CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-164/S-040, S-045, and S-046

Name: Lovenox® (Enoxaparin Sodium) Injection

Sponsor: Aventis Pharmaceuticals Products, Inc.

Approval Date: January 9, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-040, S-045, and S-046

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-040, S-045, and S-046

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Aventis Pharmaceuticals Products Inc.
Attention: Joseph A. Carrado, M.Sc., R.Ph.
Global Drug Regulatory Affairs
Global Therapeutic Area Head
Route 202-206
PO Box 6800
Bridgewater, NJ 08807-0800

Dear Mr. Carrado:

Please refer to your supplemental new drug applications dated August 23, 2000, received August 24, 2000 [S-040], and August 14, 2001, received August 15, 2001 [S-045 and S-046], 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 27, and December 1 and 29, 2000, and July 11, August 14, November 12 and 28, 2001, to S-040.

These supplemental new drug applications provide for the following:

> Supplement 040, submitted as a "Supplement - Changes Being Effected" (CBE) supplement, provides for the following changes: (1) in the WARNINGS section, the addition of a new subsection, titled "Prosthetic Heart Valves"; and (2) in the PRECAUTIONS section, the "Pregnancy" subsection,, the "*Non-teratogenic Effects*" sub-subsection, the addition of a third paragraph in the sub-subsection describing a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1 mg/kg bid) to prevent thromboembolism.
>
> Supplement 045, submitted as a prior approval supplement, provides for revisions to the ADVERSE REACTIONS section, the "Ongoing Safety Surveillance" subsection of the package insert, specifically updating the number of spinal epidural hematomas.
>
> Supplement 046, submitted as a prior approval supplement, provides for the revisions to the PRECAUTIONS section, the "Pregnancy" subsection of the package insert.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon final printed labeling (FPL) submitted August 14, 2001. Accordingly, these supplemental applications are approved effective on the date of this letter.

However, at the next printing, we request that you revise the Maison-Alfort PI as follows: in the ADVERSE REACTIONS section, the "Major bleeding Episodes Following Hip or Knee Replacement Surgery" table, information pertinent to that table should be the same column to facilitate continuity and ease of readability. As submitted, the table is located at the bottom of column 4 and at the top of column 5.

Submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

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

We request that the letter (draft submitted November 28, 2001) communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care within 30 days of receipt of this letter. Further, please submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Karen Oliver, Regulatory Project Manager, at (301) 827-7457.

Sincerely,

Victor F. C. Raczkowski, M.D., M.Sc.
Acting Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Joyce Korvick
1/9/02 10:51:18 AM
For Dr. Victor Raczkowski

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-040, S-045, and S-046

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-164/S-040

Aventis Phamaceuticals Products Inc.
C/O Quintiles, Inc.
Attention: Ms. Michelle Kliewer
Post Office Box 9708
Kansas City, MO 64134-0708

Dear Ms. Kliewer:

Please refer to your supplemental new drug application dated August 23, 2000, received August 24, 2000, 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 27, and December 1 and 18, 2000.

This "Changes Being Effected" supplemental new drug application proposes the following changes: (1) in the WARNINGS section, the addition of a new subsection, titled "Prosthetic Heart Valves", to read: "

(see PRECAUTIONS: Pregnancy)."; and (2) in the PRECAUTIONS section, the "Pregnancy" subsection, the addition of a third paragraph in the subsection, to read: "In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1 mg/kg bid) to

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

1. In the PRECAUTIONS section, in the new subsection entitled "Prosthetic Heart Valves", revise the subsection to read as follows:

Prosthetic Heart Valves:

[redacted]

(see PRECAUTIONS: Pregnancy).

2. In the PRECAUTIONS section, the "Pregnancy" subsection, the "*Non-teratogenic Effects*" sub-subsection, the second, stand-alone paragraph, in the sub-subsection should be revised to read as follows:

> In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1mg/kg bid) to [redacted]

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 paper copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Further, we recommend that you issue a "Dear Doctor" letter to inform physicians of the important safety information regarding the use of enoxaparin in patients with prosthetic heart valves, particularly in pregnant women. Please submit the draft "Dear Doctor" letter to the Agency for comment prior to issuance.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form,

not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

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

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. 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.

If you have any questions, call Karen Oliver, Regulatory Project Manager, at (301) 827-7457.

Sincerely,

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

/s/

Lilia Talarico
12/21/00 04:15:17 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-040, S-045, and S-046

LABELING

LOVENOX® (enoxaparin sodium) Injection

Labeling: SLR-07 Rev. 07/01
50063316
NDA No: 20-164 Rec'd 8-14-01
Reviewed by: KOliver 8/07 Rx only
AP 01/09/02

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**).

50063316
Rev. 07/01

LOVENOX® (enoxaparin sodium) Injection

FPO Bar Code

DESCRIPTION

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

Lovenox Injection is available in two concentrations:

1 100 mg per mL of Water for Injection

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

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

2 150 mg per mL of Water for Injection

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

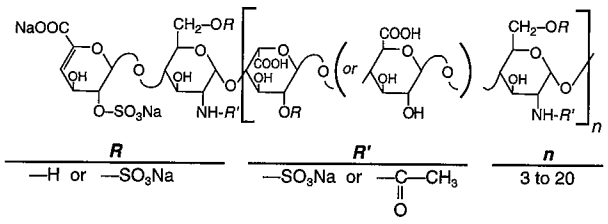
Lovenox Injection 150 mg/mL Concentration contains 15 mg enoxaparin sodium (or appropriate anti-Factor Xa activity of 1500 IU [with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard]) per 0.1 mL Water for Injection.

The solutions are preservative-free and intended for use only as a single-dose injection. (See **DOSAGE AND ADMINISTRATION** and **HOW SUPPLIED** for dosage unit descriptions.) The pH of the injection is 5.5 to 7.5. Nitrogen is used in the headspace to inhibit oxidation.

Enoxaparin is obtained by alkaline degradation of heparin benzyl ester derived from porcine intestinal mucosa. Its structure is characterized by a 2-O-sulfo-4-enepyranosuronic acid group at the non-reducing end and a 2-N,6-O-disulfo-D-glucosamine at the reducing end of the chain. The substance is the sodium salt. The average molecular weight is about 4500 daltons. The molecular weight distribution is:

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

STRUCTURAL FORMULA



CLINICAL PHARMACOLOGY

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

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

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

Apparent clearance and A_{max} derived from anti-Factor Xa values following single and multiple SC dosing in elderly subjects were close to those observed in young subjects. Following once a day SC dosing of 40 mg enoxaparin, the Day 10 mean area under anti-Factor Xa activity versus time curve (AUC) was approximately 15% greater than the mean Day 1 AUC value. In subjects with moderate renal impairment (creatinine clearance 30 to 80 mL/min), anti-Factor Xa CL/F values were similar to those in healthy subjects. However, mean CL/F values of subjects with severe renal impairment (creatinine clearance <30 mL/min), were approximately 30% lower than the mean CL/F value of control group subjects. (See **PRECAUTIONS.**)

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

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

	Concentration	Anti-Xa	Anti-IIa	Heptest	aPTT
Amax (IU/mL or Δ sec)	100 mg/mL	1.37 (±0.23)	0.23 (±0.05)	104.5 (±16.6)	19.3 (±4.7)
	200 mg/mL	1.45 (±0.22)	0.26 (±0.05)	110.9 (±17.1)	22 (±6.7)
	90% CI	102-110%		102-111%	
tmax** (h)	100 mg/mL	3 (2-6)	4 (2-5)	2.5 (2-4.5)	3 (2-4.5)
	200 mg/mL	3.5 (2-6)	4.5 (2.5-6)	3.3 (2-5)	3 (2-5)
AUC (ss) (h*IU/mL or h* Δ sec)	100 mg/mL	14.26 (±2.93)	1.54 (±0.61)	1321 (±219)	
	200 mg/mL	15.43 (±2.96)	1.77 (±0.67)	1401 (±227)	
	90% CI	105-112%		103-109%	

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

CLINICAL TRIALS

Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery in Patients at Risk for Thromboembolic Complications: Abdominal surgery patients at risk include those who are over 40 years of age, obese, undergoing surgery under general anesthesia lasting longer than 30 minutes or who have additional risk factors such as malignancy or a history of deep vein thrombosis or pulmonary embolism.

