

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 20-164/S-030

Name: Lovenox® (Enoxaparin Sodium) Injection

Sponsor: Aventis Pharmaceuticals Products Inc.

Approval Date: June 2, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-164/S-030

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-164/S-030

APPROVAL LETTER

126.1

NDA 20-164/S-030

JUN 2 2000

Aventis Pharmaceuticals Products Inc.
Attention: Edmond Roland, Ph.D.
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

Dear Dr. Roland:

Please refer to your supplemental new drug application dated July 6, 1999, received July 8, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium) Injection.

We acknowledge receipt of your submission of December 29, 1999, that constituted a complete response to our December 13, 1999 action letter.

This supplemental new drug application provides for the following change: qualification of a new concentration of Lovenox® (enoxaparin sodium) Injection, 150mg/mL solution of enoxaparin sodium in Water for Injection, to supply 90 mg/0.6mL, 120mg/0.8mL, and 150 mg/1mL pre-filled syringes.

We have completed the review of this supplemental application, 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 labeling text submitted, and with the minor editorial revisions listed below. Accordingly, the supplemental application is approved effective on the date of this letter.

PACKAGE INSERT

1. In the DESCRIPTION section, delete the phrase "Each dosage unit of" in the following sentences to read:

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.

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

2. After the HOW SUPPLIED section, revise the name of the manufacturer to read "Aventis Pharmaceuticals Products Inc."

IMMEDIATE CONTAINER LABELS

3. Provide more distinctive colors for the visual differentiation of the strengths of the various drug products. Specifically, the purple and blue colors used in Lovenox 120 and Lovenox 150 labels are quite similar and could be easily confused.
4. Provide identical color (as much as possible) across a specific package line (i.e., the 90 mg/0.6 mL [150 mg/mL Concentration] immediate container label, blister, and carton).
5. Revise the name of the manufacturer to read "Aventis Pharmaceuticals Products Inc."

BLISTER LABELS

6. Delete _____
7. Revise the name of the manufacturer to read "Aventis Pharmaceuticals Products Inc."

CARTONS

8. Revise the name of the manufacturer to read "Aventis Pharmaceuticals Products Inc."

The Agency wishes to advise you that the phrase "NEW CONCENTRATION" on the cartons should be deleted after 6 months. Further, consider moving the "Rx Only" phrase from the back panel to the front panel of the cartons.

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted draft labeling (package insert submitted December 29, 1999, immediate container and carton labels submitted December 29, 1999). These revisions are terms of the approval of this application.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. The submission should include the appropriate number of copies of the package insert from both the Maison-Alfort and the Dagenham printing sites. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-164/S-030." Approval of this submission by FDA is not required before the labeling is used.

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-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter 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, we request that you 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

Please submit one market package of the drug product when it is available.

Finally, the Agency wishes to advise you that the proposed labeling changes to the prefilled syringes (30 mg/0.3 mL and 40 mg/0.4 mL, the graduated prefilled syringes (60 mg/0.6mL, 80 mg/0.8mL, and 100 mg/1mL), and ampule (30 mg/0.3mL) outlined in your December 29, 1999 submission (pages 1-146-1-152) will require a supplemental application to the NDA.

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,

LT 6-6-00

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

cc:

Archival NDA 20-164/S-030

HFD-180/Div. Files

HFD-180/K.Oliver

HFD-180/L.Talarico

HFD-180/L.Zhou

HFD-180/J.Sieczkowski

HF-2/MedWatch (with labeling)

HFD-002/ORM (with labeling)

HFD-103/ADRA (with labeling)

HFD-40/DDMAC (with labeling)

HFI-20/Press Office (with labeling)

HFD-400/OPDRA (with labeling)

HFD-613/OGD (with labeling)

HFD-21/ACS (with labeling) - ONLY for drug discussed at advisory committee meeting.

HFD-095/DDMS-IMT (with labeling)

HFD-820/DNDC Division Director

DISTRICT OFFICE

Drafted by: KO/May 24, 2000

Initialed by: J.Sieczkowski 05/26/00

Initialed by: L.Zhou 05/26/00

Initialed by: L.Talarico 05/29/00 *K.Oliver 05/30/00*

final: KO/05/30/00/c:\data\mydocuments\NDA20164-S-030-05-24-00-AP.DOC

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-164/S-030

APPROVABLE LETTER

NDA 20-164/S-030

Rhone-Poulenc Rorer Pharmaceuticals Inc.
Attention: Mr. Dennis Jurgens
500 Arcola Avenue
P.O. Box 1200
Collegeville, PA 19426-0107

DEC 13 1999

Dear Mr. Jurgens:

Please refer to your supplemental new drug application dated July 6, 1999, received July 8, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium) Injection.

This supplement proposes the following change: qualification of a new concentration of Lovenox® (enoxaparin sodium) Injection, 150 mg/mL solution of enoxaparin sodium in Water for Injection, to supply 90 mg/0.6mL, 120mg/0.8mL, and 150mg/1mL pre-filled syringes.

We have completed the review of this application and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. Provide an adequate response to the November 18, 1999 information request letter.
2. Submit revised draft package insert labeling as follows:
 - a. In the CLINICAL PHARMACOLOGY section, the "Pharmacodynamics" subsection, delete the sentences _____" and insert the following sentences to read:

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).
 - b. In the DESCRIPTION section, delete the following dosing information from this section (as requested in the November 18, 1999 information request letter):

[

]

[]

Further comments on the labeling for the cartons, immediate container, and package insert will be provided after tradename, logo design, and nomenclature issues (identified in the November 18, 1999 information request letter) have been resolved, and revised draft labeling has been submitted.

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.

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

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.

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

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

Sincerely,

LT 12-13-99

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

cc:

Archival NDA 20-164/S-030

HFD-180/Div. Files

HFD-180/K.Oliver

HFD-180/L.Talarico

HFD-180/L.Zhou

HFD-180/J.Sieczkowski

DISTRICT OFFICE

Drafted by: KO/December 10, 1999

Initialed by: L.Zhou 12/10/99

Initialed by: L.Talarico 12/10/99 *KO Oliver 12/13/99*

final: KO/12/13/99/c:\data\mydocuments\NDA20-164-S-030-12-10-99-ae.doc

APPROVABLE (AE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-164/S-030

LABELING

SPINAL / EPIDURAL HEMATOMAS

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

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

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

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

DESCRIPTION

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

Lovenox Injection is available in two concentrations:

1 100 mg per mL of Water for Injection

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

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

2 150 mg per mL of Water for Injection

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

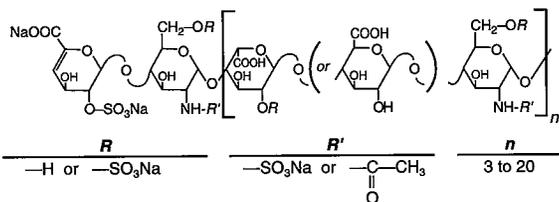
Lovenox Injection 150 mg/mL Concentration contains 15 mg enoxaparin sodium (or appropriate anti-Factor Xa activity of 1500 IU [with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard]) per 0.1 mL Water for Injection.

The solutions are preservative-free and intended for use only as a single-dose injection. (See **DOSE 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 bistrimethyl ester derived from porcine intestinal mucosa. Its structure is characterized by a 2-O-sulfo-4-enepryanosuronic 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 antithrombin (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 concentration. 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
A _{max} (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%	
t _{max} ** (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) (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

Indication	Dosing Regimen	
	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

Indication	Dosing Regimen	
	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

Indication	Dosing Regimen	
	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

Indication	Dosing Regimen		
	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

Indication	Dosing Regimen	
	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

Indication (Post-Discharge)	Post-Discharge Dosing Regimen	
	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

Indication	Dosing Regimen		
	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 Interval¹

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 IU) followed by a continuous infusion (adjusted to achieve an aPTT of 55 to 85 seconds). A total of 3171 patients were enrolled in the study, and 3107 patients were treated. Patients ranged in age from 25-94 years (median age 64 years), with 33.4% of patients female and 66.6% male. Race was distributed as follows: 89.8% Caucasian, 4.8% Black, 2.0% Oriental, and 3.5% other. All patients were also treated with aspirin 100 to 325 mg per day. Treatment was initiated within 24 hours of the event and continued until clinical stabilization, revascularization procedures, or hospital discharge, with a maximal duration of 8 days of therapy. The combined incidence of the triple endpoint of death, myocardial infarction, or recurrent angina was lower for Lovenox Injection compared with heparin therapy at 14 days after initiation of treatment. The lower incidence of the triple endpoint was sustained up to 30 days after initiation of treatment. These results were observed in an analysis of both all-randomized and all-treated patients. The efficacy data are provided below.

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

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

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

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

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

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

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

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

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

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

Indication	Dosing Regimen ¹		
	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

Indication	Dosing Regimen ¹	
	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 **DOSE 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/mm³ and 50,000/mm³) 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/mm³ 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/mm³, 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.

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), dipyridamol, or sulfipyrazone. 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/m²/day. The maximum human dose in clinical trials was 2.0 mg/kg/day or 78 mg/m²/day (for an average body weight of 70 kg, height of 170 cm, and body surface area of 1.8 m²).

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/m²/day and 410 mg/m²/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.

Non-teratogenic Effects: There have been a few spontaneous post-marketing reports of fetal death when pregnant women received Lovenox Injection. Causality of the cases has not been determined. In one case, placental hemorrhage and detachment were found in association with the fetal death. If Lovenox Injection is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

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 Surgery¹

Indications	Dosing Regimen	
	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 Surgery¹

Indications	Dosing Regimen		
	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 Illness¹

Indications	Dosing Regimen		
	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

Indication	Dosing Regimen	
	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 Treatment¹

Indication	Dosing Regimen ²		
	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 Patients¹ Undergoing Abdominal or Colorectal Surgery

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

¹ Excluding unrelated adverse events.

**Lovenox®
(enoxaparin sodium) Injection**

**Lovenox®
(enoxaparin sodium) Injection**

**Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Patients¹
Undergoing Hip or Knee Replacement Surgery**

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 Syringes³				
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 Syringes³				
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 Syringes³				
120 mg / 0.8 mL	12,000 IU	10 syringes	Purple	2912-01
150 mg / 1 mL	15,000 IU	10 syringes	Navy Blue	2915-01

¹ Strength represents the number of milligrams of enoxaparin sodium in Water for Injection. Lovenox Injection 120 and 150 mg graduated prefilled syringes contain **15 mg enoxaparin sodium per 0.1 mL Water for Injection.**

² Approximate anti-Factor Xa activity based on reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard.

³ Each Lovenox Injection graduated prefilled syringe is affixed with a 27 gauge x 1/2 inch needle.

Store at 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 May 2001A.

50062180

Adverse Event	Dosing Regimen									
	Lovenox Inj. 40 mg q.d. SC		Lovenox Inj. 30 mg q12h SC		Heparin 15,000 U/24h SC		Placebo q12h SC			
	Severe	Total	Severe	Total	Severe	Total	Severe	Total	Severe	Total
	n = 288 ²		n = 131 ³		n = 1080		n = 766		n = 115	
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 Patients¹
With Severely Restricted Mobility During Acute Illness**

Adverse Event	Dosing Regimen	
	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**

Adverse Event	Dosing Regimen	
	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 Patients¹
Undergoing Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism**

Adverse Event	Dosing Regimen					
	Lovenox Inj. 1.5 mg/kg q.d. SC		Lovenox Inj. 1 mg/kg q12h SC		Heparin aPTT Adjusted i.v. Therapy n = 544	
	Severe	Total	Severe	Total	Severe	Total
	n = 298		n = 559		n = 544	
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 more than 68 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 injection 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 anaphylactoid 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.

DOSE 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**).

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 neurological compromise is noted, urgent treatment is necessary.

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

DESCRIPTION

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

Lovenox Injection is available in two concentrations:

1 100 mg per mL of Water for Injection

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

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

2 150 mg per mL of Water for Injection

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

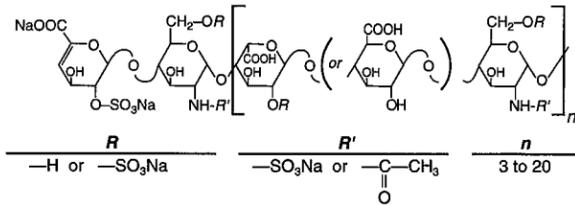
Lovenox Injection 150 mg/mL Concentration contains 15 mg enoxaparin sodium (or appropriate anti-Factor Xa activity of 1500 IU [with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard]) per 0.1 mL Water for Injection.

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

Enoxaparin is obtained by alkaline degradation of heparin benzyl ester derived from porcine intestinal mucosa. Its structure is characterized by a 2-O-sulfo-4-enepranosuronic 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**.)

Though 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
A _{max} (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%	
t _{max} ** (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) i*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

Indication	Dosing Regimen	
	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: 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

Indication	Dosing Regimen	
	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: 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

Indication	Dosing Regimen	
	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

Indication	Dosing Regimen		
	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

Indication	Dosing Regimen	
	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: 1 to 21)	32 (62) (95% CI: 47 to 76)
Proximal DVT (%)	0 (0) ³ (95% Upper CI: 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 CI = 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

Indication (Post-Discharge)	Post-Discharge Dosing Regimen	
	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: 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

Indication	Dosing Regimen		
	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)

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

¹ All patients were also treated with aspirin 100 to 325 mg per day.

² Evaluation timepoints are after initiation of treatment. Therapy continued for up to 8 days (median duration of 2.6 days).

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

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

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

¹ All patients were also treated with aspirin 100 to 325 mg per day.

² Evaluation timepoints are after initiation of treatment. Therapy continued for up to 8 days (median duration of 2.6 days).

In a survey one year following treatment, with information available for 92% of enrolled patients, the combined incidence of death, myocardial infarction, or recurrent angina remained lower for Lovenox Injection versus heparin (32.0% vs 35.7%).

Urgent revascularization procedures were performed less frequently in the Lovenox Injection group as compared to the heparin group, 6.3% compared to 8.2% at 30 days (p = 0.047).

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

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

Indication	Dosing Regimen ¹		
	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

Indication	Dosing Regimen ¹	
	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/mm³ and 50,000/mm³) 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/mm³ 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/mm³, 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.

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 sulfipyrazone. 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/m²/day. The maximum human dose in clinical trials was 2.0 mg/kg/day or 78 mg/m²/day (for an average body weight of 70 kg, height of 170 cm, and body surface area of 1.8 m²).

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/m²/day and 410 mg/m²/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.

Non-teratogenic Effects: There have been a few spontaneous post-marketing reports of fetal death when pregnant women received Lovenox Injection. Causality of the cases has not been determined. In one case, placental hemorrhage and detachment were found in association with the fetal death. If Lovenox Injection is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

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 Surgery¹

Indications	Dosing Regimen	
	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 Surgery¹

Indications	Dosing Regimen		
	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 Illness¹

Indications	Dosing Regimen		
	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

Indication	Dosing Regimen	
	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 last 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 Treatment¹

Indication	Dosing Regimen ²		
	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 Patients¹ Undergoing Abdominal or Colorectal Surgery

Adverse Event	Dosing Regimen			
	Lovenox Inj. 40 mg q.d. SC n = 1228		Heparin 5000 U q8h SC n = 1234	
	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 Patients¹ Undergoing Hip or Knee Replacement Surgery

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

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 Patients¹ With Severely Restricted Mobility During Acute Illness

Adverse Event	Dosing Regimen	
	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

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

Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Patients¹ Undergoing Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism

Adverse Event	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
	Severe	Total	Severe	Total	Severe
Injection Site Hemorrhage	0%	5%	0%	3%	<1%
Injection Site Pain	0%	2%	0%	2%	0%
Hematuria	0%	2%	0%	<1%	<1%

¹ Excluding unrelated adverse events.

