supplement #055), the sponsor has disclosed the presence of a 1,6 anhydro structure at the reducing end of enoxaparin molecule. The sponsor conducted several *in vitro* pharmacological studies with the two groups of oligosaccharides containing either <7% of the anhydro group (DIA) or 15-25% of the anhydro group (WSD). The following oligosaccharides were used in the study: hexasaccharides, octasaccharides, decasaccharides, dodecasaccharides, <hexadecasaccharides and ≥hexadecasaccharides.

The anti-FXa and anti-FIIa activities of six WSD groups of enoxaparin were compared with that of those of DIA counterparts with the same chain length. The anti-FXa and anti-FIIa activities of the DIA fractions were significantly higher than those of the WSD fractions, suggesting that the concentrations of the anhydro fraction in the polysaccharide chain can affect its anti-coagulant activity. The DIA hexadecasaccharides were also more potent than the WDS hexadecasaccharides in inhibiting thrombin generation in fresh platelet rich plasma. There were some differences in the hemostatic parameters (TT, PTT, prothrombin time and thrombin generation) between the DIA and the WSD fractions. The DIA hexadecasaccharides were more potent than WSD hexadecasaccharides in reducing TT, while the WSD decasaccharides caused more prolongation of APTT than the DIA counterparts. Differences in the cell proliferating effects were also observed between these two groups of compounds. No apparent differences in *in vitro* HIT cross reactivity and CD62-mediated platelet neutrophil adhesion were observed between the WSD and the DIA fractions. Thus, the concentration of the 1,6-anhydro derivative at the reducing end of the enoxaparin chain may affect the *in vitro* anticoagulant and antithrombotic potency of the molecule. This lacks *in vivo* confirmation.

RECOMMENDATIONS:

None.

Jasti B. Choudary, B.V.Sc., Ph.D. Date
Supervisory Pharmacologist, HFD-180

CC:

NDA
HFD- 180
HFD- 181/CSO
HFD- 180/Dr. Chakder
HFD- 180/Dr. Choudary
HFD-180/Dr. Justice
HFD-180/Dr. Korvick
HFD-180/Dr. Robie-Suh
HFD-180/Ms. Furness
HFD-180/Dr. Scroggs
HFD-180/Ms. Moore
HFD-180/Dr. AL-Hakim
HFD-180/Dr. Zhou
HFD-180/Ms. Dubeau
HFD-180/Mr. Strongin

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/s/

Jasti Choudary
7/22/04 03:06:14 PM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-055

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 09, 2004

FROM: Sushanta Chakder, Ph. D., Pharmacologist, HFD-180

SUBJECT: NDA 20-164, Labeling Supplements #— dated ———— and #055S dated March 22, 2004.

TO: NDA 20-164

In Supplement #055, the sponsor has disclosed the presence of a 1, 6 anhydro derivative at the reducing end the enoxaparin molecule. No specific pharmacology/toxicology information for the new molecule was submitted under this Supplement. Labels, submitted under Supplements #—and #055, had no changes in the preclinical portion of the labeling.

Sushanta Chakder, Ph.D. Date
Pharmacologist

Comments:

Jasti B. Choudary, B.V.Sc., Ph.D Date
Supervisory Pharmacologist

Cc:

NDA 20-164
HFD-180
HFD 181/CSO
HFD-180/Dr. Chakder
HFD-180/Dr. Choudary
HFD-180/Dr. Al-Hakim
HFD-180/Dr. Zhou
HFD 181/CPMS/Ms Dubeau

R/D Init.: J Choudary 6/9/04

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/s/

Sushanta Chakder
6/9/04 09:38:13 AM
PHARMACOLOGIST

Jasti Choudary
6/9/04 03:44:13 PM
PHARMACOLOGIST

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: July 22, 2004

From: Kathy M. Robie-Suh, M.D., Ph.D.
Medical Team Leader, Hematology, HFD-180

Subject: NDA 20-164/SCS-055, letter date 3/22/04
Response to FDA Approvable Letter dated November 13, 2003