In a double-blind, parallel group study of patients undergoing elective cancer surgery of the gastrointestinal, urological, or gynecological tract, a total of 1116 patients were enrolled in the study, and 1115 patients were treated. Patients ranged in age from 32 to 97 years (mean age 67 years) with 52.7% men and 47.3% women. Patients were 98% Caucasian, 1.1% Black, 0.4% Oriental, and 0.4% others. Lovenox Injection 40 mg SC, administered once a day, beginning 2 hours prior to surgery and continuing for a maximum of 12 days after surgery, was comparable to heparin 5000 U every 8 hours SC in reducing the risk of deep vein thrombosis (DVT). The efficacy data are provided below.

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

	Dosing Regimen	
Indication	**Lovenox Inj.** 40 mg q.d. SC n (%)	**Heparin** 5000 U q8h SC 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	
Indication	**Lovenox Inj.** 40 mg q.d. SC n (%)	**Heparin** 5000 U q8h SC 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	
Indication	**Lovenox Inj.** 30 mg q12h SC n (%)	**Placebo** q12h SC 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		
Indication	**10 mg q.d. SC** n (%)	**30 mg q12h SC** n (%)	**40 mg q.d. SC** 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	
Indication	**Lovenox Inj.** 30 mg q12h SC n (%)	**Placebo** q12h SC 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	
Indication (Post-Discharge)	**Lovenox Inj.** 40 mg q.d. SC n (%)	**Placebo** q.d. SC n (%)
All Treated Extended Prophylaxis Patients	90 (100)	89 (100)
Treatment Failures		
Total DVT (%)	6 (7)[1] (95% CI[2]: 3 to 14)	18 (20) (95% CI: 12 to 30)
Proximal DVT (%)	5 (6)[3] (95% CI: 2 to 13)	7 (8) (95% CI: 3 to 16)

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

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

Prophylaxis of Deep Vein Thrombosis (DVT) In Medical Patients with Severely Restricted Mobility During Acute Illness: In a double blind multicenter, parallel group study, Lovenox Injection 20 mg or 40 mg once a day SC was compared to placebo in the prophylaxis of DVT in medical patients with severely restricted mobility during acute illness (defined as walking distance of <10 meters for ≤3 days). This study included patients with heart failure (NYHA Class III or IV); acute respiratory failure or complicated chronic respiratory insufficiency (not requiring ventilatory support): acute infection (excluding septic shock); or acute rheumatic disorder [acute lumbar or sciatic pain, vertebral compression (due to osteoporosis or tumor), acute arthritic episodes of the lower extremities]. A total of 1102 patients were enrolled in the study, and 1073 patients were treated. Patients ranged in age from 40 to 97 years (mean age 73 years) with equal proportions of men and women. Treatment continued for a maximum of 14 days (median duration 7 days). When given at a dose of 40 mg once a day SC, Lovenox Injection significantly reduced the incidence of DVT as compared to placebo. The efficacy data are provided below.

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

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

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

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

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

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

	Dosing Regimen[1]			
Indication	**Lovenox Inj.** 1 mg/kg q12h SC n (%)	**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)

	Dosing Regimen[1]			
Indication	**Lovenox Inj.** 1 mg/kg q12h SC n (%)	**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]		
Indication	**Lovenox Inj.** 1.5 mg/kg q.d. SC n (%)	**Lovenox Inj.** 1 mg/kg q12h SC n (%)	**Heparin** aPTT Adjusted i.v. Therapy 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]	
Indication	**Lovenox Inj.** 1 mg/kg q12h SC n (%)	**Heparin** aPTT Adjusted i.v. Therapy n (%)
All Treated DVT Patients	247 (100)	254 (100)
Patient Outcome Total VTE[2] (%)	13 (5.3)[3]	17 (6.7)
DVT Only (%)	11 (4.5)	14 (5.5)
Proximal DVT (%)	10 (4.0)	12 (4.7)
PE (%)	2 (0.8)	3 (1.2)

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

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS

Lovenox Injection is not intended for intramuscular administration.
Lovenox Injection cannot be used interchangeably (unit for unit) with heparin or other low molecular weight heparins as they differ in manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units, and dosage. Each of these medicines has its own instructions for use.
Lovenox Injection should be used with extreme caution in patients with a history of heparin-induced thrombocytopenia.
Hemorrhage: Lovenox Injection, like other anticoagulants, should be used with extreme caution in conditions with increased risk of hemorrhage, such as bacterial endocarditis, congenital or acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disease, hemorrhagic stroke, or shortly after brain, spinal, or ophthalmological surgery, or in patients treated concomitantly with platelet inhibitors.
Cases of epidural or spinal hematomas have been reported with the associated use of Lovenox Injection and spinal/epidural anesthesia or spinal puncture resulting in long-term or permanent paralysis. The risk of these events is higher with the use of post-operative indwelling epidural catheters or by the concomitant use of additional drugs affecting hemostasis such as NSAIDs (see boxed WARNING; ADVERSE REACTIONS, Ongoing Safety Surveillance; and PRECAUTIONS, Drug Interactions).
Major hemorrhages including retroperitoneal and intracranial bleeding have been reported. Some of these cases have been fatal.
Bleeding can occur at any site during therapy with Lovenox Injection. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.
Thrombocytopenia: Thrombocytopenia can occur with the administration of Lovenox Injection.
Moderate thrombocytopenia (platelet counts between 100,000/mm^3 and 50,000/mm^3) occurred at a rate of 1.3% in patients given Lovenox Injection, 1.2% in patients given heparin, and 0.7% in patients given placebo in clinical trials. Platelet counts less than 50,000/mm^3 occurred at a rate of 0.1% in patients given Lovenox Injection, in 0.2% of patients given heparin, and 0.4% of patients given placebo in the same trials.
Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm^3, Lovenox Injection should be discontinued. Cases of heparin-induced thrombocytopenia with thrombosis have also been observed in clinical practice. Some of these cases were complicated by organ infarction, limb ischemia, or death.
Prosthetic Heart Valves: The use of Lovenox Injection is not recommended for thromboprophylaxis in patients with prosthetic heart valves. Cases of prosthetic heart valve thrombosis have been reported in patients with prosthetic valves who have received enoxaparin for thromboprophylaxis. Some of these cases were pregnant women in whom thrombosis led to maternal deaths and fetal deaths. Pregnant women with prosthetic heart valves may be at higher risk for thromboembolism **(see PRECAUTIONS: Pregnancy).**