Lovenox®
(enoxaparin sodium) Injection

Ongoing Safety Surveillance: Since 1993, there have been more than 68 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 Syringes³				
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 Syringes³				
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 Syringes³				
120 mg / 0.8 mL	12,000 IU	10 syringes	Purple	2912-01
150 mg / 1 mL	15,000 IU	10 syringes	Navy Blue	2915-01

¹ Strength represents the number of milligrams of enoxaparin sodium in Water for Injection. Lovenox Injection 120 and 150 mg graduated prefilled syringes contain **15 mg enoxaparin sodium per 0.1 mL Water for Injection**.

² Approximate anti-Factor Xa activity based on reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard.

³ Each Lovenox Injection graduated prefilled syringe is affixed with a 27 gauge x 1/2 inch needle.

Store at 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.

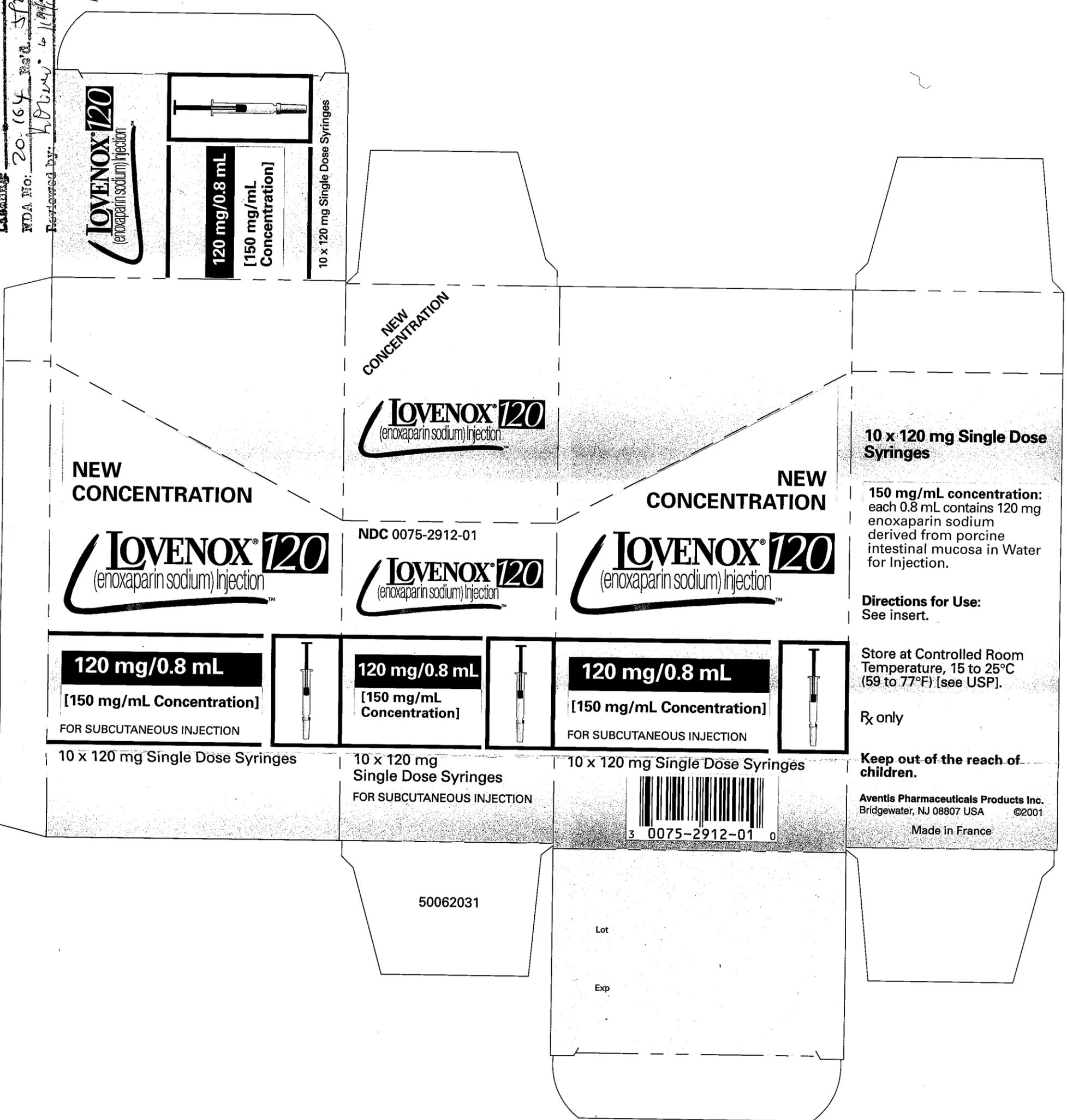
Aventis Pharmaceuticals Products Inc.

BRIDGEWATER, NJ 08807

Prescribing information as of May 2001A.

Labeling
 SCL - 30-FA
 NDA No: 20-164 Rev. 5/23/01
 Reviewed by: h.d.v. & l.m.

M 6/2/00



<p>LOVENOX[®] 120 (enoxaparin sodium) Injection 120 mg/0.8 mL</p>	<p>150 mg/mL concentration: each 0.8 mL contains 120 mg of enoxaparin sodium in Water for Injection. See insert for directions. FOR SUBCUTANEOUS INJECTION. Store at Controlled Room Temperature, 15 to 25°C (59 to 77°F) [see USP]. Rx only</p>	<p>NDC 0075-2912-01 Made in France 1 Single Dose Prefilled Syringe - 0.8 mL Aventis Pharmaceuticals Products Inc. Bridgewater, NJ 08807 USA 50062030</p>
<p>LOVENOX[®] 120 (enoxaparin sodium) Injection 120 mg/0.8 mL</p>	<p>150 mg/mL concentration: each 0.8 mL contains 120 mg of enoxaparin sodium in Water for Injection. See insert for directions. FOR SUBCUTANEOUS INJECTION. Store at Controlled Room Temperature, 15 to 25°C (59 to 77°F) [see USP]. Rx only</p>	<p>NDC 0075-2912-01 Made in France 1 Single Dose Prefilled Syringe - 0.8 mL Aventis Pharmaceuticals Products Inc. Bridgewater, NJ 08807 USA 50062030</p>





Labeling: SCF-30-FA
 NDA No: 20-164 Rev. S(23/01)
 Approved by: [Signature]
 H 6/2/00



NEW CONCENTRATION

LOVENOX[®] 150
 (enoxaparin sodium) Injection

NEW CONCENTRATION

LOVENOX[®] 150
 (enoxaparin sodium) Injection

10 x 150 mg Single Dose Syringes

150 mg/mL concentration:
 each 1 mL contains 150 mg enoxaparin sodium derived from porcine intestinal mucosa in Water for Injection.

Directions for Use:
 See insert.

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

Rx only

Keep out of the reach of children.

Aventis Pharmaceuticals Products Inc.
 Bridgewater, NJ 08807 USA ©2000
 Made in France

LOVENOX[®] 150
 (enoxaparin sodium) Injection

NDC 0075-2915-01

LOVENOX[®] 150
 (enoxaparin sodium) Injection

LOVENOX[®] 150
 (enoxaparin sodium) Injection

150 mg/1 mL
 [150 mg/mL Concentration]

FOR SUBCUTANEOUS INJECTION



150 mg/1 mL
 [150 mg/mL Concentration]



150 mg/1 mL
 [150 mg/mL Concentration]

FOR SUBCUTANEOUS INJECTION



10 x 150 mg Single Dose Syringes

10 x 150 mg Single Dose Syringes
 FOR SUBCUTANEOUS INJECTION

10 x 150 mg Single Dose Syringes



50062034

Lot

Exp

<p>LOVENOX[®] 150 (enoxaparin sodium) Injection 150 mg/1 mL</p>	<p>150 mg/mL concentration: each 1 mL contains 150 mg of enoxaparin sodium in Water for Injection. See insert for directions. FOR SUBCUTANEOUS INJECTION. Store at Controlled Room Temperature, 15 to 25°C (59 to 77°F) [see USP]. Rx only</p>	<p>NDC 0075-2915-01 Made in France 1 Single Dose Prefilled Syringe - 1 mL Aventis Pharmaceuticals Products Inc. Bridgewater, NJ 08807 USA 50062492</p>
<p>LOVENOX[®] 150 (enoxaparin sodium) Injection 150 mg/1 mL</p>	<p>150 mg/mL concentration: each 1 mL contains 150 mg of enoxaparin sodium in Water for Injection. See insert for directions. FOR SUBCUTANEOUS INJECTION. Store at Controlled Room Temperature, 15 to 25°C (59 to 77°F) [see USP]. Rx only</p>	<p>NDC 0075-2915-01 Made in France 1 Single Dose Prefilled Syringe - 1 mL Aventis Pharmaceuticals Products Inc. Bridgewater, NJ 08807 USA 50062492</p>



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-164/S-030

LABELING REVIEW

02j

**Division of Gastrointestinal & Coagulation Drug Products
CONSUMER SAFETY OFFICER REVIEW**

Application Number: NDA 20-164/S-030

JUN 2 2000

Name of Drug: Lovenox® (enoxaparin sodium) Injection

Sponsor: Aventis Pharmaceuticals Products Inc.

Material Reviewed

Submission Date(s): December 29, 1999

Receipt Date(s): December 29, 1999

Background and Summary Description: Supplement 30, submitted July 6, 1999 (received July 8, 1999), provides for the qualification of a new concentration of Lovenox® (enoxaparin sodium) Injection, 150 mg/mL solution of enoxaparin sodium in Water for Injection, to supply 90 mg/0.6mL, 120mg/0.8mL, and 150mg/1mL pre-filled syringes. The December 29, 1999 submission is in response to a December 13, 1999 approvable letter.

Review

PACKAGE INSERT

Draft labeling for the package insert, identified as "IN-1107_ Rev. _/___ 508539", submitted December 29, 1999, was compared to the final printed labeling (FPL), identified as "IN-1107T Rev. 6/99" (labeling printed at the Maison Alfort site), approved October 5, 1999 in Supplement 031. This reviewer notes that the draft labeling for the package insert printed at the Dagenham site was not submitted. The package inserts are identical except for the following:

1. The "Rx only" phrase has been relocated from the upper right corner of the first column of page 1 below the name of the drug in the title section of page 1 to read:



Rx only

This revision is ACCEPTABLE.

2. In the DESCRIPTION section:
- a. The first two paragraphs were changed

from:

Lovenox is a sterile solution for injection containing enoxaparin sodium, a low molecular weight heparin for injection. It is available in prefilled syringes (30 mg) and calibrated prefilled syringes (60, 80, and 100 mg). Each syringe contains 10 mg enoxaparin sodium per 0.1 mL Water for Injection. The solution is preservative-free and intended for use only as a single-dose injection. (see **HOW SUPPLIED** for the individual presentation descriptions.)

The pH of the injection is 5.5-7.5, with an approximate anti-Factor Xa activity per syringe of 1,000 IU per every 10 mg of drug (with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard). Nitrogen is used in the headspace to inhibit oxidation

to:

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 / 1mL
- *Ampules* 30 mg / 0.3 mL

Each dosage unit of **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* 90 mg / 0.6 ml, 120 mg / 0.8mL, 150 mg / 1mL

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

The solutions are preservative-free and intended for use only as single-dose injections. (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.

These changes were reviewed by the REVIEW CHEMIST, Dr. Joseph Sieczkowski, and they are UNACCEPTABLE. The following sentences should be revised

from:

Each dosage unit of **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.

to:

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.

from:

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

to:

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

- b. The underlined molecular weight distribution was changed

from:

The molecular weight distribution is:

<2000 daltons	≤20%
2000 to 8000 daltons	≥68%
>8000 daltons	≤15%

to:

The molecular weight distribution is:

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

This change was reviewed by the REVIEW CHEMIST, Dr. Joseph Sieczkowski, and they are ACCEPTABLE.

3. In the CLINICAL PHARMACOLOGY section:

- a. In the last sentence of the first paragraph, the underlined words were added in the following sentence to read:

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).

This revision was reviewed by the Biopharmaceutics Reviewer, Dr. Suliman Al-Fayoumi, and it is ACCEPTABLE.

- b. In the “Pharmacodynamics” subsection, the underlined words were added to the subsection title to read:

Pharmacodynamics (conducted using 100 mg/mL concentration)

This revision was reviewed by the Biopharmaceutics Reviewer, Dr. Suliman Al-Fayoumi, and it is ACCEPTABLE.

- c. In the second sentence of the “Pharmacodynamics” subsection, the underlined phrase in the sentence was changed:

from:

Mean peak anti-Factor Xa activity was 0.16 IU/mL (1.58 μ g/mL) and 0.38 IU/mL (3.83 μ g/mL) after the 20 mg and the 40 mg clinically tested SC doses, respectively. Mean (n = 46) peak anti-Factor Xa activity was IU/mL at steady state in patients with unstable angina receiving 1.0 mg/kg SC every 12 hours for 14 days.

to:

Mean peak anti-Factor Xa activity was 0.16 IU/mL (1.58 μ g/mL) and 0.38 IU/mL (3.83 μ g/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.

This change was reviewed by the BIOPHARMACEUTICS REVIEWER, Dr. Suliman Al-Fayoumi, and it is ACCEPTABLE.

- d. The following information was added as the last paragraph of the “Pharmacodynamics” subsection, followed by a table entitled “**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**”.

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)

This information was reviewed by the BIOPHARMACEUTICS REVIEWER, Dr. Suliman Al-Fayoumi, and it is ACCEPTABLE.

4. In the CLINICAL TRIALS section:

- a. In the text and table titles in this section, and throughout the PI, the drug name, "Lovenox Injection" has been changed to a bolded type-face to read "**Lovenox Injection**" and references to "enoxaparin" have been deleted and replaced with the phrase (in bold type-face) "**Lovenox Injection**". Further, within the rows and columns of the tables in the PI, the phrase "Inj." was added after the word "Lovenox" and the words have been changed to a bolded type-face to read "**Lovenox Inj.**".

These changes were reviewed by the DIVISION DIRECTOR, Dr. Lilia Talarico, and they are ACCEPTABLE.

- b. In the "Treatment of Deep Vein Thrombosis and Pulmonary Embolism" subsection, the underlined phrase in the first sentence of the first paragraph was changed

from:

In a multicenter, parallel group study, 900 patients with acute lower vein thrombosis (DVT) with or without pulmonary embolism (PE) were randomized to an inpatient (hospital) treatment of either (i) **Lovenox Injection 1.5 mg/kg** once a day SC, (ii) **Lovenox Injection 1.0 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).

to:

In a multicenter, parallel group study, 900 patients with acute lower vein thrombosis (DVT) with or without pulmonary embolism (PE) were randomized to an inpatient (hospital) treatment of either (i) **Lovenox Injection 1.5 mg/kg** once a day SC, (ii) **Lovenox Injection 1mg/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).

This change is ACCEPTABLE.

- c. In the "Treatment of Deep Vein Thrombosis and Pulmonary Embolism" subsection, in the (2) tables (and within the other tables throughout the PI), the following phrase was changed

from:

1.0 mg/kg

to:

1mg/kg.

This change is ACCEPTABLE.

5. In the DOSAGE AND ADMINISTRATION section, after the first paragraph, the following information was added:

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/0.4mL 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:** 90 mg/0.6 mL, 120 mg/0.8 mL, and 150 mg/1 mL prefilled, graduated, single-dose syringes.

This additional information was reviewed by the CHEMISTRY REVIEWER, Dr. Joseph Sieczkowski, and it is ACCEPTABLE.