To: NDA 20-164

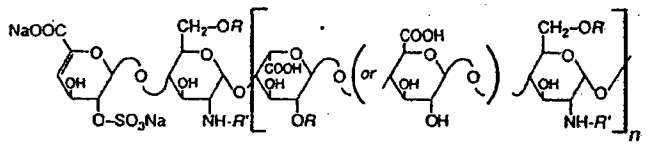
Lovenox (enoxaparin sodium) is a low molecular weight heparin derived from unfractionated heparin and approved for use as an anticoagulant for multiple clinical indications. In this chemistry supplement the sponsor has provided for additional characterization and structural information on enoxaparin sodium, the drug substance for Lovenox^{R} Injection. The supplement was originally submitted on July 11, 2003 and was found to be approvable pending submission of additional Chemistry, Manufacturing and Controls (CMC) information. An approvable letter was issued on November 13, 2003. In the current submission the sponsor responded to the deficiencies listed in the letter.

Labeling changes proposed by the sponsor include:

1. Under the **DESCRIPTION** section, revision of the last paragraph of text as follows:

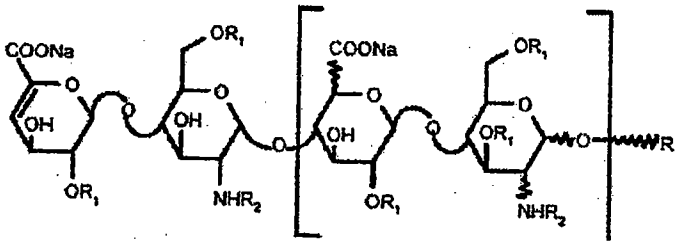
> Enoxaparin sodium is obtained by alkaline degradation~~depolymerization~~ of heparin benzyl ester derived from porcine intestinal mucosa. Its structure is characterized by a 2-O-sulfo-4-enepyranosuronic acid group at the non-reducing end and a 2-N,6-O-disulfo-D-glucosamine at the reducing end of the chain. About 20% (ranging between 15% and 25%) of the enoxaparin structure contains an 1,6, anhydro derivative on the reducing end of the polysaccharide 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% |

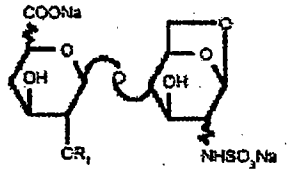
2. Under the **STRUCTURAL FORMULA** section, replacement of the current following structural formula:



R	R'	n
—H or —SO_3Na	—SO_3Na or —C(=O)—CH_3	3 to 20

with the following new structural formula:



R	X*= 15 to 25%		n= 0 to 20
	100 - X	H	n =1 to 21

*X = Percent of polysaccharide chain containing 1,6 anhydro derivative on the reducing end

Comments:
FDA Chemistry has reviewed the supplement and concluded: "The applicant provided satisfactory information regarding the activity, structural, dentermination, presence and content of 1,6 anhydro in enoxaparin sodium with the proposed content obtained from clinical and recent commercial batches. Therefore, the supplement is recommended for approval." (See Chemist's Review #2, A. Al-Hakim, 7/9/04).

The sponsor has provided information from *in vitro* studies on the effect of the 1,6 anhydro ring structure on anti Factor Xa and anti Factor IIa and other biological activities of enoxaparin. FDA Pharmacology Review (J. Choudary, 7/22/04) found that the concentration of the 1,6-anhydro derivative at the reducing end of the enoxaparin chain may affect the *in vitro* anticoagulant and antithrombotic potency of the molecule. However, there have been no studies done in animals or clinical studies done in humans to examine *in vivo* effects of enoxaparin fractions of varying 1,6 anhydro content.

From a clinical point-of-view, the application may be approved. However, it should be understood that while the information provided by the sponsor is adequate to support the desired labeling changes, the clinical importance of these additional chemical characteristics is unclear. The *in vitro* studies suggest that the 1,6 anhydro content may be important with regard to anticoagulant activity; however, no *in vivo* studies have been done to demonstrate correlation of the *in vitro* activities with *in vivo* measures or clinical outcomes. Evidence from non-clinical and/or clinical studies is needed to establish the clinical importance of this chemical characteristic.

cc:
NDA 20-164
HFD-180/RJustice
HFD-180/ JKorvick
HFD-180/KRobie-Suh
HFD-180/DMoore
HFD-180/JChoudary
HFD-180/SDoddapaneni
HFD-720/SGrosser
HFD-180/LZhou

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/s/

Kathy Robie-Suh
7/22/04 04:34:55 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-055

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-164/S-055

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

Dear Dr. Smith:

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-055
Date of supplement:	July 11, 2003
Date of receipt:	July 14, 2003

This supplemental application, submitted as "Supplement - Changes Being Effected" proposes the following change: additional characterization and new structural information on the active ingredient of the drug product, enoxaparin sodium.