PRECAUTIONS

General: Lovenox Injection should not be mixed with other injections or infusions.
Lovenox Injection should be used with care in patients with a bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration, diabetic retinopathy, and hemorrhage. Elderly patients and patients with renal insufficiency may show delayed elimination of enoxaparin. Lovenox Injection should be used with care in these patients. Adjustment of enoxaparin sodium dose may be considered for low weight (<45 kg) patients and/or for patients with severe renal impairment (creatinine clearance <30 mL/min).
If thromboembolic events occur despite Lovenox Injection prophylaxis, appropriate therapy should be initiated.
Laboratory Tests: Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with Lovenox Injection. When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of Lovenox Injection activity and, therefore, unsuitable for monitoring. Anti-Factor Xa may be used to monitor the anticoagulant effect of Lovenox Injection in patients with significant renal impairment. If during Lovenox Injection therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa levels may be used to monitor the anticoagulant effects of Lovenox Injection (see **CLINICAL PHARMACOLOGY: Pharmacodynamics**).
Drug Interactions: Unless really needed, agents which may enhance the risk of hemorrhage should be discontinued prior to initiation of Lovenox Injection therapy. These agents include medications such as: anticoagulants, platelet inhibitors including acetylsalicylic acid, salicylates, NSAIDs (including ketorolac tromethamine), dipyridamole, or sulfinpyrazone. If co-administration is essential, conduct close clinical and laboratory monitoring (see **PRECAUTIONS: Laboratory Tests**).
Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of enoxaparin. Enoxaparin was not mutagenic in *in vitro* tests, including the Ames test, mouse lymphoma cell forward mutation test, and human lymphocyte chromosomal aberration test, and the *in vivo* rat bone marrow chromosomal aberration test. Enoxaparin was found to have no effect on fertility or reproductive performance of male and female rats at SC doses up to 20 mg/kg/day or 141 mg/m^2/day. The maximum human dose in clinical trials was 2.0 mg/kg/day or 78 mg/m^2/day (for an average body weight of 70 kg, height of 170 cm, and body surface area of 1.8 m^2).
Pregnancy: *Teratogenic Effects:* Pregnancy Category B: Teratology studies have been conducted in pregnant rats and rabbits at SC doses of enoxaparin up to 30 mg/kg/day or 211 mg/m^2/day and 410 mg/m^2/day, respectively. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
There have been reports of congenital anomalies in infants born to women who received enoxaparin during pregnancy including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia, and cardiac defect. A cause and effect relationship has not been established nor has the incidence been shown to be higher than in the general population.
Non-teratogenic Effects: There have been post-marketing reports of fetal death when pregnant women received Lovenox Injection. Causality for these cases has not been determined. Pregnant women receiving anti-coagulants, including enoxaparin, are at increased risk for bleeding. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women receiving enoxaparin should be carefully monitored. Pregnant women and women of child-bearing potential should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.
In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 7 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. There are postmarketing reports of prosthetic valve thrombosis in pregnant women with prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. These events resulted in maternal death or surgical interventions. The use of Lovenox Injection is not recommended for thromboprophylaxis in pregnant women with prosthetic heart valves (see **WARNINGS: Prosthetic Heart Valves).**
Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Lovenox Injection is administered to nursing women.
Pediatric Use: Safety and effectiveness of Lovenox Injection in pediatric patients have not been established.
Geriatric Use: Over 2800 patients, 65 years and older, have received Lovenox Injection in pivotal clinical trials. The efficacy of Lovenox Injection in the elderly (≥65 years) was similar to that seen in younger patients (<65 years). The incidence of bleeding complications was similar between elderly and younger patients when 30 mg every 12 hours or 40 mg once a day doses of Lovenox Injection were employed. The incidence of bleeding complications was higher in elderly patients as compared to younger patients when Lovenox Injection was administered at doses of 1.5 mg/kg once a day or 1 mg/kg every 12 hours. The risk of Lovenox Injection-associated bleeding increased with age. Serious adverse events increased with age for patients receiving Lovenox Injection. Other clinical experience (including postmarketing surveillance and literature reports) has not revealed additional differences in the safety of Lovenox Injection between elderly and younger patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised. Monitoring of geriatric patients with low body weight (<45 kg) and those predisposed to decreased renal function should be considered. (see **CLINICAL PHARMACOLOGY** and **General** and **Laboratory Tests** subsections of **PRECAUTIONS**)

ADVERSE REACTIONS

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

Major Bleeding Episodes Following Abdominal and Colorectal Surgery[1]

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

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

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

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

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

	Dosing Regimen	
Indication	**Lovenox Inj.[1]** 1 mg/kg q12h SC	**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 5 (2%)	n = 559 9 (2%)	n = 554 9 (2%)

[1] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal, intraocular, and intracranial hemorrhages were always considered major.
[2] All patients also received warfarin sodium (dose-adjusted according to PT to achieve an INR of 2.0 to 3.0) commencing within 72 hours of Lovenox Injection or standard heparin therapy and continuing for up to 90 days.

Thrombocytopenia: see **WARNINGS: Thrombocytopenia**.
Elevations of Serum Aminotransferases: Asymptomatic increases in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels greater than three times the upper limit of normal of the laboratory reference range have been reported in up to 6.1% and 5.9% of patients, respectively, during treatment with Lovenox Injection. Similar significant increases in aminotransferase levels have also been observed in patients and healthy volunteers treated with heparin and other low molecular weight heparins. Such elevations are fully reversible and are rarely associated with increases in bilirubin.
Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, elevations that might be caused by drugs like Lovenox Injection should be interpreted with caution.
Local Reactions: Mild local irritation, pain, hematoma, ecchymosis, and erythema may follow SC injection of Lovenox Injection.
Other: Other adverse effects that were thought to be possibly or probably related to treatment with Lovenox Injection, heparin, or placebo in clinical trials with patients undergoing hip or knee replacement surgery, abdominal or colorectal surgery, or treatment for DVT and that occurred at a rate of at least 2% in the Lovenox Injection group, are provided below.

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

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

[1] Excluding unrelated adverse events.

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

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

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

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

	Dosing Regimen	
Adverse Event	**Lovenox Inj.** 40 mg q.d. SC n = 360 %	**Placebo** q.d. SC n = 362 %
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	
Adverse Event	**Lovenox Inj.** 1 mg/kg q12h SC n = 1578 n (%)	**Heparin** aPTT Adjusted i.v. Therapy n = 1529 n (%)
Atrial fibrillation	11 (0.70)	3 (0.20)
Heart failure	15 (0.95)	11 (0.72)
Lung edema	11 (0.70)	11 (0.72)
Pneumonia	13 (0.82)	9 (0.59)

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

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

[1] Excluding unrelated adverse events.

Ongoing Safety Surveillance: Since 1993, there have been over 80 reports of epidural or spinal hematoma formation with concurrent use of Lovenox Injection and spinal/epidural anesthesia or spinal puncture. The majority of patients had a post-operative indwelling epidural catheter placed for analgesia or received additional drugs affecting hemostasis such as NSAIDs. Many of the epidural or spinal hematomas caused neurologic injury, including long-term or permanent paralysis. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.
Other Ongoing Safety Surveillance Reports: local reactions at the injection site (i.e., skin necrosis, nodules, inflammation, oozing), systemic allergic reactions (i.e., pruritus, urticaria, anaphylactoid reactions), vesiculobullous rash, purpura, thrombocytosis, and thrombocytopenia with thrombosis (see **WARNINGS, Thrombocytopenia**). Very rare cases of hyperlipidemia have been reported, with one case of hyperlipidemia, with marked hypertriglyceridemia, reported in a diabetic pregnant woman; causality has not been determined.

OVERDOSAGE

Symptoms/Treatment: Accidental overdosage following administration of Lovenox Injection may lead to hemorrhagic complications. Injected Lovenox Injection may be largely neutralized by the slow i.v. injection of protamine sulfate (1% solution). The dose of protamine sulfate should be equal to the dose of Lovenox Injection injected: 1 mg protamine sulfate should be administered to neutralize 1 mg Lovenox Injection. A second infusion of 0.5 mg protamine sulfate per 1 mg of Lovenox Injection may be administered if the aPTT measured 2 to 4 hours after the first infusion remains prolonged. However, even with higher doses of protamine, the aPTT may remain more prolonged than under normal conditions found following administration of heparin. In all cases, the anti-Factor Xa activity is never completely neutralized (maximum about 60%). Particular care should be taken to avoid overdosage with protamine sulfate. Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulfate, it should be given only when resuscitation techniques and treatment of anaphylactic shock are readily available. For additional information consult the labeling of Protamine Sulfate Injection, USP, products.
A single SC dose of 46.4 mg/kg enoxaparin was lethal to rats. The symptoms of acute toxicity were ataxia, decreased motility, dyspnea, cyanosis, and coma.

DOSAGE AND ADMINISTRATION

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

Note: Lovenox Injection is available in two concentrations:

1 100 mg/mL Concentration: 30 mg / 0.3 mL ampules, 30 mg / 0.3 mL and 40 mg / 0.4 mL prefilled single-dose syringes, 60 mg / 0.6 mL, 80 mg / 0.8 mL, and 100 mg / 1 mL prefilled, graduated, single-dose syringes.
2 150 mg/mL Concentration: 120 mg / 0.8 mL and 150 mg / 1 mL prefilled, graduated, single-dose syringes.