6. In the HOW SUPPLIED section, the content and format of the information was revised

from:

Lovenox® (enoxaparin sodium) Injection is available in:

Dosage Unit	Strength¹	Package Size (per carton)	Anti-Xa Activity²	NDC # 0075-
Ampules	30 mg / 0.3 mL	10 ampules	3000 IU	0624-03
Prefilled Syringes³	30 mg / 0.3 mL	10 syringes	3000 IU	0624-30
	40 mg / 0.4 mL	10 syringes	4000 IU	0620-40
Graduate Prefilled				
Syringes³	60 mg /0.6 mL	10 syringes	6000 IU	0621-60
	80 mg / 0.8 mL	10 syringes	8000 IU	0622-80
	100 mg / 1.0 mL,	10 syringes	10 000 IU	0623-00

¹ Strength represents the number of milligrams of enoxaparin sodium in Water for Injection. Lovenox ampules and prefilled syringes contain 10 mg enoxaparin sodium per 0.1 mL Water for Injection.

² Anti-Factor Xa activity based on reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard.

³ Each Lovenox prefilled syringe is affixed with a 27 gauge x • inch needle.

to:

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

100 mg/mL Concentration

Dosage Unit / Strength¹	Anti-Xa Activity²	Package Size (per carton)	Syringe Label Color	NDC # 0075-
Ampules				
30 mg / 0.3 mL	3000 IU	10 ampules	Medium Blue	0624-03
Prefilled Syringes³				
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 Syringes³				
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 / Strength¹	Anti-Xa Activity²	Package Size (per carton)	Syringe Label Color	NDC # 0075-
Graduated Prefilled Syringes³				
90 mg / 0.6 mL	9000 IU	10 syringes	Hot Pink	2909-01
120 mg / 0.8 mL	12 000 IU	10 syringes	Lavender	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** 90, 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.

These changes were reviewed by the CHEMISTRY REVIEWER, Dr. Joseph Sieczkowski, and they are ACCEPTABLE.

NOTE: After the HOW SUPPLIED section, the name of the manufacturer should be revised to read "Aventis Pharmaceuticals Products Inc."

IMMEDIATE CONTAINER LABELS

The color mock-ups for the 90 mg, 120 mg, and 150 mg syringe labels for the 150 mg/mL concentration products were compared to the approved immediate container labels for the 60 mg/ 0.6 mL, 80 mg/ 0.8 mL, and 100 mg/1 mL concentration products, submitted May 28, 1999, in annual report 006, and they are identical except for the following:

7. In the title section, the drug product name(s) and concentration(s) have been changed as follows:

Current: Lovenox (enoxaparin sodium) Injection 60mg;
(approved) Lovenox (enoxaparin sodium) Injection 80mg;
 Lovenox (enoxaparin sodium) Injection 100mg.

Proposed: Lovenox 90 (enoxaparin sodium) Inj. 90 mg/0.6mL;
 Lovenox 120 (enoxaparin sodium) Inj. 120 mg/0.8 mL;
 Lovenox 150 (enoxaparin sodium) Inj. 150 mg/1 mL.

These changes were reviewed by the CHEMISTRY REVIEWER, Dr. Joseph Sieczkowski, and they are ACCEPTABLE.

8. A color coding has been assigned to the various products as follows:

Current: (orange) Lovenox (enoxaparin sodium) Injection 60mg;
(approved) (brown) Lovenox (enoxaparin sodium) Injection 80mg;
 (black) Lovenox (enoxaparin sodium) Injection 100mg.

Proposed: (dark pink) Lovenox 90 (enoxaparin sodium) Inj. 90 mg/0.6mL;
 (purple) Lovenox 120 (enoxaparin sodium) Inj. 120 mg/0.8 mL;
 (dark blue) Lovenox 150 (enoxaparin sodium) Inj. 150 mg/1 mL.

This color coding was reviewed by the CHEMISTRY REVIEWER, Dr. Joseph Sieczkowski, and it is UNACCEPTABLE. The purple and blue colors used in Lovenox 120 and Lovenox 150 labels are quite similar and could easily be confused. Recommend more distinctive colors for differentiating the strengths. In

addition, the color across a specific package line (i.e., the 90 mg/0.6 mL [150 mg/mL Concentration immediate container label, blister, and carton) should be as identical as possible.

9. The identification numbers, placed vertically, to the left of the drug product name, are unique for each drug product as follows:

Current: (L-0060) Lovenox (enoxaparin sodium) Injection 60mg;
 (approved) (L-0080) Lovenox (enoxaparin sodium) Injection 80mg;
 (L-0100) Lovenox (enoxaparin sodium) Injection 100mg.

Proposed: ——— Lovenox 90 (enoxaparin sodium) Inj. 90 mg/0.6mL;
 ——— Lovenox 120(enoxaparin sodium) Inj. 120 mg/0.8 mL;
 ——— Lovenox 150 (enoxaparin sodium) Inj. 150 mg/1 mL.

This change is ACCEPTABLE.

10. The identification numbers, placed horizontally below the drug product name, are not present on the proposed labels.

Current: Lovenox (enoxaparin sodium) Injection 60mg;
 (approved) 507941
 Lovenox (enoxaparin sodium) Injection 80mg;
 507942
 Lovenox (enoxaparin sodium) Injection 100mg.
 507943

Proposed: Lovenox 90 (enoxaparin sodium) Inj. 90 mg/0.6mL;
 Lovenox 120 (enoxaparin sodium) Inj. 120 mg/0.8 mL;
 Lovenox 150 (enoxaparin sodium) Inj. 150 mg/1 mL.

This is ACCEPTABLE.

11. The name of the manufacturer, "Rhone-Poulenc Rorer", has been added.

This is UNACCEPTABLE. Since the sponsor's name change, the manufacturer name should be revised to read "Aventis Pharmaceuticals Products Inc."

Blister Labels

The color mock-ups for the 90 mg, 120 mg, and 150 mg blister labels for the 150 mg/mL concentration products were compared to the approved blister labels for the 60 mg/ 0.6 mL,

80 mg/ 0.8 mL, and 100 mg/1 mL concentration products, submitted May 28, 1999, in annual report 006, and they are identical except for the following:

12. In the title section, the drug product name(s) and concentration(s) have been changed as follows:

Current: Lovenox (enoxaparin sodium) Injection 60mg;
(approved) Lovenox (enoxaparin sodium) Injection 80mg;
Lovenox (enoxaparin sodium) Injection 100mg.

Proposed:



These changes were reviewed by the CHEMISTRY REVIEWER, Dr. Joseph Sieczkowski, and they are UNACCEPTABLE. The _____

_____ should be deleted.

13. The text to the right of the drug name has changed

from:

Each --mL contains --mg of enoxaparin sodium derived from porcine intestinal mucosa in Water for Injection. See insert for directions for use.

to:

150 mg/mL concentration: each --- mL contains --- mg of enoxaparin in Water for Injection. See insert for directions.

This change was reviewed by the CHEMISTRY REVIEWER, Dr. Joseph Sieczkowski, and it is ACCEPTABLE.

14. The NDC numbers have changed as follows:

Current (approved)	Lovenox (enoxaparin sodium) Injection 60mg; NDC 0075-0061-60
	Lovenox (enoxaparin sodium) Injection 80mg; NDC 0075-0622-80
	Lovenox (enoxaparin sodium) Injection 100mg. NDC 0075-0623-100
Proposed:	Lovenox 90 (enoxaparin sodium) Injection 90 mg/0.6mL; NDC 0075-2901-01
	Lovenox 120(enoxaparin sodium) Injection 120 mg/0.8 mL; NDC 0075-2912-01
	Lovenox 150 (enoxaparin sodium) Injection 150 mg/1 mL. NDC 0075-2915-01

These changes are ACCEPTABLE.

15. The identification numbers, placed vertically, to the left of the drug product name, are not present on the proposed labels.

Current: (approved)	(507947A) Lovenox (enoxaparin sodium) Injection 60mg; (507949A) Lovenox (enoxaparin sodium) Injection 80mg; (507950A) Lovenox (enoxaparin sodium) Injection 100mg.
Proposed:	Lovenox 90 (enoxaparin sodium) Injection 90 mg/0.6mL; Lovenox 120(enoxaparin sodium) Injection 120 mg/0.8 mL; Lovenox 150 (enoxaparin sodium) Injection 150 mg/1 mL.

These deletions are ACCEPTABLE.

16. Identification numbers, placed horizontally, to the left of the address of the manufacturer as follows:

Current: (approved)	(MP-0600A) Lovenox (enoxaparin sodium) Injection 60mg; (MP-0800A) Lovenox (enoxaparin sodium) Injection 80mg; (MP-1000A) Lovenox (enoxaparin sodium) Injection 100mg.
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Proposed: ~~_____~~ Lovenox 90 (enoxaparin sodium) Injection
 90 mg/0.6mL;
~~_____~~ Lovenox 120(enoxaparin sodium) Injection
 120 mg/0.8 mL;
~~_____~~ Lovenox 150 (enoxaparin sodium) Injection
 150 mg/1 mL.

These changes are ACCEPTABLE.

17. The name of the manufacturer has not been changed.

This is UNACCEPTABLE. The manufacturer name should be revised to read "Aventis Pharmaceuticals Products Inc."

CARTONS

The color mock-ups for the 90 mg, 120 mg, and 150 mg carton labels for the 150 mg/mL concentration products were compared to the approved carton labels for the 60 mg/ 0.6 mL, 80 mg/ 0.8 mL, and 100 mg/1 mL concentration products, submitted May 28, 1999, in annual report 006, and they are identical except for the following:

18. On the front and back panels, both side panels, and the top flap, the drug product name(s) and concentration(s) have been changed as follows:

Current: Lovenox® (enoxaparin sodium) Injection 60mg;
 (approved) Lovenox® (enoxaparin sodium) Injection 80mg; and
 Lovenox® (enoxaparin sodium) Injection 100mg.

Proposed: Lovenox® 90 (enoxaparin sodium) Injection 90 mg/0.6mL;
 Lovenox® 120 (enoxaparin sodium) Injection 120 mg/0.8 mL;
 Lovenox® 150 (enoxaparin sodium) Injection 150 mg/1 mL.

These changes were reviewed by the CHEMISTRY REVIEWER, Dr. Joseph Sieczkowski, and they are ACCEPTABLE

19. On the front panel, the NDC numbers, located in the left corner, have changed as follows:

Current Lovenox (enoxaparin sodium) Injection 60mg;
 (approved) NDC 0075-0061-60
 Lovenox (enoxaparin sodium) Injection 80mg;
 NDC 0075-0622-80

Lovenox (enoxaparin sodium) Injection 100mg.
NDC 0075-0623-100

Proposed: Lovenox 90 (enoxaparin sodium) Injection 90 mg/0.6mL;
NDC 0075-2901-01
Lovenox 120 (enoxaparin sodium) Injection 120 mg/0.8 mL;
NDC 0075-2912-01
Lovenox 150 (enoxaparin sodium) Injection 150 mg/1 mL.
NDC 0075-2915-01

These changes are ACCEPTABLE.

20. On the front panel and back panel, both side panels, and the top flap, the words “[150 mg/mL Concentration]”, printed in red ink, are located in a white box, located directly below the concentration, to read as follows:

Current: 60mg/0.6 mL;
(approved) 80mg/0.8 mL
100mg/1.0 mL

Proposed: 90 mg/0.6mL;
[150 mg/mL Concentration]

120 mg/0.8 mL
[150 mg/mL Concentration]

150 mg/1 mL
[150 mg/mL Concentration]

**This additional information was reviewed by the REVIEW CHEMIST,
Dr. Joseph Sieczkowski, and it is ACCEPTABLE.**

21. On the front and back panels, both side panels, and the top flap, the quantity of box is correctly identified as follows:

Current: 10 x 60 mg Single Dose Syringes
(approved) 10 x 80 mg Single Dose Syringes
10 x 100 mg Single Dose Syringes

Proposed: 10 x 90 mg Single Dose Syringes
10 x 120 mg Single Dose Syringes
10 x 150 mg Single Dose Syringes

These changes are ACCEPTABLE.

22. On the front panel (the right corner) and the back panel (the left corner) in a white triangle tab, the words "NEW CONCENTRATION", printed in red ink, have been added.

This additional information is ACCEPTABLE. However, the sponsor should be advised that the "New Concentration" phrase should only be used for 6 months.

23. On the back panel, the bar coding numbers have changed as follows:

Current (approved)	Lovenox (enoxaparin sodium) Injection 60mg; 0075-0621-60
	Lovenox (enoxaparin sodium) Injection 80mg; 0075-0622-80
	Lovenox (enoxaparin sodium) Injection 100mg. 0075-0623-00
Proposed:	Lovenox 90 (enoxaparin sodium) Injection 90 mg/0.6mL; 0075-2909-01
	Lovenox 120 (enoxaparin sodium) Injection 120 mg/0.8 mL; 0075-2912-01
	Lovenox 150 (enoxaparin sodium) Injection 150 mg/1 mL. 0075-2915-01

These changes are ACCEPTABLE.

24. On the back panel, the text has been changed as follows:

from:

Each --mL contains --mg of enoxaparin sodium derived from porcine intestinal mucosa in Water for Injection.

to:

150 mg/mL concentration: each --- mL contains --- mg of enoxaparin derived from porcine intestinal mucosa in Water for Injection.

This change was reviewed by the CHEMISTRY REVIEWER, Dr. Joseph Sieczkowski, and it is ACCEPTABLE.

25. On the front and back panels, the name of the manufacturer has not been changed.

The sponsor should be requested to revise the manufacturer name to read "Aventis Pharmaceuticals Products Inc."

26. The "Rx Only" phrase is located on the back panel.

The sponsor should be requested to move the "Rx Only" phrase to the front panel.

Conclusions

1. The following changes are ACCEPTABLE: 1., 2.b., 3.a.-3.d., 4.a.-4.c., 5., 6., 7., 9., 10., 11., 13., 14., 15., 16., 18., 19., 20., 21., 22., 23., and 24.
2. The following changes are UNACCEPTABLE: 2.a., 8., 11., 12., and 17.
3. The sponsor should be requested to make the following changes: 11., 17., 22., 25., and 26.


Karen Oliver, RN, MSN
Regulatory Health Project Manager


Lilia Talarico, M.D.
Division Director

cc:

Original NDA 20-164/S-030

HFD-180/Div. Files

HFD-180/L.Talarico

HFD-180/A.Farrell

HFD-180/K.Oliver

HFD-180/J.Sieczkowski

HFD-180/L.Zhou

R/D init: J.Sieczkowski 05/24/00

R/D init: L.Talarico 05/30/00

draft: KO/April 10, 2000 *K.Oliver 05/24/00*

final: KO/05/30/00/c:\data\mydocuments\NDA20164-S-030-04-10-00-labrev

CSO REVIEW

**Division of Gastrointestinal & Coagulation Drug Products
CONSUMER SAFETY OFFICER REVIEW**

Application Number: NDA 20-164/S-020, 030, 034, 036, 037

Name of Drug: Lovenox® (enoxaparin sodium) Injection

Sponsor: Aventis Pharmaceuticals Products Inc.

Material Reviewed

Submission Date(s): December 5, 2000

Receipt Date(s): December 6, 2000

Background and Summary Description: The sponsor submitted identical final printed labeling (FPL) in two formats (Maisons-Alfort and Dagenham) for four supplements.

Supplement 020, submitted November 24, 1998, approved August 3, 2000, provides for: changes to the CLINICAL TRIALS section, the "Unstable Angina and Non-Q-Wave Myocardial Infarction" subsection, regarding the one year follow-up period.