Changes of the kind proposed cannot be put into effect immediately upon submission of the supplement. However, these changes may be implemented and distribution of the affected drug product may commence 30 days after FDA receives your submission.

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 August 15, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be January 14, 2003.

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 Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division 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
7/18/03 08:08:20 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-164/S-055

INFORMATION REQUEST LETTER

Aventis Pharmaceuticals
Attention: Shaler G. Smith, III, Ph. D.
Director and Regulatory Liaison
200 Crossing Boulevard
Bridgewater, NJ 08807-0890

Dear Dr. Smith:

Please refer to your July 11, 2003, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium, injection).

We are reviewing the chemistry, manufacturing and controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Provide test data and any related information to support the proposed changes for the following items described in your supplemental application:

1. The proposed modified structural formula for Lovenox®.

2. The proposed percentage ratio of the 1,6 anhydro ring (15-25%).

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

Sincerely,

Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal & Coagulation Drug Products, HFD-180
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Liang Zhou
7/30/03 11:50:24 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-164/S-055

Aventis Pharmaceuticals
Attention: Shaler G. Smith, III, Ph. D.
Director and Regulatory Liaison
200 Crossing Boulevard
Bridgewater, NJ 08807-0890

Dear Dr. Smith:

Please refer to your pending chemistry, manufacturing and control supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium, injection).

We also refer to our acknowledgment letter dated July 18, 2003, that stated the drug review classification for this application would be "Changes Being Effected" 30 days.

Upon further consideration of your application, we have concluded that this application should receive a prior approval review. The proposed change is to modify the current structural formula of the drug product. Therefore, these changes may not be implemented and distribution of the affected drug product may not commence 30 days after FDA received your submission. The user fee goal date is November 14, 2003.

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

Sincerely,

{See appended electronic signature page}

Diane Moore
Regulatory Health Project Manager
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Diane V. Moore
7/30/03 10:33:02 AM

July 8, 2004

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

NDA 20-164/S-055: Lovenox® (enoxaparin sodium injection)
Amendment: Labeling Information
Response to Agency Request

Dear Dr. Justice:

Please refer to a teleconference between Ms. Diane Moore, Regulatory Health Project Manager of your review division and Aventis Pharmaceuticals (Dr. Shaler Smith, Ms. Barbara Fanelli, and Dr. Dhiren Shah) on July 8, 2004 on the above-referenced Supplemental Application (S-055) to the New Drug Application (# 20-164) for Lovenox Injection. In the teleconference, Ms. Moore advised Aventis to electronically submit the proposed labeling revisions for Lovenox Injection from Supplement S-054 as an amendment to Supplement S-055.

The purpose of this electronic submission is to provide the proposed revisions to the USPI included within the latest version (April 2004) of the Prescribing Information (PI) for Lovenox Injection. This submission contains the following:

- A pdf file of the proposed labeling
- A MS Word file of the proposed labeling
- A pdf file of the annotated labeling (Summary document) showing the revisions with strike through and underlined text.

Aventis trusts that it has satisfactorily addressed the request form the Agency.

Should you have any question or comment on this submission, please contact Dr. Shaler Smith at (908) 304-6272 or in his absence, Dr. Steve Caffe at (908) 231- 5863.

Sincerely,

for D. Shah
7/8/2004

Dhiren N. Shah, Ph.D.
Director, Regulatory CMC

Enclosure

cc: Ms. Diane Moore (HFD-180)
Dr. Steve Caffe, Aventis Pharmaceuticals
Ms. Barbra Fanelli, Aventis Pharmaceuticals
Dr. Shaler Smith, Aventis Pharmaceuticals

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