Adult Dosage:
Abdominal Surgery: In patients undergoing abdominal surgery who are at risk for thromboembolic complications, the recommended dose of Lovenox Injection is **40 mg once a day** administered by SC injection with the initial dose given 2 hours prior to surgery. The usual duration of administration is 7 to 10 days; up to 12 days administration has been well tolerated in clinical trials.
Hip or Knee Replacement Surgery: In patients undergoing hip or knee replacement surgery, the recommended dose of Lovenox Injection is **30 mg every 12 hours** administered by SC injection. Provided that hemostasis has been established, the initial dose should be given 12 to 24 hours after surgery. For hip replacement surgery, a dose of **40 mg once a day** SC, given initially 12 (±3) hours prior to surgery, may be considered. Following the initial phase of thromboprophylaxis in hip replacement surgery patients, continued prophylaxis with Lovenox Injection 40 mg once a day administered by SC injection for 3 weeks is recommended. The usual duration of administration is 7 to 10 days; up to 14 days administration has been well tolerated in clinical trials.
Medical Patients During Acute Illness: In medical patients at risk for thromboembolic complications due to severely restricted mobility during acute illness, the recommended dose of Lovenox Injection is **40 mg once a day** administered by SC injection. The usual duration of administration is 6 to 11 days; up to 14 days of Lovenox Injection has been well tolerated in the controlled clinical trial.
Unstable Angina and Non-Q-Wave Myocardial Infarction: In patients with unstable angina or non-Q-wave myocardial infarction, the recommended dose of Lovenox Injection is **1 mg/kg** administered SC **every 12 hours** in conjunction with oral aspirin therapy (100 to 325 mg once daily). Treatment with Lovenox Injection should be prescribed for a minimum of 2 days and continued until clinical stabilization. To minimize the risk of bleeding following vascular instrumentation during the treatment of unstable angina, adhere precisely to the intervals recommended between Lovenox Injection doses. The vascular access sheath for instrumentation should remain in place for 6 to 8 hours following a dose of Lovenox Injection. The next scheduled dose should be given no sooner than 6 to 8 hours after sheath removal. The site of the procedure should be observed for signs of bleeding or hematoma formation. The usual duration of treatment is 2 to 8 days; up to 12.5 days of Lovenox Injection has been well tolerated in clinical trials.
Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism: In **outpatient treatment**, patients with acute deep vein thrombosis without pulmonary embolism who can be treated at home, the recommended dose of Lovenox Injection is **1 mg/kg every 12 hours** administered SC. In **inpatient (hospital) treatment**, patients with acute deep vein thrombosis with pulmonary embolism or patients with acute deep vein thrombosis without pulmonary embolism (who are not candidates for outpatient treatment), the recommended dose of Lovenox Injection is **1 mg/kg every 12 hours** administered SC **or 1.5 mg/kg once a day** administered SC at the same time every day. In both outpatient and inpatient (hospital) treatments, warfarin sodium therapy should be initiated when appropriate (usually within 72 hours of Lovenox Injection). Lovenox Injection should be continued for a minimum of 5 days and until a therapeutic oral anticoagulant effect has been achieved (International Normalization Ratio 2.0 to 3.0). The average duration of administration is 7 days; up to 17 days of Lovenox Injection administration has been well tolerated in controlled clinical trials.
Administration: Lovenox Injection is a clear, colorless to pale yellow sterile solution, and as with other parenteral drug products, should be inspected visually for particulate matter and discoloration prior to administration.
When using Lovenox Injection ampules, to assure withdrawal of the appropriate volume of drug, the use of a tuberculin syringe or equivalent is recommended.
Lovenox Injection is administered by SC injection. It must not be administered by intramuscular injection. Lovenox Injection is intended for use under the guidance of a physician. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up, as necessary. Proper training in subcutaneous injection technique (with or without the assistance of an injection device) should be provided.
Subcutaneous Injection Technique: Patients should be lying down and Lovenox Injection administered by deep SC injection. To avoid the loss of drug when using the 30 and 40 mg prefilled syringes, do not expel the air bubble from the syringe before the injection. Administration should be alternated between the left and right anterolateral and left and right posterolateral abdominal wall. The whole length of the needle should be introduced into a skin fold held between the thumb and forefinger; the skin fold should be held throughout the injection. To minimize bruising, do not rub the injection site after completion of the injection. An automatic injector, Lovenox EasyInjector™, is available for patients to administer Lovenox Injection packaged in 30 mg and 40 mg prefilled syringes. Please see directions accompanying the Lovenox EasyInjector™ automatic injection device.

HOW SUPPLIED

Lovenox® (enoxaparin sodium) Injection is available in two concentrations:

100 mg/mL Concentration

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

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

150 mg/mL Concentration

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

[1] Strength represents the number of milligrams of enoxaparin sodium in Water for Injection. **Lovenox Injection** 120 and 150 mg graduated prefilled syringes contain **15 mg enoxaparin sodium per 0.1 mL** Water for Injection.
[2] Approximate anti-Factor Xa activity based on reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard.
[3] Each **Lovenox Injection** graduated prefilled syringe is affixed with a 27 gauge x 1/2 inch needle.

Store at Controlled Room Temperature, 15-25°C (59-77°F) [see USP].
Keep out of the reach of children.
Lovenox Injection prefilled and graduated prefilled syringes manufactured in France.
Lovenox Injection ampules manufactured in England.
Aventis Pharmaceuticals Products Inc.
BRIDGEWATER, NJ 08807
Prescribing information as of July 2001.

50063316

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-040, S-045, and S-046

LABELING REVIEWS

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-164/S-040

Name of Drug: Lovenox® (enoxaparin sodium) Injection

Sponsor: Aventis Pharmaceuticals Products Inc.

Material Reviewed

Submission Date(s): August 23, 2000

Receipt Date(s): August 24, 2000

Background and Summary Description: Supplement 040, submitted as a "Supplement - Changes Being Effected" (CBE) supplement, provides for the following changes: (1) in the WARNINGS section, the addition of a new subsection, titled "Prosthetic Heart Valves", to read:

[redacted]

; and (2) in the PRECAUTIONS section, the "Pregnancy" subsection, the addition of a third paragraph in the subsection, to read: "In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1 mg/kg bid) to

[redacted]

On December 18, 2000, the sponsor submitted revised final printed labeling (FPL), incorporating the labeling changes approved November 17, 2000 in S-036. Since the CBE supplement 040 provided for FPL in the original submission (08/23/00), the revised FPL submitted December 18, 2000, will be coded as a "Correspondence" and will not be reviewed as FPL for this supplement.

Review

PACKAGE INSERT

The final printed labeling (FPL) for the package inserts, submitted August 23, 2000, identified as "50057513 Rev. 7/00 508539E" (Maison Alfort) and "50057514 Rev. 7/00" (Dagenham), was compared to the package insert text enclosed in the November 17, 2000 approval letter for S-036. The submitted FPL does not incorporate the text approved in S-036. Therefore, only the labeling changes provided for in S-040 will be reviewed.

1. In the WARNINGS section, a new subsection titled "Prosthetic heart valves" was added to read:

Prosthetic heart valves:

[redacted]

(see PRECAUTIONS: Pregnancy).

This additional information was reviewed by the Medical Officer, Dr. Min Lu (see Medical Officer's Review dated December 13, 2000) and it is UNACCEPTABLE. The subsection should be revised to read as follows:

Prosthetic Heart Valves:

[redacted]

(see PRECAUTIONS: Pregnancy).

2. In the PRECAUTIONS section, the "Pregnancy" subsection, the "*Non-teratogenic Effects*" sub-subsection, the following information was added as the second, stand-alone paragraph, in the sub-subsection to read:

In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1mg/kg bid) to

[redacted]

This additional information was reviewed by the Medical Officer, Dr. Min Lu (see Medical Officer's Review dated December 13, 2000) and it is UNACCEPTABLE. The subsection should be revised to read as follows:

In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1mg/kg bid) to

[redacted]

Conclusions

1. The following changes are UNACCEPTABLE: 1. and 2.

2. An approvable letter should be issued.

Karen Oliver, RN, MSN
Regulatory Health Project Manager

Lilia Talarico, M.D.
Division Director

cc:
Original NDA 20-164/S-040
HFD-180/Div. Files
HFD-180/L.Talarico
HFD-180/K.Robie-Suh
HFD-180/M.Lu
HFD-180/K.Oliver
R/D init: K.Robie-Suh 12/20/00
R/D init: L.Talarico 12/20/00
draft: KO/December 19, 2000
final: KO/12/21/00/c:\data\mydocuments\NDA20164-S-040-12-19-00-labrev

CSO REVIEW

/s/

Karen Oliver
12/21/00 03:02:59 PM
CSO

Lilia Talarico
12/21/00 04:14:14 PM
MEDICAL OFFICER

Division of Gastrointestinal & Coagulation Drug Products
CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-164/S-040, 045, and 046

Name of Drug: Lovenox® (enoxaparin sodium) Injection

Sponsor: Aventis Pharmaceuticals Products Inc.