Supplement 030, submitted July 6, 1999, approved June 2, 2000, provides for: qualification of a new concentration of Lovenox® (enoxaparin sodium) Injection, 150mg/mL solution of enoxaparin sodium in Water for Injection, to supply 90 mg/0.6mL, 120 mg/0.8mL, and 150 mg/1mL pre-filled syringes.

Supplement 034, submitted November 3, 1999, approved May 30, 2000, provides for: in the PRECAUTIONS section of the package insert, the addition of a "Geriatric use" subsection, in response to the final rule entitled "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs' Addition of "Geriatric Use" Subsection in the Labeling, published in August 27, 1997 Federal Register (62 FR 45313-45326).

Supplement 036, submitted December 19, 1999, approved November 17, 2000, provides for: Lovenox Injection is indicated for the thromboprophylaxis of deep vein thrombosis, which may lead to pulmonary embolism, in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

Supplement 037, submitted March 14, 2000, approved September 13, 2000, provides for: (1) in the ADVERSE REACTIONS section: (a) in the "Ongoing Safety Surveillance" subsection, updating the number of neuraxial hematoma cases, and (b) after the "Ongoing Safety Surveillance" subsection, in the paragraph titled "Other reports include", adding the phrase "thrombocytopenia with thrombosis"; (2) in the WARNINGS section: (a) in the "Hemorrhage" subsection, expanding the description of major bleeding focusing on retroperitoneal hemorrhage

and intracranial hemorrhage, and (b) in the "Thrombocytopenia" subsection, adding specific language identifying the potential outcomes of thrombocytopenia with thrombosis; and (3) in the DOSAGE AND ADMINISTRATION section, revising the second paragraph to clarify appropriate selection/training/monitoring of patients for home therapy.

Review

PACKAGE INSERTS -S-020, S-030, S-034, S-036, S-037

The FPL package inserts, submitted December 5, 2000, identified as "Rev. 11/00 508539E" (Maison-Alfort) and "Rev 11/00 50060033" (Dagenham) were compared to the package insert text in the December 19, 2000 approval letter for S-036. The package insert texts are identical except for the following:

1. The identification numbers have changed.

This change is ACCEPTABLE.

2. The location of the identification numbers has been changed

from:

below the phrase "R_x only"

to:

the right top corner of the second column
(Maisons-Alfort)

the right top corner of the first column.
(Dagenham)

This change is ACCEPTABLE.

3. The phrase "R_x only" has been relocated:

from:

below the name of the drug

to:

the right top corner of the first column, across from the name of the drug
(Maisons-Alfort)

the right side of the first column, below the identification number.
(Dagenham)

These changes are ACCEPTABLE.

4. The page numbers at the bottom of the front (Page 1) and back (Page 2) of the PIs have been deleted.

Due to the size of the package insert, and the multiple column lay-out (Maisons-Alfort PI with 8 columns and Dagenham PI with 6 columns), the sponsor should be requested to provide page numbers at the bottom of each column, as the PI will be folded vertically on the column margin.

5. The location of the running head, "Lovenox® (enoxaparin sodium) Injection", has been changed

from:

centered at the top of each column

to:

flush right, at the top of the second column of each page [Maisons-Alfort PI at the top of the fourth, sixth, and eighth columns (second, third, and fourth side of a four sided PI) and the Dagenham PI at the top of the sixth column only (side two of a two sided PI)].

The sponsor should be requested to provide the running head, "Lovenox® (enoxaparin sodium) Injection", at the top of each column of the PIs.

6. In the Dagenham PI, in the CLINICAL TRIALS section, the “Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery in Patients at Risk for Thromboembolic Complications” subsection, to the left of the “efficacy of Lovenox Injection in the Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery” table, the following information has been added (with layout position identified):

(horizontal layout)
50060033
Rev. 11/00

(vertical layout)
FPO Bar Code (with barcoding lines)
Lovenox® (enoxaparin sodium) Injection

This additional information is ACCEPTABLE. This reviewer notes that similar barcoding was not added to the Maisons-Alfort PI.

7. In the CLINICAL TRIALS section, the “Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery” subsection, the “Efficacy of Lovenox Injection in Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery” table, the reviewer notes that the term “Lovenox Dosing Regimen” is inconsistent with the other tables that utilize the term “Dosing Regimen”.

The sponsor should be requested to be consistent in the tables, and revise the phrase to read “Dosing Regimen”.

8. In the Maisons-Alfort PI, in the CLINICAL TRIALS section, the “Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery” subsection, this reviewer notes that the “Efficacy of Lovenox Injection In the Prophylaxis of Deep Vein Thrombosis Following Total Knee Replacement Surgery” table is located on side 1, at the bottom of column 2, and on side 2, at the top of column 3.

The split location makes the table very difficult to read and comprehend. The sponsor should be requested to re-locate the table such that it appears intact.

9. In the Maisons-Alfort PI, in the CLINICAL TRIALS section, the “Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction” subsection, this reviewer notes that the “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" table is located at the bottom of side 2, column 2, and the top of side 2, column 3.

The split location makes the table very difficult to read and comprehend. The sponsor should be requested to re-locate the table such that it appears intact.

10. In the Maisons-Alfort PI, in the ADVERSE REACTIONS section, the "Other" subsection, the "Adverse Events Occurring at $\geq 2\%$ Incidence in Lovenox Injection Treated Patients Undergoing Hip or Knee Replacement Surgery" table is located at the bottom of side 4, column 6, and the top of side 5, column 7.

The split location makes the table very difficult to read and comprehend. The sponsor should be requested to re-locate the table such that it appears intact.

11. In the HOW SUPPLIED section, the "100 mg/mL Concentration" table, the reviewer suggests that the following number display be changed to facilitate clarity and easy readability:

from:

10 000 IU

to:

10,000 IU

The sponsor should be requested to implement the change.

12. In the HOW SUPPLIED section, the "100 mg/mL Concentration" table, the reviewer suggests that the following number display be changed to facilitate clarity and easy readability:

from:

12 000 IU

to:

12,000 IU

from:

15 000 IU

to:

15,000 IU

13. After the HOW SUPPLIED section, information was changed as follows:

deleted:

© 2000
IN-xxxx
Mm/yy
Rev.

inserted:

Rev. 11/00

These changes are ACCEPTABLE.

14. In the DOSAGE AND ADMINISTRATION section and the HOW SUPPLIED section, the 90 mg/0.6 mL prefilled, graduated, single-dose syringe is listed under the heading "150 mg/mL Concentration. In a February 2, 2001 telephone conversation with Ms. Michelle Kliever, U.S. Agent for Aventis Pharmaceuticals Inc., the 90 mg/0.6 mL presentation will not be marketed. Therefore, the sponsor should be requested to delete the information regarding this presentation from the package insert as per 21 CFR 201.57(k).

IMMEDIATE CONTAINER LABEL – SUPPLEMENT 030

The color mock-up of the immediate container labels, identified as "50058603" (120 mg/0.8 mL) and "50058604" (150 mg/1 mL), was compared to the immediate container label submitted December 29, 1999 (see Consumer Safety Officer Review dated June 2, 2000) and the revisions requested in the June 2, 2000 approval letter. This reviewer notes that the immediate container label for the 90 mg/0.6 mL presentation was not submitted. In a telephone conversation with Ms. Michelle Kliever, U.S. Agent for Aventis Pharmaceuticals Inc., the 90 mg/0.6 mL presentation will not be marketed.

The immediate container labels are identical except for the following:

15. The identification codes were changed.

This change is ACCEPTABLE.

16. The name of the company was changed

from:

Rhone-Poulenc Rorer

to:

Aventis Pharmaceuticals Products Inc.,

This change is ACCEPTABLE.

17. The color of the immediate container labels are not accurately identified in the HOW SUPPLIED section of the package insert. The 120 mg/0.8 mL color identifier is listed as "Lavender" and the 150 mg/1.0 mL color identifier is listed as "Navy Blue".

The sponsor should be requested to accurately identify the colors in the HOW SUPPLIED section as "Purple" (120 mg/0.8 mL) and "Light Blue" (150 mg/1.0 mL). Further, the reviewer notes that the 30 mg ampules and 30 mg/0.3 mL prefilled syringes are identified in the HOW SUPPLIED section as "Medium Blue". The sponsor should be requested to provide more distinctive colors for the visual differentiation of the strengths.

BLISTERS – SUPPLEMENT 030

The color mock-up of the blister labels, identified as "50058606" (120 mg/0.8 mL) and "50058607" (150 mg/1 mL), were compared to the immediate container label submitted December 29, 1999 (see Consumer Safety Officer Review dated June 2, 2000) and the revisions requested in the June 2, 2000 approval letter. This reviewer notes that the blister label for the 90 mg/0.6 mL presentation was not submitted. In a February 2, 2001 telephone conversation with Ms. Michelle Kliewer, U.S. Agent for Aventis Pharmaceuticals Inc., the 90 mg/0.6 mL presentation will not be marketed.

The blister labels are identical except for the following:

18. The identification codes were changed.

This change is ACCEPTABLE.

19. The name of the company was changed

from:

Rhone-Poulenc Rorer

to:

Aventis Pharmaceuticals Products Inc.,

This change is ACCEPTABLE.

20. Provide identical color (as much as possible) across a specific package line. Hence, if the colors are changed (as requested in 17. above), the blister colors should change accordingly.

CARTONS – SUPPLEMENT 030

The color mock-up of the carton labels, identified as “50058608” (120 mg/0.8 mL) and “50058609” (150 mg/1 mL), were compared to the carton labels submitted December 29, 1999 (see Consumer Safety Officer Review dated June 2, 2000) and the revisions requested in the June 2, 2000 approval letter. This reviewer notes that the carton label for the 90 mg/0.6 mL presentation was not submitted. In a February 2, 2001 telephone conversation with Ms. Michelle Kliever, U.S. Agent for Aventis Pharmaceuticals Inc., the 90 mg/0.6 mL presentation will not be marketed.

The carton labels are identical except for the following:

21. The identification codes were changed.

This change is ACCEPTABLE.

22. The name of the company was changed

from:

Rhone-Poulenc Rorer

to:

Aventis Pharmaceuticals Products Inc.,

This change is ACCEPTABLE.

23. Provide identical color (as much as possible) across a specific package line. Hence, if the colors are changed (as requested in 17. above), the carton colors should change accordingly.
24. The mock up cartons submitted are a different size and shape than those submitted and reviewed on December 29, 1999. It appears that the syringes would not fit in the carton provided.

The sponsor should be requested to re-submit the cartons.

Conclusions

1. The following changes are ACCEPTABLE: 1., 2. 3., 6., 13., 15., 16., 19., 21, and 22.
2. The sponsor should be requested to implement the following changes: 4., 5., 7., 8., 9., 10., 11., 12., 14., 17., 18., 20., 23, and 24.
3. The submitted labeling should not be acknowledged and retained. A letter should be issued to the sponsor identifying the necessary changes identified in this review.

Karen Oliver, RN, MSN
Regulatory Health Project Manager

Lilia Talarico, M.D.
Division Director

cc:

Original NDA 20-164/S-020, 030, 034, 036, 037

HFD-180/Div.Files

HFD-180/L.Talarico

HFD-180/K.Robie-Suh

HFD-180/R.He

HFD-180/K.Oliver

R/D init: K.Robie-Suh 03/12/01

R/D init: L.alarico 03/13/01

/s/

Karen Oliver
3/20/01 09:27:53 AM
CSO

Lilia Talarico
3/20/01 01:43:07 PM
MEDICAL OFFICER

**Division of Gastrointestinal & Coagulation Drug Products
CONSUMER SAFETY OFFICER REVIEW**

Application Number: NDA 20-164/S-020, 030, 034, 036, 037

Name of Drug: Lovenox[®] (enoxaparin sodium) Injection

Sponsor: Aventis Pharmaceuticals Products Inc.

Material Reviewed

Submission Date(s): May 23, 2001

Receipt Date(s): May 24, 2001

Background and Summary Description: On December 5, 2000, the sponsor submitted identical final printed labeling (FPL) in two formats (Maisons-Alfort and Dagenham) for supplements 020, 030, 034, 036, and 037 (see the Consumer Safety Officer Review of the labeling dated March 20, 1001. The submitted FPL was unacceptable, and an Information Request letter was issued by the Agency on March 20, 2001. On May 23, 2001, the sponsor re-submitted identical final printed labeling (FPL) in two formats (Maisons-Alfort and Dagenham) for four supplements.

Supplement 020, submitted November 24, 1998, approved August 3, 2000, provides for: changes to the CLINICAL TRIALS section, the "Unstable Angina and Non-Q-Wave Myocardial Infarction" subsection, regarding the one year follow-up period.

Supplement 030, submitted July 6, 1999, approved June 2, 2000, provides for: qualification of a new concentration of Lovenox[®] (enoxaparin sodium) Injection, 150mg/mL solution of enoxaparin sodium in Water for Injection, to supply 90 mg/0.6mL, 120 mg/0.8mL, and 150 mg/1mL pre-filled syringes.

Supplement 034, submitted November 3, 1999, approved May 30, 2000, provides for: in the PRECAUTIONS section of the package insert, the addition of a "Geriatric use" subsection, in response to the final rule entitled "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs' Addition of "Geriatric Use" Subsection in the Labeling, published in August 27, 1997 Federal Register (62 FR 45313-45326).

Supplement 036, submitted December 19, 1999, approved November 17, 2000, provides for: Lovenox Injection is indicated for the thromboprophylaxis of deep vein thrombosis, which may lead to pulmonary embolism, in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

Supplement 037, submitted March 14, 2000, approved September 13, 2000. provides for: (1) in the ADVERSE REACTIONS section: (a) in the "Ongoing Safety Surveillance" subsection, updating the number of neuraxial hematoma cases, and (b) after the "Ongoing Safety Surveillance" subsection, in the paragraph titled "Other reports include", adding the phrase "thrombocytopenia with thrombosis"; (2) in the WARNINGS section: (a) in the "Hemorrhage" subsection, expanding the description of major bleeding focusing on retroperitoneal hemorrhage and intracranial hemorrhage, and (b) in the "Thrombocytopenia" subsection, adding specific language identifying the potential outcomes of thrombocytopenia with thrombosis; and (3) in the DOSAGE AND ADMINISTRATION section, revising the second paragraph to clarify appropriate selection/training/monitoring of patients for home therapy.

Review

PACKAGE INSERTS –S-020, S-030, S-034, S-036, S-037

The FPL package inserts, submitted May 23, 2001, identified as "Rev. 05/01A 50062180" (Maisons-Alfort) and "Rev 05/01A 50062181" (Dagenham) were compared to the package insert text in the December 19, 2000 approval letter for S-036. The package insert texts are identical except for the following:

1. The identification numbers have changed.

This change is ACCEPTABLE.

2. The location of the identification numbers has been changed

from:

below the phrase "Rx only"

to:

the right top corner of the first column.

This change is ACCEPTABLE.

3. The phrase "R_x only" has been relocated:

from:

below the name of the drug

to:

the right top corner of the first column, across from the name of the drug

- above the identification number (Maisons-Alfort)
- below the identification number (Dagenham).

These changes are ACCEPTABLE.

4. Sequential page numbers have been inserted at the bottom of each column.

This change is ACCEPTABLE.

5. The location of the running head, "Lovenox[®] (enoxaparin sodium) Injection", has been changed

from:

centered at the top of each column

to:

flush right, at the top of the second column of each page of the PI.

Note: On page 2 (only), of the Maisons-Alfort PI, the running head is located below the identification numbers "50062180".

This change is ACCEPTABLE. However, would recommend that the sponsor consider revising the running head as follows: (1) enlarge the print size; (2) use bolded letters; and (3) center the words at the top of each column.

6. In the DESCRIPTION section, and throughout the PI, reference to the 90 mg/0.6 mL graduated prefilled syringe (150 mg per mL of Water for Injection) has been deleted as the sponsor will not be manufacturing this configuration at this time.

This change is ACCEPTABLE.

7. In the DESCRIPTION section, the underlined word in the following phrase was changed

from:

Lovenox injection 100 mg/mL Concentration

to:

Lovenox Injection 100 mg/mL Concentration.

This change is ACCEPTABLE.

8. In the CLINICAL PHARMACOLOGY section, the “Pharmacodynamics” subsection, in second sentence of the third paragraph, the underlined word was changed

from:

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):

to:

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):

This change is ACCEPTABLE.

9. In the Dagenham PI, in the CLINICAL TRIALS section, the “Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery in Patients at Risk for Thromboembolic Complications” subsection, to the left of the text and the “Efficacy of Lovenox Injection in the Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery” table, the following information has been added (with layout position identified):

(vertical layout)
FPO Bar Code (with barcoding lines)

Lovenox[®] (enoxaparin 50062181
sodium) Injection Rev. 05/01A

This additional information is ACCEPTABLE. This reviewer notes that similar barcoding was not added to the Maisons-Alfort PI.

10. In the CLINICAL TRIALS section, the “Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery” subsection:
- a. In the “Efficacy of Lovenox Injection in Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery” table, the term “Lovenox Dosing Regimen” was changed to “Dosing Regimen”.

This revision is ACCEPTABLE as the wording is consistent with the other tables in the PI.

- b. In the paragraph following the “Efficacy of Lovenox Injection in Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery” table, in the second to last sentence, the underlined words were changed

from:

The incidence of proximal and total DVT after surgery was significantly lower for enoxaparin sodium compared to placebo. The efficacy data are provided below.

to:

The incidence of proximal and total DVT after surgery was significantly lower for Lovenox Injection compared to placebo. The efficacy data are provided below.

This change is ACCEPTABLE. Throughout the CLINICAL TRIALS section and the remainder of the PI, the term “enoxaparin sodium” was changed to “Lovenox Injection”.

11. In the Dagenham PI, in the CLINICAL TRIALS section, the “Prophylaxis of Deep Vein Thrombosis (DVT) In Medical Patients with Severely Restricted Mobility During Acute Illness” subsection, the last sentence of the first paragraph reads (located at the bottom of page 2: “The efficacy data are provided below”.

Although the efficacy data are not “provided below”, but actually provided above (top of column, page 3.), the wording should be retained to maintain the identical text for the Maisons-Alfort and the Dagenham PIs.

10. In the HOW SUPPLIED section, the “100 mg/mL” and the “150 mg/mL Concentration” Tables, the following numbers were changed to facilitate clarity and easy readability:

from: “10 000 IU”

to: “10,000 IU”

from: “12 000 IU”

to: “12,000 IU”

from: “15 000 IU”

to: “15,000 IU”.

These changes are ACCEPTABLE.

11. In the HOW SUPPLIED section, the “150 mg/mL Concentration” Table,
- a. Reference to the 90 mg/0.6 mL graduated prefilled syringes (150 mg/mL concentration) has been deleted.

This deletion is ACCEPTABLE, as that configuration will not be marketed at this time.

- b. The syringe label color for the 120 mg/0.8 mL graduated prefilled syringes has been changed

from: “Lavendar”

to: “Purple”.

This change is ACCEPTABLE.

12. After the HOW SUPPLIED section:

- a. The following information was deleted:

© 2000
IN-xxxxy
Mm/yy
Rev.

These deletions are ACCEPTABLE.

- b. The address of Aventis Pharmaceuticals Products Inc. was changed

from:

COLLEGEVILLE, PA 19426

to:

BRIDGEWATER, NJ 08807.

This change is ACCEPTABLE.

- c. The following phrase was added after the phrase "BRIDGEWATER, NJ 08807:

Prescribing information as of May 2001A.

This additional information is ACCEPTABLE.

- d. The identification numbers were added as follows:

Maisons-Alfort PI: located to the right of the phrase "Prescribing information as of May 2001A"

"50062180"

Dagenham PI: located below the phrase Prescribing information as of
May 2001A”

“50062181”.

This additional information is ACCEPTABLE.

CARTONS – SUPPLEMENT 030

The color mock-up of the cartons, identified as “50062031” (120 mg/0.8 mL) and “50062034” (150 mg/1 mL), was compared to the color mock-up cartons submitted December 29, 1999 (see Consumer Safety Officer Review dated June 2, 2000), the revisions requested in the June 2, 2000 approval letter, and the color mock-up cartons submitted December 5, 2000 (see Consumer Safety Officer Review dated March 20, 2001).

The cartons are identical except for the following:

13. The identification codes were changed.

This change is ACCEPTABLE.

14. The name and address of the company and the copyright date was changed

from:

Rhone-Poulenc Rorer
Collegeville, PA 19426 USA ©2000

to:

Aventis Pharmaceuticals Products Inc.
Bridgewater, NJ 08807 USA ©2001

These changes are ACCEPTABLE.

15. The color of the cartons are accurately identified in the HOW SUPPLIED section of the package insert. The 120 mg/0.8 mL color identifier is listed as "Purple" and the 150 mg/1.0 mL color identifier is listed as "Navy Blue".

This is ACCEPTABLE.

BLISTERS – SUPPLEMENT 030

The color mock-up of the blister labels, identified as "50062030" (120 mg/0.8 mL) and "50062492" (150 mg/1 mL), were compared to the immediate container label submitted December 29, 1999 (see Consumer Safety Officer Review dated June 2, 2000), the revisions requested in the June 2, 2000 approval letter, and the color mock-up cartons submitted December 5, 2000 (see Consumer Safety Officer Review dated March 20, 2001).

The blister labels are identical except for the following:

16. The identification codes were added to the bottom right corner of the blister label.

This change is ACCEPTABLE.

17. The name and address of the company was changed

from:

Rhone-Poulenc Rorer
Collegeville, PA 19426 USA

to:

Aventis Pharmaceuticals Products Inc.
Bridgewater, NJ 08807 USA

This change is ACCEPTABLE.

IMMEDIATE CONTAINER LABELS – SUPPLEMENT 030

The color mock-up of the immediate container labels, identified as "50058603" (120 mg/0.8 mL) and "50062331" (150 mg/1 mL), were compared to the carton labels submitted December 29, 1999 (see Consumer Safety Officer Review dated June 2, 2000), the revisions requested in the June 2, 2000 approval letter, and the color mock-up cartons submitted

December 5, 2000 (see Consumer Safety Officer Review dated March 20, 2001).

The carton labels are identical except for the following:

18. The identification codes were changed.

This change is ACCEPTABLE.

19. The name of the company was changed

from:

Rhone-Poulenc Rorer

to:

Aventis Pharmaceuticals Products Inc.

This change is ACCEPTABLE.

Conclusions

1. The reviewer notes that the color codes seem to be consist across the product lines [i.e., the color purple used for the immediate container, blister, and carton for the 120 mg/0.8 mL single dose, graduated, prefilled syringes (150 mg/mL concentration) and the navy blue color used for the immediate container, blister, and carton labels for the 150 mg/1mL single dose, graduated, prefilled syringes (150 mg/mL concentration).
2. The identified changes are acceptable and the submitted labeling should be acknowledged and retained.
3. Request that the sponsor consider changes to the running head as identified in 5. above.

Karen Oliver, RN, MSN
Regulatory Health Project Manager

Lilia Talarico, M.D.
Division Director

cc:

Original NDA 20-164/S-020, 030, 034, 036, 037
HFD-180/Div.Files
HFD-180/L.Talarico
HFD-180/K.Robie-Suh
HFD-180/R.He
HFD-180/K.Oliver

R/D init: K.Robie-Suh

File: c:\data\mydocuments\NDA20164-S-020-030-034-036-037-06-06-01-FAIabrev.doc

**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
6/19/01 12:58:21 PM
CSO

Lilia Talarico
6/19/01 01:40:07 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-501

CHEMISTRY REVIEWS

CHEM. REVIEW #1		1. <u>Organization:</u> HFD-180		2. <u>NDA number:</u> 20-164	
3. <u>Name and Address of Applicant (City & State):</u> Rhone-Poulenc Rorer P.O. Box 1200 500 Arcola Road Collegeville, PA 19426-0107				4. <u>AF Number</u>	
				5.	Supplements
				Numbers	Dates:
6. <u>Name of Drug:</u> Lovenox [®] Injection		7. <u>Nonproprietary Name:</u> enoxaparin sodium injection		SCF-030	06 JUL 1999
Supplement Provides For: a new enoxaparin sodium injection formulation, 150 mg of enoxaparin sodium per 1 mL Water for Injection, packaged in 1 mL graduated pre-filled syringes to give enoxaparin sodium dosage units of 90, 120, and 150 mg drug product. Manufacture will be _____ at the Rhone-Poulenc Rorer site, Maisons-Alfort, France				9. <u>Amendments and Other (Reports, etc.) Dates:</u> See page 2.	
10. <u>Pharmaceutical Category:</u> anticoagulant		11. <u>How Dispensed:</u> RX <u>XX</u> OTC <u> </u>		12. <u>Related IND/NDA/DMFs:</u> See page 2.	
13. <u>Dosage Form:</u> Injection (SVS)		14. <u>Potency:</u> 30, 40, 60, 80, 100 mg/prefilled syringes; 100 mg/mL			
15. <u>Chemical Name and Structure:</u> See NDA Chemistry Rev. #1.				16. <u>Records and Reports:</u> Current <u> </u> YES <u> </u> NO Reviewed <u> </u> YES <u> </u> NO	
17. <u>Comments:</u> See Review Notes: CC: NDA 20-164/030 HFD-180/Div.File/NDA 20-164 HFD-180/CSO/K.Oliver HFD-180/L.Talarico HFD-180/J.Sieczkowski R/D Init: L.Zhou dob DRAFT 10-27-99/WORD: c:\wordfiles\chem\S\20164030.1JS					
18. <u>Conclusions and Recommendations:</u> Based on the chemistry review including the microbiologist's review, the supplement is approvable. The deficiencies in the supplement are listed under Item H. of this chemistry review. The deficiencies are in the areas of a container/closure protocol, drug product name, package insert description and assignment of shelf life. Since the medical and Biopharmaceutics reviews have not been completed, the CSO should wait until those reviews are completed in order to craft the Agency letter.					
19. <u>Reviewer:</u>					
Name: Joseph Sieczkowski, Ph.D.		Signature:		Date Completed: October 27, 1999	

9. Amendments and Other (Reports, etc.) Dates:
- Microbiologist's Review No. 1, October 15, 1999, by Carol K. Vincent, HFD-850.
Conclusion: "We recommend approval for the subject supplement."
 - Medical Officer's Review - Not completed.
 - Biopharmaceutics Review - Not completed.

d. Chemistry Labeling Review - Completed.

12. Related IND/NDA/DMF(s):

- a. SCS-026: _____ drug product batch _____
- b. SCS-027: _____ drug product batch _____
- c. DMF [
- d. DMF [
- e. DMF [

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CHEMISTRY REVIEW #1

CHEMIST'S REVIEW #2		1. Organization: HFD-180	2. NDA Number: 20-164
3. Name and Address of Applicant (City & State): Aventis Pharmaceutical Products P.O. Box 1200 500 Arcola Road Collegeville, PA 19426-0107		4. AF Number:	
6. Name of Drug: Lovenox® Injection		7. Nonproprietary Name: enoxaparin sodium injection	Supplement (s) Number (s) Date (s) SCF-030 06 JUL 1999 AZ 29 DEC 1999
8. Supplement Provides for: a new enoxaparin sodium injection formulation, 150 mg of enoxaparin sodium per 1 mL Water for Injection, packaged in 1 mL graduated pre-filled syringes to give enoxaparin sodium dosage units of 90, 120, and 150 mg drug product. Manufacture will be _____ at the Rhone-Poulenc Rorer site, Maisons-Alfort, FRANCE.		9. Amendments and Other (Reports, etc.) Dates: See page 2.	
10. Pharmacological Category: anticoagulant	11. How Dispensed: Rx XX OTC	12. Related IND/NDA/DMF (s): See page 2.	
13. Dosage Form: Injection (SVS)	14. Potency: 30, 40, 60, 80, 100 mg/prefilled syringes; 100 mg/mL		
15. Chemical Name and Structure: See NDA Chemistry Review #1		6. Records and Reports: Current Yes No Reviewed Yes No	
17. Comments: See Review Notes. cc: NDA 20-164/030 HFD-180/Div File/NDA 20-164 HFD-181/CSO/K.Oliver HFD-180/L.Talarico HFD-180/J.Sieczkowski R/D init by: L.Zhou dob DRAFT 4-24-00/F/T 4-26-00 Word: c:\wordfiles\chem\S\20164030.2JS			
18. Conclusions and Recommendations: Based on the Aventis responses to the Agency's November 18, 1999 Information Request, the supplement should be approved from the viewpoint of Chemistry. A Consult review for changes to labeling based on the Information Request letter (12/18/99) was requested of OPDRA (See Item 9. of Review) and this Division (DGCDP) has not received their review comments as of the chemistry review date.			
19. Reviewer			
Name: JOSEPH SIECZKOWSKI, Ph.D.	Signature	Date Completed: April 21, 2000	

9. Amendments and (Other Reports, etc.) Dates:

- a. Microbiologist's Review No. 1, October 15, 1999, by Carol K. Vincent, HFD-850.
Conclusion: "We recommend approval for the subject supplement."
- b. With respect to chemistry and labeling an Information Request Letter was sent November 18, 1999.
- c. Office of Post-Marketing Drug Risk Assessment (OPDRA; HFD-400): OPDRA Consult Number 99-057 completed on CDER date October 29, 1999. Information Request Letter (IR) requests Items #5, #6, and #7 in the "Nomenclature" section of the Information Request Letter dated November 18, 1999.

12. Related IND/NDA/DMF(s):

- a. SCS-026: _____ drug product batch _____
- b. SCS-027 _____ drug product batch _____
- c. DMF
- d. DMF []
- e. DMF []

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REVIEW NOTES
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CHEMISTRY REVIEW #2

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-030

MICROBIOLOGY REVIEW

OCT 15 1999

**MICROBIOLOGIST'S REVIEW NO. 1 OF SUPPLEMENT FOR
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS, HFD-180
OFFICE OF NEW DRUG CHEMISTRY, MICROBIOLOGY STAFF, HFD-805**

OCTOBER 15, 1999

Reviewing Microbiologist: Carol K. Vincent, HFD-805

NDA / Supplement Number: 20-164 / SCS-030

Drug Product: Lovenox® [enoxaparin sodium] Injection

Document Date: July 6, 1999

Received for review: August 18, 1999

COMIS User Fee Due Date: January 8, 2000

Name and Address of Applicant:

Rhone-Poulenc Rorer Pharmaceuticals Inc.
500 Arcola Road
P O Box 1200
Collegeville, PA 19426-0107

Name and Address of Manufacturer:

Rhone-Poulenc Rorer
Pharmaspecialites
180, rue Jean Jaures
94700 Maisons-Alfort, France
CFN # FCFR218

Supplement Provides For: New concentration of Lovenox [enoxaparin sodium] injection, 150 mg / mL, to supply 90 mg / 0.6 mL, 120 mg / 0.8 mL, and 150 mg / 1.0 mL.

Dosage Form: Pre-filled syringe for injection.

Method of sterilization:

Conclusions and Recommendations: We recommend approval for the subject supplement.