Material Reviewed

Submission Date(s): August 14, 2001

Receipt Date(s): August 15, 2001

Background and Summary Description

Supplement 040: Submitted August 23, 2000 as a "Supplement - Changes Being Effected" (CBE) supplement, provides for the following changes: (1) in the WARNINGS section, the addition of a new subsection, titled "Prosthetic Heart Valves", to read: "

[redacted]

(see PRECAUTIONS: Pregnancy)."; and
(2) in the PRECAUTIONS section, the "Pregnancy" subsection, the addition of a third paragraph in the subsection, to read: "In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1 mg/kg bid) to

[redacted]

An approvable letter was issued on December 21, 2000.

Supplement 045: Submitted August 14, 2001 as a prior approval supplement, provides for the following: revisions to the ADVERSE REACTIONS section, the "Ongoing Safety Surveillance" subsection of the package insert, specifically updating the number of spinal epidural hematomas.

Supplement 046: Submitted August 14, 2001 as a prior approval supplement, provides for the following: revisions to the PRECAUTIONS section, the "Pregnancy" subsection of the package insert.

The August 14, 2001 submission contains identical final printed labeling for S-040, 045, and 046. Therefore, a single review will identify the changes to the labeling, specific to each supplement.

Review

PACKAGE INSERT (PI)

The final printed labeling (FPL) for the package inserts, submitted August 14, 2001 identified as "50063316 Rev. 07/01" (Maison-Alfort) and "50063181 Rev. 07/01" (Dagenham), was compared to the currently approved package inserts, identified as "50063314 Rev. 05/01A" (Maison-Alfort) and "50062180 Rev. 05/01A" (Dagenham); the revisions requested in the December 12, 2000 approvable letter for S-040; the changes requested in the January 4, 2001 Agency letter to the PRECAUTIONS section, the "Pregnancy" subsection of the PI, and changes requested in the January 30, 2001 Agency letter to the PRECAUTIONS section, the "Ongoing Safety Surveillance" subsection of the PI. The FPL is identical except for the following:

1. The identification numbers have changed.

   These changes are ACCEPTABLE.

2. For both the Maison-Alfort and Dagenham PIs, the running heads at the top of each have been moved from the right edge of the column to the center of the column.

   This change is ACCEPTABLE.

3. For the Maison-Alfort PI, the bar code, name of the drug, and identification number positioned vertically in the margin to the left of the DESCRIPTION section (located near the top of column 1) has been re-positioned vertically in the margin to the left of the CLINCAL TRIALS section text (located near the bottom of column 1).

   This change is ACCEPTABLE.

4. For the Maison-Alfort PI, the ADVERSE REACTIONS section, the "Major Bleeding Episodes Following Hip or Knee Replacement Surgery" table (at the bottom of column 4), information pertinent to the table is separated from the table, as it is located at the top of column 5). The information at the top of column 5 includes the following:

   > 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.

This is UNACCEPTABLE. The sponsor should be requested to revise the PI at the next printing such that information related to a table is contained in a single column of text.

5. **Supplement 040** provides for changes in the WARNINGS section, the "Prosthetic Heart Valves" subsection as follows:

As requested in the December 21, 2001 approvable letter for S-040:

PRECAUTIONS section:

Prosthetic Heart Valves:

[redacted]

(see PRECAUTIONS: Pregnancy).

Revised, as requested in the January 4, 2001 Agency letter, to read:

PRECAUTIONS section:

Prosthetic Heart Valves:

[redacted]

[(see **PRECAUTIONS: Pregnancy).**

Revised, as agreed upon in a March 2, 2001 facsimile, and submitted for Agency review on July 11, 2001, to read:

WARNINGS section:

Prosthetic Heart Valves: The use of Lovenox Injection is not recommended for thromboprophylaxis in patients with prosthetic heart valves. Cases of prosthetic heart valve thrombosis have been reported in patients with prosthetic valves who have received enoxaparin for thromboprophylaxis. Some of these cases were pregnant women in whom thrombosis led to maternal deaths and fetal deaths. Pregnant women with prosthetic heart valves may be at higher risk for thromboembolism **(see PRECAUTIONS: Pregnancy).**

These revisions, reviewed by Dr. Kathy Robie-Suh on July 19, 2001 (SLR-040 submission of 07/11/01), are ACCEPTABLE.

6. **Supplement 040** provides for changes in the PRECAUTIONS section, the "Pregnancy" subsection, the "*Non-teratogenic Effects*" sub-subsection. The second, stand-alone paragraph, in the sub-subsection has been changed:

As requested in the December 21, 2001 approvable letter for S-040:

In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1mg/kg bid) to

[ ]

Revised, as requested in the January 4, 2001 Agency letter, and agreed upon in a March 2, 2001 facsimile, to read:

> In a clinical study of pregnant women with prosthetic valves given enoxaparin (1mg/kg bid) to reduce the risk of thromboembolism, 2 of 7 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. There are ——— reports of ——— prosthetic valve thrombosis in pregnant women with prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. These events [ ]

Submitted July 11, 2001 and re-submitted August 14, 2001, to read:

> In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 7 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. There are postmarketing reports of prosthetic valve thrombosis in pregnant women with prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. These events resulted in maternal death or surgical interventions. The use of Lovenox Injection is not recommended for thromboprophylaxis in pregnant women with prosthetic heart valves (see **WARNINGS: Prosthetic Heart Valves**).

These revisions, reviewed by Dr. Kathy Robie-Suh on July 19, 2001 (SLR-040 submission of 07/11/01), are ACCEPTABLE.

7. **Supplement 045** provides for changes in the ADVERSE REACTIONS section, the "Ongoing Safety Surveillance" subsection. The number of reports of epidural or spinal hematoma has been revised

from:

> Since 1993, there have been ——— reports of epidural or spinal hematoma formation with concurrent use of Lovenox Injection and spinal/epidural anesthesia or spinal puncture.

to:

> 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.

This change, as requested by the Agency based on the current number of epidural or spinal hematoma events, is ACCEPTABLE.

8. **Supplement 046** provides for changes to the PRECAUTIONS section, the "Pregnancy" subsection, the *Teratogenic Effects* sub-subsection, a second paragraph was added:

> As requested in the January 4, 2001 Agency letter and agreed upon in the March 2, 2001 facsimile, to read:
>
> > There have been reports of congenital anomalies in infants born to women who received enoxaparin during pregnancy [redacted] cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia, and cardiac defect. A cause and effect relationship has not been established.
>
> Submitted July 11, 2001 and re-submitted August 14, 2001, to read:
>
> > There have been reports of congenital anomalies in infants born to women who received enoxaparin during pregnancy including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia, and cardiac defect. A cause and effect relationship has not been established nor has the incidence been shown to be higher than in the general population.
>
> **These revisions, reviewed by Dr. Kathy Robie-Suh on July 19, 2001 (SLR-040 submission of 07/11/01), are ACCEPTABLE.**

9. **Supplement 046** provides for changes to the PRECAUTIONS section, the "Pregnancy" subsection, the *Non-Teratogenic Effects* sub-subsection, a first paragraph was added:

As requested in the January 4, 2001 Agency letter

There have been [redacted] of child-bearing potential should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.

Submitted July 11, 2001, and re-submitted August 14, 2001, to read:

There have been post-marketing reports of fetal death when pregnant women received Lovenox Injection. Causality for these cases has not been determined. Pregnant women receiving anti-coagulants, including enoxaparin, are at increased risk for bleeding. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women receiving enoxaparin should be carefully monitored. Pregnant women and women of child-bearing potential should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.