See E: Review Notes: below.

cc:
NDA 20-164 / SCS-030
HFD-180/JSieczkowski/KOliver/
HFD-160/Consult file/CKVincent [HFD-805]
Drafted by: CKVincent/10-01-99

C:\CKV99\NDA20164.030

Carol K. Vincent
Carol K. Vincent, HFD-805 10-15-99

*T. Guzman 10/15/99
for P.H. Conroy*

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MICROBIOLOGY REVIEW #1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-030

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS
REVIEW

NOV 23 1999

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-164/SCF-030**Submission Date:** 7/6/1999**Trade Name:** LOVENOX[®] Injection**Stamp Date:** 7/8/1999**Active Ingredient:** Enoxaparin Sodium**Review Date:** 10/20/1999**Sponsor:** Rhône-Poulenc Rorer Pharmaceuticals Inc.**Draft Date:** 10/20/1999,

11/22/1999

Reviewer: Suliman I. Al-Fayoumi, Ph.D.**Final Review Date:** 11/22/1999**Type of Submission:** Supplemental New Drug Application for New Dose strength**Synopsis**

Lovenox[®] (Enoxaparin sodium) injection is a low molecular weight heparin currently approved for prevention of deep vein thrombosis (DVT). It is administered as subcutaneous (S.C.) injection, 30 mg B.I.D. in patients undergoing hip or knee surgery and 40 mg Q.D. in patients undergoing abdominal surgery and may be at risk of thromboembolic complications.

The current supplemental application to NDA 20-164 is submitted in support of proposed new enoxaparin (Lovenox) dose strength of 150 mg/ml. In this supplemental NDA, the Firm aims at assessing the effect of enoxaparin concentration and injection volume over the 100-200 mg/ml range on pharmacokinetics and tolerance. The two studies submitted in support of this application do not contain data that directly relate to the 150 mg/ml formulation. The Firm suggests that bioequivalence and similar tolerance of 100 and 200 mg/ml formulations would imply the same for 150 mg/ml formulation. Ultimately, the Firm aims at demonstrating the interchangeability of the 150 mg/ml and 100 mg/ml Lovenox formulations.

Recently, Lovenox has been approved by the Agency for treatment of deep vein thrombosis (DVT) and pulmonary embolism at a S.C. dose of 1.0 mg/kg every 12 hours or 1.5 mg/kg once a day. Lovenox injection is currently marketed at 100 mg/ml concentration. The Lovenox 100 mg/ml formulation would pose practical difficulties with respect to dose calculations for the 1.5 mg/kg dose. A concentration of 150 mg/ml would facilitate dose calculations for the 1.5 mg/kg dose by allowing a simpler relationship between the weight of the patient and the volume to be administered.

The current application includes two study reports entitled,

“A Phase 1, Randomized, 3-Period, cross-Over Study Comparing the Pharmacokinetic Profile of Two Formulations of RP54563: Single Concentration Ampule (1-Shot / 2-Shots) Versus Double Concentration Ampules, Administered as 1.5 mg/kg Once a Day Subcutaneous Treatment for 5 Days to Healthy Male and Female Volunteers” (Study RP54563Q-133).

“A Study to Compare the Bioavailability of Single and Double Concentration Enoxaparin Formulations (40 mg, Single Dose, S.C.) in 16 Healthy Male Volunteers” (Study RP54563Q-129).

Study TSR133**Study Design**

Open, randomized, 3-period, crossover study

Subjects 24 subjects; 12 males and 12 females

Treatments A dose of 1.5 mg/kg once a day administered S.C. over 5 days with one of the following formulations in each period:

- 100 mg/ml solution as a single injection (Treatment 1)
- 100 mg/ml solution as a two simultaneous injections at different sites (Treatment 2)
- 200 mg/ml solution as a single injection (Treatment 3)

Analytical Assay

Four pharmacodynamic markers were used to determine the activity of enoxaparin in biological samples for the assessment of enoxaparin pharmacokinetics: anti-Xa and anti-IIa activities (using amidolytic methods) and APTT and Heptest clotting time.

The amidolytic methods are based on an enzymatic reaction in which the target enzyme interacts with a specific substrate. This substrate is an oligopeptide, which contains a specific site for binding to a given enzyme, with an attached chromophore end group: paranitroaniline. The binding of the substrate with the target enzyme (factor Xa or factor IIa) releases the chromophore group, which can be quantified spectrophotometrically at 405 nm.

Results

Table 1. Pharmacokinetic parameters at day 5 after repeated S.C. enoxaparin administration at 1.5 mg/kg once daily in different volumes and concentrations

Parameter	Treatment	Anti-Xa (IU/ml)	Anti-IIa (IU/ml)	Heptest (Δ sec)	APTT (Δ sec)
Amax	Treatment 1	1.37 \pm 0.23	0.23 \pm 0.05	104.5 \pm 16.6	19.3 \pm 4.7
	Treatment 2	1.46 \pm 0.22	0.24 \pm 0.05	108.4 \pm 15.8	20.1 \pm 6.4
	Treatment 3	1.45 \pm 0.22	0.26 \pm 0.05	110.9 \pm 17.1	22.0 \pm 6.7
Tmax (hr)	Treatment 1	3 (2-6)	4 (2-5)	2.5 (2-4.5)	3 (2-4.5)
	Treatment 2	2.5 (2-4)	4 (3-5)	2.5 (1-4.5)	3 (2-5)
	Treatment 3	3.5 (2-6)	4.5 (2.5-6)	3.3 (2-5)	3 (2-5)
AUC ₀₋₅	Treatment 1	14.26 \pm 2.93	1.54 \pm 0.61	1321 \pm 219	ND
	Treatment 2	14.68 \pm 2.98	1.52 \pm 0.56	1323 \pm 187	ND
	Treatment 3	15.43 \pm 2.96	1.77 \pm 0.67	1401 \pm 227	ND

Statistical analysis showed that the 90% confidence intervals of the ratios of log-transformed AUC and Amax values for anti-Xa and Heptest for all three treatments were all within the 80-125% interval (see attachment 1).

Study TSR129

Study Design

Open, randomized, 2-period, crossover study

Subjects 16 healthy male subjects

Treatments A single dose of 40 mg administered S.C. with one of the following enoxaparin formulations in each period:

- 100 mg/ml solution
- 200 mg/ml solution

Results

Table 2. Pharmacokinetic parameters after a single S.C. enoxaparin administration at 40 mg in two concentrations

Parameter	Treatment	Anti-Xa (IU/ml)	Anti-IIa (IU/ml)	Heptest (Δ sec)	APTT (Δ sec)
Amax	100 mg/ml	0.496 \pm 0.072	0.076 \pm 0.024	51.8 (42.9-74.0)	9.4 \pm 3.0
	200 mg/ml	0.479 \pm 0.068	0.078 \pm 0.026	48.6 (38.8-73.9)	8.9 \pm 2.6
Tmax (hr)	100 mg/ml	3 (2.5-4)	3 (2-5)	3 (2-4)	3.3 (1.5-5)
	200 mg/ml	2.5 (2-4.5)	3.5 (2.5-6)	2.5 (1.5-4)	3 (1.5-5)
AUC _{0-t}	100 mg/ml	4.182 \pm 0.476	0.336 \pm 0.115	422 \pm 84	ND
	200 mg/ml	4.058 \pm 0.529	0.336 \pm 0.121	400 \pm 100	ND
AUC _{0-∞}	100 mg/ml	4.459 \pm 0.511	ND	434 (337-701)	ND
	200 mg/ml	4.344 \pm 0.594	ND	448 (248-695)	ND

Statistical analysis showed that the 90% confidence intervals of the ratios of log-transformed AUC_{0-t}, AUC_{0- ∞} and Amax values for the quantified biomarkers were all within the 80-125% interval (see attachment 2).

Discussion

The two supporting studies show that both 100 mg/ml and 200 mg/ml enoxaparin formulations are bioequivalent at the same enoxaparin dose. Hence, for a given fixed enoxaparin dose, e.g., 40 mg enoxaparin, it might be inferred that neither volume nor concentration of enoxaparin within the range of 100-200 mg/ml have any appreciable impact on pharmacokinetic or pharmacodynamic parameters. It would also be reasonable to presume that the 150 mg/ml formulation will result in a similar bioequivalence and tolerance profile as those of the 100 mg/ml and 200 mg/ml formulations. It should be noted that both studies have been earlier reviewed by the Agency (see attachments).

Recommendations

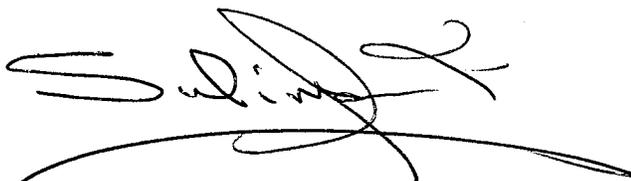
The supplemental application to NDA 20-164 was submitted on Jul 8, 1999 in support of proposed new enoxaparin (Lovenox) dose strength of 150 mg/ml. The submission has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/Division of Pharmaceutical Evaluation II) and is found to be acceptable. It might be inferred that neither volume nor concentration of enoxaparin within the range of 100-200 mg/ml have any appreciable impact on pharmacokinetic or pharmacodynamic parameters. The 150 mg/ml enoxaparin formulation is projected to result in a similar bioequivalence and tolerance profile as those of the 100 mg/ml and 200 mg/ml formulations.

Labeling

The labeling proposed by the Firm has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/Division of Pharmaceutical Evaluation II) and is found to be acceptable except for the following statement,

[] []
The statement should be changed to,

“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)”.

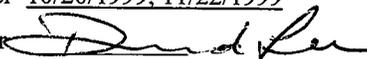


11/23/1999

Suliman I. Al-Fayoumi, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD initialed by David Lee, Ph.D., Team leader 10/20/1999, 11/22/1999

FT initialed by David Lee, Ph.D., Team leader



11/23/99

cc: HFD-180: NDA 20,164 (1x); DIV FILE (1x); KOLIVER (1x); DLEE (1x); HFD-870 JHUNT (1x); MCHEN (1x); HFD-850 SHUANG (1x); CDR: ATTN Barbara Murphy

Attachment 1

JUL 14 1997

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20-164 SE1-15 and SE1-16

Enoxaparin Injection (SC)

Lovenox

Rhone Poulenc Rorer

Submission Dates: February 28th, 1997

March 18th, 1997.

Reviewer: Lydia C. Kaus

Type of Submission: Supplements for two new indications and new dosing regimens.

SYNOPSIS:

The sponsors have approved labeling for prevention of deep vein thrombosis, which may lead to pulmonary embolism, following hip or knee replacement surgery. The recommended dose is 30 mg every 12 hours administered by SC injection up to 14 days. The currently marketed formulation has a concentration of 100mg/1mL enoxaparin sodium. A 0.5 mL pre-filled syringe is approved. In these submissions the concentration of enoxaparin sodium remains the same, the formulation is the same, however there is a new size of the pre-filled syringe, 1.0 mL.

This is a joint review for two supplements (SE1-15 and SE1-16) since the same pharmacokinetic/pharmacodynamic studies were submitted for both supplements.

Supplement SE1-16 is a priority submission with information on

- ▶ a new indication - the treatment of unstable angina and non-Q-wave infarction with concurrent administered with aspirin
- ▶ a new dosing regimen of 1.0 mg/Kg q 12h SC
- ▶ new packages 60 mg/0.6 mL, 80 mg/0.8mL and 100 mg/1.0 mL in pre-filled syringes
- ▶ a new manufacturing line

Supplement SE1-15 is a nonpriority submission with information on

- ▶ a new indication, the treatment of deep vein thrombosis and pulmonary embolism
- ▶ new packages 60 mg/0.6 mL, 80 mg/0.8mL and 100 mg/1 mL in pre-filled syringes
- ▶ a new manufacturing line
- ▶ new dosing regimens, 1.5 mg/Kg qd SC or 1.0 mg/Kg q12h SC

The new packages and new manufacturing line provide the same information in both supplements. The new dosing regimen of 1.0 mg/Kg q 12h SC is common to both submissions, although it is for different patient populations.

An open single ascending dose pharmacokinetic study (Protocol Report K 9001006) of enoxaparin after subcutaneous administration of 1.0 mg/Kg, 1.25 mg/Kg, 1.5 mg/Kg and 2.0 mg/Kg in 16 healthy volunteers shows approximate dose proportionality for Anti-Xa activity based on clearance, normalized AUC and normalized Amax. Enoxaparin showed approximate dose proportionality for Anti-IIa activity based on clearance except at the 1.0 mg/Kg dose. This deviation at the lower dose may be related to the lower levels being measured rather than some other mechanism such as induction. The original submission for enoxaparin showed dose proportionality for anti-Xa activity from 20 to 80 mg given S.C. In this study the ratio of the AUC of anti-Xa to anti-IIa activity is 3 to 5.5 times higher than the potency ratio of 3.56 reported in the original submission for enoxaparin.

A randomized, three period crossover study (Protocol Report RP 54563Q-133) compared the pharmacokinetic profile of two formulations of enoxaparin: single concentration (100 mg/mL) enoxaparin in ampoules (1 shot vs. 2 shots) versus double concentration (200 mg/mL) enoxaparin in ampoules, administered as 1.5 mg/Kg once a day subcutaneous treatment for 5 days to healthy males and females. Single strength vs. double strength enoxaparin was shown to be bioequivalent in a single dose study, PK129, reviewed in April 1996 (NDA 20-164/SE1 (008)). The present study uses doses of enoxaparin (1.5 mg/Kg) likely to be used in the treatment of thrombosis or unstable angina. Gender effect was tested in an ANOVA model incorporating the terms treatment, period, sequence, gender and subject(sequence). In terms of anti-Xa: the Amin activities comparing Day 3 to Day 5 were not significantly different for the three treatment groups. Steady-state has probably been reached by Day 3. A gender effect was noticed in terms of the AUC being lower in females, but not on Amax nor AUC(0-24h), $p < 0.05$. A statistically significant gender-effect ($p < 0.0001$) was noticed on parameters such as volume of distribution and terminal half-life, but not on total body clearance. In terms of anti-IIa: steady-state based on Amin was evident by Day 3. No significant gender effects were noticed on pharmacokinetic parameters except a borderline significance for AUC_{0-4} ($p = 0.0324$). In terms of Heptest™: there was a significantly lower extent of absorption ($p < 0.001$) in females vs. males and the MRT of Heptest™ activity was significantly longer in males vs. females ($p < 0.001$). The average exposure in females is lower than in males ($p < 0.001$) and the apparent elimination half-life is prolonged in males vs. females. No significant gender effects were observed for aPTT. The results from the two one-sided test show that many of the parameter comparisons had the lower bound of the 90% CI greater than 100%. This lends some doubt as to the conclusions of bioequivalence, however, as stated previously, an earlier submission showed bioequivalence of the single to double strength enoxaparin (PK129, reviewed in April 1996 (NDA 20-164/SE1 (008))).

**APPEARS THIS WAY
ON ORIGINAL**

A randomized pilot trial (Protocol Report RP 54563Q-260) of 5 weeks enoxaparin 60 mg sc plus aspirin alone following conventional medical therapy was undertaken in patients admitted to hospital with diagnosis of unstable angina or acute non-Q-wave myocardial infarction. The

sponsors concluded that the clearance in Study RP54563-260 is within that found in earlier studies, however the study shows a mean clearance about 70% longer than that reported in previous studies (mean 1.02 L/hr vs. mean 0.6 L/hr).