These revisions, reviewed by Dr. Kathy Robie-Suh on July 19, 2001 (SLR-040 submission of 07/11/01), are ACCEPTABLE.

10. At the end of the package insert, the prescribing information date has been updated to July 2001.

This change is ACCEPTABLE.

Conclusions

The identified changes are ACCEPTABLE. The sponsor should be requested to revise the PI, as the next printing, as identified in 4. above.

Karen Oliver, RN, MSN
Regulatory Health Project Manager

Victor F. C. Raczkowski, M.D.,
Division Director

cc:
Original NDA 20-164/S-040, 045, 046
R/D init: K.Robie-Suh 01/03/02
R/D init: J.Korvick 01/07/02
draft: KO/October 3, 2001
final: KO/01/08/02/c:\data\mydocuments\NDA20164-S-040-045-046-10-02-01-labrev

CSO REVIEW

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

/s/

Karen Oliver
1/8/02 12:15:09 PM
CSO

Joyce Korvick
1/9/02 10:49:07 AM
MEDICAL OFFICER
for Dr. Victor Raczkowski

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-040, S-045, and S-046

MEDICAL REVIEWS

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	20-164 (SLR-040, BM)
Sponsor:	Aventis Pharmaceuticals Products Inc.
Drug name:	Lovenox® (enoxaparin sodium) Injection
Submission:	Labeling Supplement
Date submitted:	August 23, 2000; October 27, 2000; December 4, 2000
Review completed:	December 8, 2000
Medical reviewer:	Min Lu, M.D., M.P.H.

1. Introduction and Background
The sponsor has submitted a supplement for labeling change as "Changes Being Effected" to include safety information for pregnant women with prosthetic heart valves in Warnings and Precautions sections as follows.

1). Warnings section

The sponsor proposes to add a new section under Warnings that reads:

"Prosthetic heart valves:

[

(see Precautions: Pregnancy)".

]

2). Precautions section

The sponsor propose to add the following paragraph at the end of Pregnancy section under Precautions:

"In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1 mg/kg bid) to

[

]

2. Material reviewed
NDA 20-164 SLR-040 –Summary, submitted August 23, 2000
NDA 20-164 SLR-040 BM, Volume 160.1-160.4, Study ENO-ZA-301 study and case report forms, submitted October 27, 2000.

3. Enoxaparin and its use in patients with prosthetic heart valves

Use of enoxaparin for thromboembolism prophylaxis in patients with prosthetic heart valves is not approved as an indication in current labeling. Patients with artificial heart valves, when undergoing non-cardiac surgery or upon becoming pregnant, are often switched from oral anticoagulation to intravenous or subcutaneous unfractionated heparin. Recently, ten cases of obstruction of prosthetic valves, secondary to thrombosis, were reported internationally when patients were receiving enoxaparin subcutaneous injection for thromboembolism prophylaxis. These patients included seven pregnant women. There were no reports in the United States. Since enoxaparin is not indicated in patients with prosthetic heart valves in United States, it is difficult to estimate the use of enoxaparin in this situation.

1) The Sponsor's Safety Database Search
The sponsor's safety database search for reports regarding enoxaparin and prosthetic heart valve obstruction/failure from first launch of enoxaparin in 1986 to March 13, 2000

have identified 10 cases. The database search was based on prosthesis and artificial heart valves (reporter term). Among the 10 cases, 2 were reported from South Africa and 8 were reported from Israel. Two Israeli cases had been published in "The Annals of Thoracic Surgery". The remaining 6 Israeli cases were reported by a solitary physician. The sponsor reported that 3 of these reports had been communicated to this physician by a cardiac surgeon. The following table summarizes the available information for the 10 cases.

Summary of ten cases with prosthetic heart valve thrombosis

Case #	Sources	Patients	Enoxaparin received	Adverse reactions	Outcomes
IL01-00100 Israel	Reported by physician	Pregnant woman, unknown age	20 mg daily, unknown duration	Prosthetic mitral valve thrombosis	death
IL01-00101 Israel	Reported by physician	Woman, unknown age	40mg bid, unknown duration	Aortic prosthetic valves clotted	Surgical repair
IL01-00102 Israel **3 cases**	Reported by physician	Pregnant women, Unknown age	40 mg daily, unknown duration	Prosthetic heart valve clotted	Surgical repair
IL01-00110 Israel	Reported by physician	Woman, Unknown age	40 mg daily, unknown duration	"stuck" heart valves	Surgical repair
IL01-00103 Israel	Literature report	72 year man	40 mg bid for 37 weeks	Aortic prosthetic valve thrombosis	Urgent aortic valve replacement
IL01-00104 Israel	Literature report	29 year pregnant woman	40 mg daily for 32 weeks	Prosthetic mitral valve thrombosis	Mitrial valve replacement
ZA01-00209 South Africa	Study ENO-ZA-301	32 year pregnant woman	80 mg bid for 37 days	Prosthetic mitral valve thrombosis	Death and death of the fetus
ZA01-00210 South Africa	Study ENO-ZA-301	36 year pregnant woman	80 mg bid for 35 days	Aortic prosthetic valves clotted	Death and death of the fetus

Reviewer's table

Among the ten cases, there were 3 deaths caused by prosthetic valve thrombosis in pregnant women with deaths of fetus. Remaining 7 patients required surgical repair. Seven of 10 cases were pregnant women with prosthetic valves. Others were 2 women with unknown age and one 72-year-old man. Enoxaparin dosage varied from 20 mg daily to 80 mg (1 mg/kg) twice a day. The duration of enoxaparin use was up to 37 days.

2) Clinical Studies in Patients with Artificial Heart Valves

Some enoxaparin studies have been carried out or are presently in progress in patients with prosthetic heart valves.

Study ENO-ZA-301 (HIPCAT Study):
The study ENO-ZA-301 was a multi-center, open, randomized, controlled trial to assess the maternal and fetal safety and efficacy of high dose enoxaparin for the anticoagulation of pregnant patients with prosthetic heart valves, in comparison to standard therapy (warfarin/unfractionated heparin). This study was carried out in South Africa and was scheduled to enroll 110 pregnant women. The patients in this study were all treated with either enoxaparin 1 mg/kg bid sc or warfarin/heparin, beginning at the time of pregnancy diagnosis. The study was terminated after only 11 patients had been enrolled (7 into the enoxaparin group and 4 into the control group) because two deaths due to prosthetic valve thrombosis occurred in enoxaparin-treated patients. These cases were considered therapeutic failure. The safety board requested that the study be terminated. The two cases are summarized above (ZA01-00209 and ZA01-00210). The narratives of the two cases are attached in Appendix 1.

In this study, other reported adverse events included one case of severe hemorrhage that occurred in an enoxaparin-treated patient 8 days postpartum and was caused by retained placenta fragments, one case of vaginal bleeding with incomplete miscarriage at 12-weeks in warfarin/unfractionated heparin-treated patients, and one case of intrauterine death at 19-weeks in warfarin-treated patients.

Grant-in-Aid study
A Grant-in-Aid study is presently being carried out in the United States by Dr. ———— ————, M.D., et. al., Division of Cardiovascular Diseases and Internal Medicine, ———— ———————— (IND ————). The protocol is to explore the use of [redacted] The investigator was informed of the two fatalities having occurred in pregnant patients in the ENO-ZA-301 study and the reports from Israel. The study has been put on hold until IRB review.

Argentina study
A clinical study is presently in progress in Argentina to evaluate efficacy and safety of enoxaparin in patients with either mechanical valvular prosthesis, or chronic atrial fibrillation, or with rheumatic mitral stenosis, or previous embolism, or presence of thrombus in left atrium, who undergo surgical procedures requiring that oral anticoagulation be stopped. A total of 15 patients have been enrolled. The number of enrolled patients with mechanical valvular prosthesis is not provided by the sponsor. The dose of enoxaparin is 1 mg/kg bid, to be administered perioperatively. The total number of patients scheduled is 200 with 3 centers participating. Until now, no case of thrombosis of prosthetic heart has been reported. The investigators have been informed of the reports from South Africa and Israel.