A multi center trial of safety and tolerability of two doses of enoxaparin was undertaken in patients with unstable angina and non-Q-wave myocardial infarction (Protocol Report RP 54563Q-261). The trough anti-Xa activities were 20 to 33% higher in the 1.25 mg/Kg group compared to the 1.0 mg/Kg group. Also "peak" anti-Xa activities were 45 to 50% higher in the 1.25 mg/Kg group compared to the 1.0 mg/Kg group. The "peak" activity is not an exact figure since single samples were taken approximately 3 hours postdose, however Protocol Report K 9001006 in this submission showed that there was dose linearity between 1.0 to 2.0 mg/Kg in healthy adults. After the third dose of 1.25 mg/Kg there was a statistically significant higher "peak" anti-Xa activity (p<0.01) in patients experiencing major hemorrhage than those without major hemorrhage. Also, the rate of major hemorrhage was 6.5 % in the 1.25 mg/Kg group compared to a rate of 1.9% in the 1.0 mg/Kg group of patients. Comparison of median trough and peak levels for the third vs. last dose showed similar values, indicating lack of accumulation for bid dosing.

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APPENDIX I:

Clinical Pharmacokinetic/Pharmacodynamic Studies

1. Report K9001006: An open single ascending dose pharmacokinetic study of enoxaparin after subcutaneous administration of 1.0 mg/kg, 1.25 mg/kg, 1.5 mg/kg and 2.0 mg/kg (additionally, two subjects were given a 2.5 mg/kg dose) in 16 healthy volunteers. The concentration of enoxaparin sodium was 200 mg/mL in this study, presented as in a vial (100 mg/0.5 mL).....7
 2. Report PK 54563Q-133: A bioequivalence study between two formulations: the 100 mg/mL formulation, administered at the 1.5 mg/kg dose for 5 days to healthy male and female volunteers11
 3. RP 54563Q-260: A pharmacokinetic study performed in patients with unstable angina given 60 mg once daily after the acute phase.....20
 4. RP 54563Q-261: A multi center trial designed to compare the safety and tolerability of two weight adjusted (1.25 mg/kg q 12h and 1.0 mg/kg q 12h) regimens of subcutaneous injections of enoxaparin in patients with unstable angina or non Q-wave myocardial infarction.24

APPENDIX II

Contains the following information relating to clinical studies listed in APPENDIX I:

- * dose proportionality data
- * graphs

ABBREVIATIONS:

AUC.....	area under the plasma concentration versus time profile
CL/F.....	total body clearance for anti-Xa activity
Amax.....	maximum plasma concentration
MRT.....	mean residence time
t1/2 β	half-life for anti-Xa activity
SS.....	steady-state
Tmax.....	time when Amax observed
Vdss.....	volume of distribution at steady-state
Vd β	volume of distribution
aPTT.....	activated partial thromboplastin time
PT.....	prothrombin time
s.c or SC.....	subcutaneous

BACKGROUND

Enoxaparin is a low molecular weight heparin (LMWH) obtained by partial and controlled depolymerization of benzyl ester of porcine heparin. The antithrombotic activity of enoxaparin depends on anti-Xa activity derived from short and highly bioavailable glycosaminoglycan fragments (M.Wt. <5400 daltons), anti-IIa activity derived from fragments with M.Wt. in the 5400-10000 dalton range and release of TFPI (tissue factor pathway inhibitor) from the vessel wall. This results in a delay and a decrease in prothrombinase activity and thrombin generation. Anti-Xa activity is mostly used to define the antithrombotic and anticoagulant effects.

Rationale for Selection of Starting Dose and Treatment Regimen:

The selection of 1.0 mg/Kg every 12 hours is based on a preliminary safety study where patients were on a dose of 1.0 mg/Kg or 1.25 mg/Kg. Patients dosed at 1.25 mg/Kg had a greater incidence of major hemorrhagic events.

Comments (to send to sponsors):

1. An alternate model to use for gender analysis would be:

$$Y = \frac{\text{Weight sequence gender sequence} * \text{gender subject}(\text{sequence} * \text{gender})}{\text{period product product} * \text{gender weight} * \text{product sequence} * \text{product} * \text{period} * \text{gender}}$$

Using this model, if the interaction term "*sequence*product*period*gender*" is not significant at the $p < 0.1$ level, this term could be dropped from the model and the data re-analyzed. If no terms show significance at the 0.05 level then the analysis could then be repeated dropping the weight term. It is noted that to some extent weight is taken into account through the dose being given on a weight basis. The model further explores gender effects in terms of the *gender*product* interaction.

The sponsors are requested to carry out the above statistical analysis on the data in Study RP 54563Q-133 and to forward the SAS code and ASCII data set to the Agency.

2. The sponsors need to address the difference in mean clearance of anti-Xa activity in the population studied under Protocol Report RP 54563Q-260 as compared to earlier studies. The sponsors should be aware of consistency in units when comparing mean clearance across studies i.e. whether clearance is based on IU anti-Xa or mg enoxaparin. Comparison of ranges should be avoided since these are dependent on the number of subjects used in the analyses. The present study suggests that clearance is 70% higher than shown previously in healthy subjects.
3. The sponsors may want to consider a drug-interaction study in healthy elderly subjects with two treatment arms: enoxaparin and enoxaparin with aspirin.
4. The sponsors are encouraged to undertake non-linear mixed effect modeling of the data in this study and studies where sampling for determination of anti-Xa activity etc. has occurred. If undertaken correctly this would give a much better picture of the handling of enoxaparin by different populations and the influence of cofactors such as age, co-administered drugs.

Labeling Comments (to be sent to sponsor):

1. The sponsors should consider updating the labeling to include information on the *in vitro* potency vs. the *in vivo* ratio of anti-Factor Xa to IIa activity. The statement should reflect the more recent information on the higher *in vivo* ratio of anti-Factor Xa to IIa activity shown in the submission. A possible statement in the labeling would be:

"Enoxaparin is a low molecular weight heparin which has antithrombotic properties. The ratio of anti-Factor Xa to anti-Factor IIa activity in vitro is . In man, enoxaparin at a dose of 1.5 mg/Kg is characterized by a higher ratio of anti-Factor Xa to anti-Factor IIa activity (14.0 ± 3.1) based on area under curves than unfractionated heparin (1.22 ± 0.13)".

2. The sponsors should consider incorporating the gender differences shown in the healthy volunteer study. A possible statement in the labeling would be:

"In healthy subjects, there was a statistically significant gender effect shown for anti-Factor Xa in terms of extent of exposure (AUC), volume of distribution and terminal half-life, but not for total body clearance nor maximum peak activity. A borderline significant gender effect was shown for anti-Factor IIa activity in terms of extent of exposure (AUC):

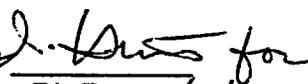
enter Tabulated results here. "

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II finds NDA20-164 SE1-15 and SE1-16 satisfactory. The comments and labeling comments should be forwarded to the sponsors.


6/9/97
7/14/97

Lydia C. Kaus, M.S., Ph.D.
Team Leader, Gastrointestinal and Coagulation Drug
Products, Division of Pharmaceutical Evaluation II.

FT initialed by 
Mei-Ling Chen, Ph.D. 7/8/97
Director, DPEII

cc:NDA 20-164, HFD-180, HFD-870 (Chen, Kaus), HFD-850 (Lesko), Central Document Room (Barbara Murphy).

Attachment 2

Clinical Pharmacology & Biopharmaceutics Review

APR 23 1996

NDA 20-164/SE1 (008)

Submission Date: 12-27-95 and 1-11-96

Lovenox[®]

Enoxaparin Sodium Injection (40 mg)

Sponsor: Rhone-Poulenc Pharmaceuticals, Inc.
500 Arcola Road, Collegeville, PA 19426

Priority: 1P

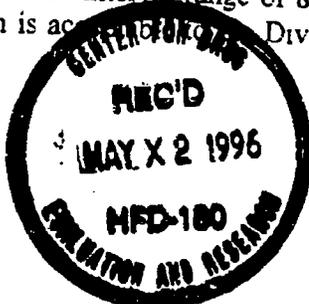
Reviewer: Rajendra S. Pradhan

Type of Submission: Efficacy Supplement/New Dosage Strength

Background:

Sponsor's NDA 20-164 for Lovenox (enoxaparin sodium) Injection, approved on 3-29-93, is indicated for prevention of deep vein thrombosis, which may lead to pulmonary embolism, following hip or knee replacement surgery. The sponsor is now submitting a Supplemental NDA for Lovenox Injection which claims the safety and efficacy of the product in the prevention of deep vein thrombosis in patient undergoing high risk abdominal, gynecological or urological surgeries, or undergoing colorectal surgery. This submission contains information to support the bioequivalence between a 40 mg (40 mg/0.2 ml) formulation used in one pivotal clinical trial and 40 mg (40 mg/0.4 ml) formulation used in another pivotal clinical trial and which is also the to-be-marketed formulation. The proposed dosage is 40 mg QD in the additional indication.

Recommendation: The single strength (40 mg/0.4 ml) and double strength (40 mg/0.2 ml) enoxaparin formulations are bioequivalent according to the two one-sided tests procedure and 90% confidence interval range of 80 to 125% using log transformed data. Therefore, this submission is acceptable. Division of Pharmaceutical Evaluation II (DPE II).



Rajendra S. Pradhan 4-23-96

Rajendra S. Pradhan, Ph.D.
Division of Pharmaceutical Evaluation II

FT initialed by Lydia Kaus, Ph.D. *Lcn 4/23/96*

cc: NDA 20-164, HFD-180, HFD-870 (DPEII Chenrne, Kaus, Pradhan) HFD-860 (DPEI Malinowski), HFD-880 (DPEIII Fleischer), HFD-340 (Viswanathan), HFD-850 (Chron, Drug, Reviewer), HFD-19 (FOI)

BEST POSSIBLE COPY

NDA 20164/SE1 (008)

A study to compare the bioavailability of single and double concentration enoxaparin formulations (40 mg, single dose, s.c.) in 16 healthy male volunteers.

Study#: PK129

Investigator and Site:



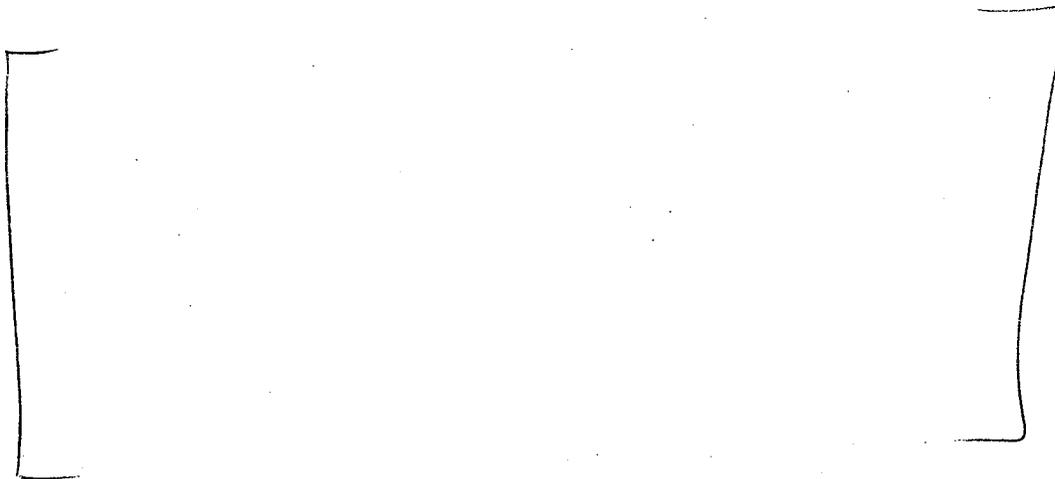
Objectives: To demonstrate that single (40 mg/0.4 ml) and double (40 mg/0.2 ml) concentrations of preservative-free enoxaparin formulations are bioequivalent.

Design: This was a double-blind, randomized, cross-over study, conducted at a single center, consisting of two sequences of one single s.c. injection of 2 enoxaparin concentrations (40 mg/ 0.4 ml, reference and 40 mg/0.2 ml, test) at a two-week interval carried out in 16 healthy male volunteers. A wash-out period of 14 days separated the two treatments. The injections were given at anterolateral part of the abdominal wall.

Specimens: Twenty specimens of 4.5 ml each were collected for a total of 90 ml of blood per subject for one treatment at following times:

Prior to injection (0 min) and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 16.0 and 24.0 hours post dose.

Assay:





Results:

Table 1 shows the pharmacokinetic parameters for the test (40 mg/0.2 ml) formulation. Table 2 shows the pharmacokinetic parameters for the reference (40 mg/0.4 ml) formulation. Figure 1 shows the plasma anti Xa and anti IIa activities versus time plot for test and reference formulation.

Table 1

Parameters	Mean	SD	Min	Max
Amax (U Xa/ml)	0.479	0.068		
AUCinf (U Xa.h/ml)	4.344	0.594		
tmax (hr)				
terminal t1/2 (hr)				
Amax (U IIa/ml)	0.078	0.026		
AUC _{0-t} (U IIa.h/ml)	0.336	0.121		
tmax (hr)				

Table 2

Parameters	Mean	SD	Min	Max
Amax (U Xa/ml)	0.496	0.072		
AUCinf (U Xa.h/ml)	4.459	0.511		
tmax (hr)				
terminal t1/2 (hr)				
Amax (U IIa/ml)	0.076	0.024		
AUC _{0,t} (U IIa.h/ml)	0.336	0.115		
tmax (hr)				

The following table summarizes the bioequivalence results.

Anti-Xa activity	Estimate (test/reference)	90% Confidence Interval
AUCinf	97.2	94.4 - 100.0
AUC _{0,t}	96.8	94.2 - 99.5
Amax	96.5	92.5 - 100.6
Anti-IIa activity		
AUC _{0,t}	97.5	82.8 - 114.9
AUC _{0-5hr}	91.4	79.8 - 104.8
Amax	102.9	88.5 - 119.6

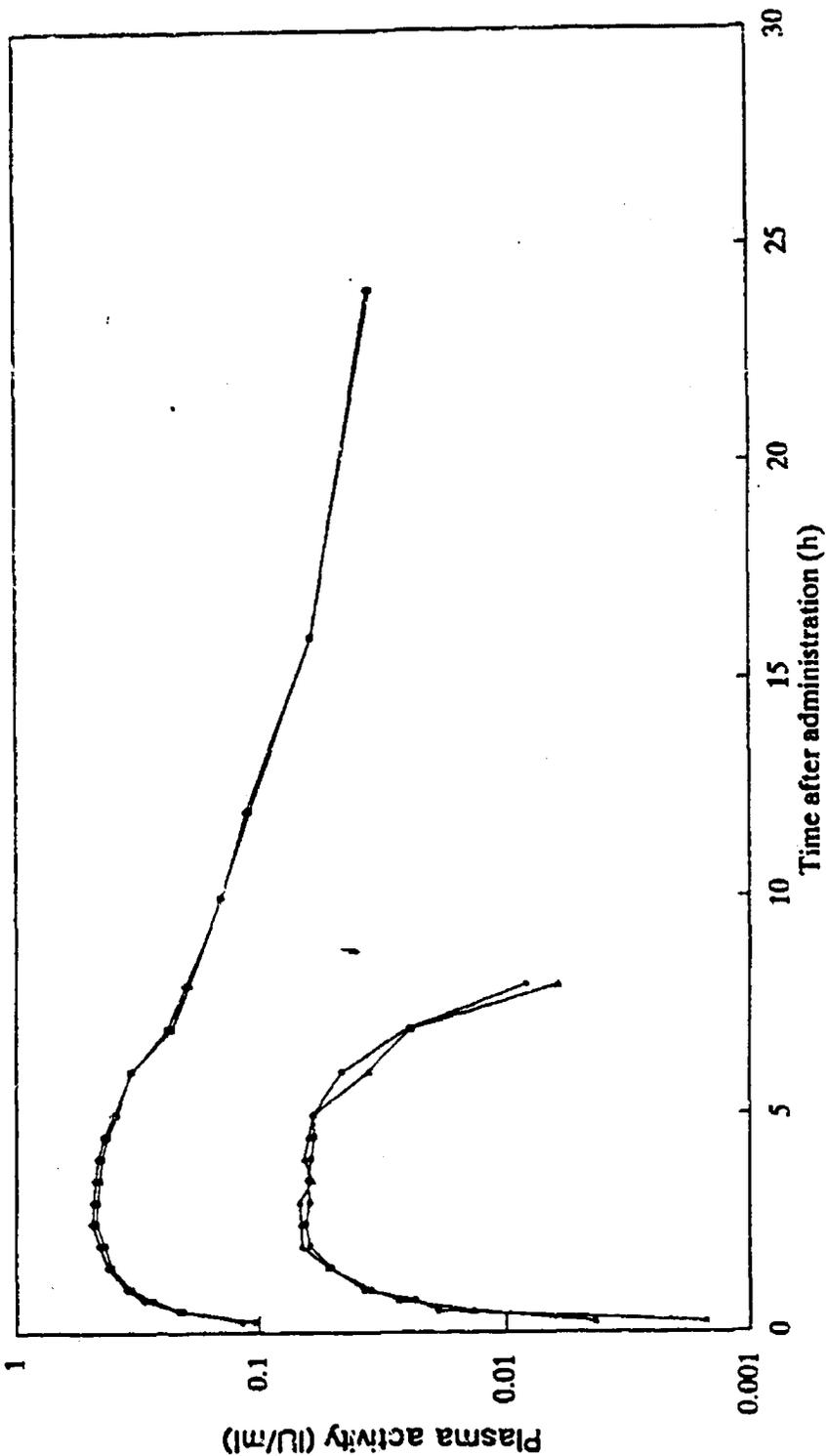
Conclusion: The single strength (40 mg/0.4 ml) and double strength (40 mg/0.2 ml) enoxaparin formulations are bioequivalent according to the two one-sided tests procedure and 90% confidence interval range of 80 to 125% using log_e transformed data.