3) Literature Reports
Two cases of thrombosed mechanical heart valves in pregnant women having received enoxaparin were published in Annals of Thoracic Surgery 2000; 69(1): 264-6 by Lev-Ran et. al. These two cases have been summarized above. No additional report was identified from Medline search by this reviewer at the present time.

4) Adverse Event Reporting System (AERS) Search
No additional cases of prosthetic valve thrombosis have been identified from the search of the FDA AERS database conducted by this reviewer on 11/22/2000.

4. Conclusions and Recommendations
The sponsor has submitted a supplement for labeling changes as "change being effected" to include safety information in warnings and precautions for pregnant women with prosthetic valve.

A total of 10 cases of prosthetic heart valve thrombosis have been reported in patients with prosthetic heart valves who had received enoxaparin for thrombosis prophylaxis from post-marketing spontaneous report system. Seven of these cases were pregnant women and 3 of them died due to prosthetic heart valve thrombosis, which led to deaths of fetus.

Two deaths of pregnant women were reported in 7 enoxaparin-treated patients in a clinical trial (ENO-ZA-301) in South Africa. This trial was terminated after only 11 patients had been enrolled into the study because of the two deaths. The remaining 8 cases of prosthetic valve thrombosis including one death of a pregnant woman were reported from Israel.

Enoxaparin dosage that was used in seven pregnant women with prosthetic heart valves ranged from 20mg daily to 80 mg (1mg/kg) twice a day. The duration of treatment was up to 37 days. The sponsor considered these cases as treatment failure. The reasons for therapy failure were not clear.

There has been no adequate and well-controlled study for enoxaparin use in pregnant women with prosthetic heart valves. The indication for enoxaparin use in pregnant women with prosthetic heart valves is not approved in the current labeling.

Pregnant women with prosthetic heart valves may be at higher risk for thromboembolism. Important safety information for enoxaparin use in pregnant women with prosthetic heart valves should be included in the U.S. labeling.

This reviewer has the following recommendations:
1. The request to add safety information for pregnant women with prosthetic heart valves in Warnings and Precautions sections should be approved with labeling recommendation (See attached Appendix 1).
2. All seven cases of prosthetic valve thrombosis including 3 deaths and 4 requiring surgical repair in pregnant women should be described in precautions section in the labeling (See attached Appendix 1).

3. The sponsor should provide a "Dear Doctor" letter to inform physicians the important safety information for enoxaparin use in pregnant women with prosthetic heart valves.

Min Lu, M.D., M.P.H.

cc:
NDA 20-164/SLR-040
HFD-180/Division file
HFD-180/L Talarico
HFD-180/K Robie-Suh
HFD-180/M Lu
HFD-180/K Oliver
HFD-180/J Choudary
HFD-720/T Permutt
HFD-180/L Zhou
HFD-180 S Doddapaneni

12/8/2000

Appendix 1. Labeling comments

1). Warnings section

"Prosthetic heart valves:

[redacted]

(see Precautions: Pregnancy)".

2). Precautions section

[redacted]

APPEARS THIS WAY
ON ORIGINAL

Appendix 2. The Narratives of the Two Deaths in Study ENO-ZA-301

Case #ZA01-00209

An investigator reported a 32 year old pregnant woman developed thrombosis of her prosthetic mitral valve and died on ———. The mother's death subsequently led to the death of the fetus. The patient presented to the hospital on ——— complaining of hematemesis, dyspnea, and orthopnea. She was treated with diuretics, and transferred to another hospital where she was diagnosed with restricted notion of the prosthetic valve. She developed cardiogenic shock and became acidotic. She was transferred to a third hospital for emergency valve replacement, but died before the operation could be performed. Her medical history was significant for rheumatic heart disease with prosthetic mitral valve (carbo medics size 3]) placement on ———. The patient was approximately 12 weeks pregnant at the time of her death. Enoxaparin (80 mg subcutaneouly twice daily) was administered from ——— to ——— for prosthetic valve thrombosis prophylaxis. Tissue plasminogen activator complex was given at the third itospita1, in an attempt to improve her condition. Her anti-Xa levels on 18-Oct-99 at 1100 and 1400 hours were 0.33 and 0.78 IU/ml, respectively. Examination on admission to the second hospital revealed florid pulmonary edema with extensive crackles in the chest. Valve clicks were not audible. Echocardiography revealed very restricted motion of the valve disc and a mean gradient across the mitral valve prosthesis of approximately 20 mm Hg. Transesophageal Echo performed at the third institution revealed an extensive thrombus around the valve ring with prolapse into and obstruction of the valve orifice in diastole. Her ejection fraction was 52%. Examinations of the fetus early in pregnancy did not reveal any abnormality. The investigator considered the events as probably related to inadequate coagulation afforded by enoxaparin. No autopsy was performed.

Case #ZA01-00210

An investigator reported a 36 year-old pregnant woman developed cardiogenic shock and a clotted aortic prosthetic valve. These events subsequently led to her death, as well as the death of the fetus. During the evening of ——— the patient awoke with severe dyspnea. She was brought to the hospital, where she was diagnosed with cardiogenic shock secondary to aortic valve dysfunction. She died approximately one hour after admission. Her medical history was significant for a prosthetic mitral valve (23 hall kaster) ——— due to mitral stenosis, and a prosthetic aortic valve (27 hall kaster) ——— secondary to mixed aortic valve disease. She had two miscarriages previously while receiving warfarin. The patient was 31 weeks pregnant at the time of her death. Enoxaparin (80 mg twice daily) was administered from 2-Aug-99 to 6-Nov-99 for prosthetic valve thrombosis prophylaxis. Her anti-Xa level on 18-Oct-99 was 0.43 IU/ml. Examination on admission revealed sinus tachycardia, loud systolic and early diastolic murmur and the lack of audible aortic valve clicks. Post-mortem examination was significant for biventricular cardiomegaly, associated with prosthetic replacement of aortic and mitral valve. Fibrin thrombi on the inferior aspect of both aortic and mitral rings were noted. Inflammatory cells and microorganisms were absent. Chronic rheumatic tricuspid valve disease with stenosis and incompetence was demonstrated, as well as obliterative pericarditis related to previous cardiac surgery. Hepatosplenomegaly, mild pulmonary congestion, edema and minimal pleural effusion was also fond. Post-mortem examinations also revealed a normal fetus, with the umbilical cord loosely looped twice around the neck. The investigator considered the events as probably related to enoxaparin therapy.

/s/

Min Lu
12/13/00 09:46:38 AM
MEDICAL OFFICER

Kathy Robie-Suh
12/13/00 12:21:21 PM
MEDICAL OFFICER

Lilia Talarico
12/13/00 07:15:28 PM
MEDICAL OFFICER

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

NDA: 20-164/SLR-040-AF

Sponsor: Aventis Pharmaceuticals Products Inc.
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

Drug name: **Lovenox** (enoxaparin sodium)

Route of Administration: Subcutaneous Injection

Subject: Submission of Final Printed Labeling and a Draft "Dear Doctor" Letter

Date submitted: August 14, 2001

Date received: August 15, 2001

Date assigned: October 3, 2001

Review completed: November 1, 2001

Reviewer: Ruyi He, M.D.

1 BACKGROUND:

In this submission, the sponsor submitted the final printed labeling and a draft "Dear Doctor" letter, after multiple communications with the sponsor as following:

- December 21, 2000 Agency approvable letter for S-040 (Prosthetic Heart Valve)
- January 4, 2001 Agency request letter for changes in labeling (Pregnancy/congenital)
- January 30, 2001 Agency request letter for changes in labeling (Ongoing Safety Surveillance)
- March 2, 2001 Agency revised draft labeling (fax)
- June 19, 2001 Agency approvable letter for FPL for S-020, 030, 034, 036, and 037
- July 11, 2001 Aventis Response to Request: Proposed Labeling for S-040, Pregnancy/congenital, and Ongoing Safety Surveillance.

The revised labeling is acceptable. In this review, I will provide my comments and recommendations for the "Dear Doctor" letter.

2 THE REVIEWER'S COMMENTS AND RECOMMENDATIONS

There are two significant changes in the revised labeling for Lovenox. One is addition of a subsection entitled **Prosthetic Heart Valves** under the section of **WARNINGS** and another significant change is revision of the section of **PRECAUTIONS, Pregnancy** which included adding new paragraph to *Teratogenic Effects* subsection regarding congenital anomalies and revised *Non-teratogenic Effects* subsection. However, only the information regarding warnings for patients with prosthetic heart valves was specifically included in the draft "Dear Doctor" letter. No information about the new paragraph in the *Teratogenic Effects* subsection regarding congenital anomalies or the revised *Non-teratogenic Effects* subsection were mentioned in this letter. The sponsor should add this information into the "Dear Doctor" letter. The new "Dear Doctor" letter should be as follows:

IMPORTANT PRESCRIBING INFORMATION

Dear Health Care Professional:

This letter is to inform you about recent changes to the Lovenox® (enoxaparin sodium) Injection product labeling. Please note the following additions to the **WARNINGS** and **PRECAUTIONS** sections of the Lovenox prescribing information.

In the **WARNINGS** section the following subsection has been added:

> **Prosthetic Heart Valves:** The use of Lovenox Injection is not recommended for thromboprophylaxis in patients with prosthetic heart valves. Cases of prosthetic heart valve thrombosis have been reported in patients with prosthetic valves who have received enoxaparin for thromboprophylaxis Some of these cases were pregnant women in whom thrombosis led to maternal deaths and fetal deaths. Pregnant women with prosthetic heart valves may be at higher risk for thromboembolism (see **PRECAUTIONS: Pregnancy**).

In the **PRECAUTIONS** section, **Pregnancy** subsection a new paragraph has been added to the *Teratogenic Effects* subsection regarding congenital anomalies:

> There have been reports of congenital anomalies in infants born to women who received enoxaparin during pregnancy including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia, and cardiac defect. A cause and effect relationship has not been established nor has the incidence been shown to be higher than in the general population.

The *Non-teratogenic Effects* subsection has been revised:

> *Non-teratogenic Effects:* There have been post-marketing reports of fetal death

when pregnant women received Lovenox Injection. Causality for these cases has not been determined. Pregnant women receiving anti-coagulants, including enoxaparin, are at increased risk for bleeding. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women receiving enoxaparin should be carefully monitored. Pregnant women and women of child-bearing potential should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.

In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 7 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. There are postmarketing reports of prosthetic valve thrombosis in pregnant women with prosthetic heart valves while receiving enoxaparin for thromhoprophylaxis. These events resulted in maternal death or surgical interventions. The use of Lovenox Injection is not recommended for thromboprophylaxis in pregnant women with prosthetic heart valves (see **WARNINGS: Prosthetic Heart Valves).**

We hope this information will be helpful to you in caring for your patients. Please see the enclosed full prescribing information. For more information about Lovenox or the updated prescribing information please contact your Aventis Pharmaceuticals sales representative or Aventis Pharmaceuticals Medical Informatics Department at 1-800-633-1610.

Please report all adverse events to Aventis Pharmaceuticals Product Surveillance a 1-800-633-1610 or to the FDA MedWatch program: by phone at 1-800-FDA-1088; by Fax at 1-800-FDA-0178; via the MedWatch Website *a www.fda.gov/medwatch;* or by mail (using postage paid form) at MedWatch, 5600 Fishers Lane, Rockville, MID 20857-9787.

Sincerely,

Francois Nader, MD
Senior Vice President
North American Regulatory and Medical Affairs.

3 CONCLUSION

The draft "Dear Doctor" letter is not acceptable. The letter should be revised as recommended above.

The recommendations and requests for "Dear Doctor" letter should be communicated to the sponsor.

RUYI HE, MD

CC:
NDA 20-164/SLR-040AF
HFD-180/Div. Files
HFD-180/V. Raczkowski
HFD-180/J. Korvick
HFD-180/K.Robie-Suh
HFD-180/R.He
HFD-180/L.Zhou
HFD-180/J. Choudary
HFD-181/K. Oliver
f/t 11/1/01 rh
N20164/SLR-040-AF/RH

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/s/

Ruyi He
11/1/01 02:32:12 PM
MEDICAL OFFICER

Kathy Robie-Suh
11/1/01 03:40:20 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-040, S-045, and S-046

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 20-164/S-040

CBE-0 SUPPLEMENT

Aventis Pharmaceuticals Products Inc.
Attention: Edmond Roland, M.D.
500 Arcola Road
Collegeville, PA 19426

Dear Dr. Roland:

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: NDA 20-164

Supplement Number: S-040

Date of Supplement: August 23, 2000

Date of Receipt: August 24, 2000

This supplemental application, submitted as a "Supplement - Changes Being Effected" supplement, proposes the following changes: (1) in the WARNINGS section, the addition of a new subsection, titled "Prosthetic Heart Valves", to read:

[ ]

(see PRECAUTIONS: Pregnancy)."; and (2) in the PRECAUTIONS section, the "Pregnancy" subsection, the addition of a third paragraph in the subsection, to read: "In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1 mg/kg bid) to

[ ]

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 23, 2000, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be a February 24, 2001.

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

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room, 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7457.

Sincerely,

Karen Oliver
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 20-164/S-040
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/L.Talarico
HFD-180/K.Robie-Suh
HFD-180/M.Lu

DISTRICT OFFICE

Drafted by: KO/August 28, 2000
filename: KO 08/28/00/c:\data\mydocuments\NDA20164-S040-08-28-00-cbe0.doc

CBE-0 SUPPLEMENT ACKNOWLEDGEMENT (AC)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-164/S-040

Aventis Pharmaceuticals, Inc.
Attention: Joseph A. Carrado, M.Sc., R.Ph.
Global Drug Regulatory Affairs
Global Therapeutic Area Head
Route 202-206, P.O. Box 6800
Bridgewater, NJ 08807-0800

Dear Dr. Carrado:

We acknowledge receipt on August 15, 2001 of your August 14, 2001 resubmission to your supplemental new drug application for Lovenox® (enoxaparin sodium) Injection.

This resubmission contains final printed labeling (FPL) submitted in response to our December 21, 2000 action letter.

With this amendment, we have received a complete response to our December 21, 2000 action letter.

If you have any questions, call me at (301) 827-7457.

Sincerely,

{See appended electronic signature page}

Karen Oliver, RN, MSN
Regulatory Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Karen Oliver
8/30/01 02:23:52 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-164/S-045

PRIOR APPROVAL SUPPLEMENT

Aventis Pharmaceuticals, Inc.
Attention: Joseph A. Carrado, M.Sc., R.Ph.
Global Drug Regulatory Affairs
Global Therapeutic Area Head
Route 202-206, P.O. Box 6800
Bridgewater, NJ 08807-0800

Dear Dr. Carrado:

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-045

Date of Supplement: August 14, 2001

Date of Receipt: August 15, 2001

This supplement proposes the following: revisions to the ADVERSE REACTIONS section, the "Ongoing Safety Surveillance" subsection of the package insert, specifically updating the number of spinal epidural hematomas.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 14, 2001 in accordance with 21 CFR 314.101(a).

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

U.S. Postal/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room, 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7457.

Sincerely,

{See appended electronic signature page}

Karen Oliver, RN, MSN
Regulatory Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Karen Oliver
9/5/01 10:51:16 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-164/S-046

PRIOR APPROVAL SUPPLEMENT

Aventis Pharmaceuticals, Inc.
Attention: Joseph A. Carrado, M.Sc., R.Ph.
Global Drug Regulatory Affairs
Global Therapeutic Area Head
Route 202-206, P.O. Box 6800
Bridgewater, NJ 08807-0800

Dear Dr. Carrado:

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-046

Date of Supplement: August 14, 2001

Date of Receipt: August 15, 2001

This supplement proposes the following: revisions to PRECAUTIONS section, the "Pregnancy" subsection of the package insert.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 14, 2001 in accordance with 21 CFR 314.101(a).

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

U.S. Postal/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room, 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7457.

Sincerely,

{See appended electronic signature page}

Karen Oliver, RN, MSN
Regulatory Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Karen Oliver
9/5/01 10:45:50 AM