APPEARS THIS WAY
ON ORIGINAL

Figure 3 1.

Plasma Anti-Xa and Anti-IIa activities - Mean (n = 16)

Study PK 129 - following a S.C. injection of enoxaparin to healthy volunteers



—●— Anti-IIa: 40mg/0.2ml —●— Anti-IIa: 40mg/0.4ml —●— Anti-Xa: 40mg/0.2ml —●— Anti-Xa: 40mg/0.4ml



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-164/S-030

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

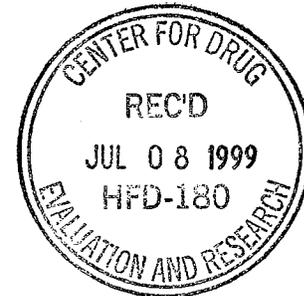
SCS-03C
SCF
Berse

Rhône-Poulenc Rorer Pharmaceuticals Inc.

500 Arcola Road
PO Box 1200
Collegeville, PA 19426-0107
Tel 610-454-8000

July 6, 1999

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



**NDA 20-164
RP 54563**

Lovenox® (enoxaparin sodium) Injection

**SUPPLEMENTAL NEW DRUG APPLICATION
NEW CONCENTRATION: 150MG/1.0ML
ENOXAPARIN SODIUM IN
90mg/0.6mL, 120mg/0.8mL and 150mg/1mL
Pre-filled Syringes**

Dear Dr. Talarico:

Reference is made to NDA 20-164, approved March 29, 1993. The purpose of this supplementary application is to qualify a new concentration for Lovenox® pre-filled syringes. Currently Lovenox® is supplied as 30mg/0.3mL, 40mg/0.4mL, 60mg/0.6mL, 80mg/0.8mL and 100mg/1mL pre-filled syringe, all containing a 100mg/mL solution of enoxaparin sodium in Water for Injection. Given the clinical dosage applications for Lovenox®, a 150mg/mL concentration was developed.

In this application we are presenting data to qualify a 150mg/mL concentration which will be used to supply 90mg/0.6mL, 120mg/0.8mL and 150mg/1mL pre-filled syringes.

Summary of the information presented in this sNDA:

Drug Substance:

- There are no changes to the manufacture of enoxaparin sodium starting material. The approved suppliers for heparin sodium, USP, which is the starting material for enoxaparin sodium are _____



_____ Porcine intestinal mucosa used to manufacture heparin sodium is only sourced from _____ for product intended for the US markets.

- There are no changes to the approved specifications and analytical methods for the drug substance.

Drug Product:

The formulation for the 150mg/mL concentration and for the Lovenox® marketed products both contain enoxaparin sodium in Water for Injection. All presentations are packaged in Type I USP clear glass syringes. The difference is:

- The approved 30mg/0.3mL, 40mg/0.4mL, 60mg/0.6mL, 80mg/0.8mL and 100mg/1mL pre-filled syringes contain a **100mg/1mL** solution of enoxaparin sodium in water for injection. The 90mg/0.6mL, 120mg/0.8mL and 150mg/1mL pre-filled syringes contain a **150mg/1mL** solution of enoxaparin sodium in water for injection.
- The pre-filled syringes used for the 90mg/0.6mL, 120mg/0.8mL and 150mg/1mL presentation are exactly the same 1 mL syringes which are used for the approved 60mg/0.6mL, 80mg/0.8mL and 100mg/1mL pre-filled syringes except for the **graduations printed** on the outside of the syringes.
- The following minor modifications have been made to accommodate the increased batch size:



The current approved site for the manufacture of the 30mg/0.3mL, 40mg/0.4mL, 60mg/0.6mL, 80mg/0.8mL and 100mg/1mL pre-filled syringes and the site of manufacture for the 90mg/0.6mL, 120mg/0.8mL and 150mg/1mL pre-filled syringes is:

Rhône-Poulenc Rorer
PHARMASPECIALITES
180, rue Jean Jaures
94700 Maisons-Alfort, France
CFN # FCFR218

Site Contact: Mr. _____, Director, Quality





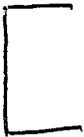
This site is ready for inspection and was last inspected for Lovenox® January 18 through January 25, 1999.

The currently approved — at Maisons-Alfort are as follows:

Approved — for Approved Products	
	30mg/0.3mL pre-filled syringe (0.5mL Type I USP Clear Glass) NDA 20-164 Approved on March 29, 1993.
	40mg/0.4mL pre-filled syringe (0.5mL Type I USP Clear Glass) sNDA S-008 Approved on May 06, 1997.
	30mg/0.3mL pre-filled syringe (0.5mL Type I USP Clear Glass) sNDA S-012 Approved on October 23, 1996
	40mg/0.4mL pre-filled syringe (0.5mL Type I USP Clear Glass) sNDA S-013 Approved on May 16, 1997
	60mg/0.6mL pre-filled syringe (1mL Type I USP Clear Glass) sNDA S-016 Approved on March 27, 1998
	80mg/0.8mL pre-filled syringe (1mL Type I USP Clear Glass) sNDA S-016 Approved on March 27, 1998
	100mg/1mL pre-filled syringe (1mL Type I USP Clear Glass) sNDA S-016 Approved on March 27, 1998

The 90mg/0.6mL, 120mg/0.8mL and 150mg/1mL pre-filled syringes will be manufactured using line —

There are no changes to the approved analytical methods for the drug product. There has been a modification in the



We are providing the pertinent documentation to support a 150mg/mL concentration which will be used to supply 90mg/0.6mL, 120mg/0.8mL and 150mg/1mL pre-filled syringes in accordance with 21 CFR 314.70(b) (2).

This submission contains an application form FDA 356h, both an archival copy and 2 review copies. This submission contains a User Fee Form. This certifies that a field copy of this submission has been provided to the Philadelphia, PA District Office, the home office of the NDA holder, Rhône-Poulenc Rorer Pharmaceuticals Inc (RPR). This submission letter contains 2 diskettes providing a Word 6.0 version of the Unannotated Labeling provided in Item 2.2.

RPR certifies that the methods used in and the facilities and controls used for the processing, packaging and holding of Lovenox® 90mg/0.6mL, 120mg/0.8mL and 150mg/1mL pre-filled syringes are in conformance with current Good Manufacturing Practice in accordance with 21 CFR, Chapter 1, parts 210 and 211. All initial and stability testing of Lovenox® 30 & 40 mg pre-filled syringes is performed in accordance with approved procedures.

Dr. Lilia Talarico
Page 4 of 4
July 6, 1999
NDA 20-164



If you have any questions concerning this submission please contact the undersigned or Connie Gombatz,
(Manager, CMC) at (610)454-5430.

Sincerely,

A handwritten signature in cursive script that reads "Dennis Jurgens". The signature is written in black ink and extends across the width of the page.

Dennis Jurgens
Associate Director, CMC Conformance
Regulatory Affairs
Phone: (610) 454-3364
FAX: (610) 454-2949

Attachments:
Word 6.0 Diskettes (2)

Field Copy:

Debra L. Pagano
Philadelphia District Pre-Approval Manager
U.S. Food and Drug Administration
Room 900, U.S. Customhouse
2nd and Chestnut Streets
Philadelphia, PA 19106-2973

**APPEARS THIS WAY
ON ORIGINAL**

NDA 20-164/S-030

Rhone-Poulenc Rorer Pharmaceuticals Inc.
Attention: Mr. Dennis Jurgens
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

Dear Mr. Jurgens:

We acknowledge receipt of your manufacturing supplemental 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-030

Date of Supplement: July 6, 1999

Date of Receipt: July 8, 1999

This supplement proposes the following change: qualification of a new concentration of Lovenox[®] (enoxaparin sodium) Injection, 150mg/mL solution of enoxaparin sodium in Water for Injection, to supply 90mg/0.6mL, 120mg/0.8mL, and 150mg/1mL pre-filled syringes.

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 September 6, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be November 8, 1999 and the secondary user fee goal date will be January 8, 2000.

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
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact me at (301) 827-7310.

Sincerely,

Karen Oliver, RN, MSN
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-030
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/Reviewers and Team Leaders
DISTRICT OFFICE

Drafted by: mk 7/21/99
Initialed by: K. Oliver 7/21/99
final: M. Kidwell 7/23/99
filename: N20164S030701.ko

SUPPLEMENT ACKNOWLEDGEMENT (AC)

NDA 20-164/S-030

INFORMATION REQUEST LETTER

Rhone-Poulenc Rorer Pharmaceuticals Inc.
Attention: Mr. Dennis Jurgens
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

NOV 18 1999

Dear Mr. Jurgens:

Please refer to your July 6, 1999 supplemental new drug application for Lovenox® (enoxaparin sodium) Injection. The supplement provides for the following change: qualification of a new concentration of Lovenox® (enoxaparin sodium) Injection, 150 mg/mL solution of enoxaparin sodium in Water for Injection, to supply 90 mg/0.6mL, 120mg/0.8mL, and 150mg/1mL pre-filled syringes.

We are reviewing the Chemistry, Manufacturing and Controls (CMC) section and the proposed proprietary name review and have the following comments and information requests. We need your prompt written response to continue our evaluation of your supplemental application.

CMC

1. Regarding changes in the approved container/closure system, submit an amended Change Protocol specifying that any change(s) to the approved container/closure will be made via a prior approval supplement or that which complies with current, appropriate Agency guideline(s).
2. Regarding the DESCRIPTION section of the proposed package insert, delete the following dosing information from this section:

[

]

3. Determine the tradename and the logo design of this higher concentration product and submit to the Agency for review.

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confidential commercial

information from

11/18/1999 FDA LETTER

[]

*Represents the new formulation

If you have any questions, contact Karen Oliver, Regulatory Health Project Manager,
at (301) 827-7310.

Sincerely,

KJ 11/18/99

Kati Johnson
Supervisory Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Archival NDA 20-164/S-030

HFD-180/Div. Files

HFD-180/K.Oliver

HFD-180/Reviewers and Team Leaders

HFD-400/J.Phillips

HFD-400/P.Honig

HFD-400/C.Holquist

HFD-820/DNDC Division Director (only for CMC related issues)

DISTRICT OFFICE

Drafted by: KO/November 9, 1999

Initialed by: J.Sieczkowski 11/10/99

Initialed by: L.Zhou 11/10/99

Initialed by: L.Talarico 11/16/99

Initialed by: K.Johnson 11/18/99

K.Oliver 11/18/99

filename: KO/11/18/99/c:\data\mydocuments\NDA20164-S-030-11-09-99-IR.doc

INFORMATION REQUEST (IR)



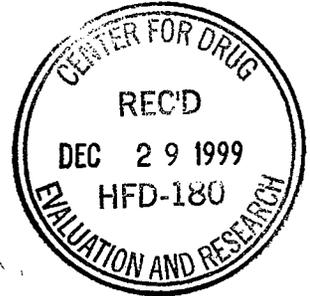
Rhône-Poulenc Rorer Pharmaceuticals Inc.

500 Arcola Road
PO Box 1200
Collegeville, PA 19426-0107
Tel 610-454-8000

FEDERAL EXPRESS 8125 3679 7697

December 29, 1999

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



**NDA 20-164/S-030
RP 54563**

Lovenox® (enoxaparin sodium) Injection

RESPONSE TO INFORMATION REQUEST FOR:

**SUPPLEMENTAL NEW DRUG APPLICATION
NEW CONCENTRATION: 150MG/1.0ML
ENOXAPARIN SODIUM IN
90mg/0.6mL, 120mg/0.8mL and 150mg/1mL
Pre-filled Syringes**

Dear Dr. Talarico:

Reference is made to NDA 20-164, supplement S-030, filed on 06 July 1999. Further reference is made to an agency information request letter dated 18 November 1999 and an approvable letter dated 13 December 1999. The purpose of this complete response is to provide the agency with the information requested in the letters referenced above.

FDA 18 November Information Request 1:

Regarding changes in the approved container/closure system, submit an amended Change Protocol specifying that any change(s) to the approved container/closure will be made via a prior approval supplement or that which complies with current, appropriate Agency guideline(s).

RPR Response:

The Change Protocol is hereby amended as follows: Change(s) to the approved container/closure will be made via a prior approval supplement or that which complies with current, appropriate Agency guideline(s).



FDA 18 November Information Request 2:

Regarding the DESCRIPTION section of the proposed package insert, delete the following dosing information from this section:

[]

RPR Response:

The following information in the DESCRIPTION section of the proposed package insert, is amended to delete the following dosing information from this section:

[]

FDA 18 November Information Request 3:

Determine the tradename and the logo design of this higher concentration product and submit to the Agency for review.

RPR Response:

RPR has accepted FDA's suggestion to modify the product nomenclature to

[]

FDA 18 November Information Request 4:

Provide a statement assigning a drug product shelf-life of _____ months, based on the submitted stability data supporting that expiry period.

RPR Response:

[]

W 1-5-00

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confidential commercial

information from

12/29/1999 SPONSOR LETTER



FDA Approvable Letter Request 1.:

Provide an adequate response to the November 18, 1999 information request letter.

RPR Response:

A complete response to the November 18, 1999 information request letter is provide herein.

FDA Approvable Letter Request 2:

Submit revised draft package insert labeling as follows:

- a. In the CLINICAL PHARMACOLOGY section, the "Pharmacodynamics" subsection, delete the sentences _____

_____ and insert the following sentences to read:

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).

- b. In the DESCRIPTION section, delete the following dosing information from this section (as requested in the November 18, 1999 information request letter:





RPR Response:

In the CLINICAL PHARMACOLOGY section, the "Pharmacodynamics" subsection, RPR will delete the following sentences: _____

_____ The following sentences will be inserted to read:

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).

As previously stated, a complete response to the November 18, 1999 information request letter is provide herein.

We are providing the pertinent documentation to support a 150 mg/mL concentration which will be used to supply 90 mg/0.6mL, 120 mg/0.8mL and 150 mg/1mL pre-filled syringes in accordance with 21 CFR 314.70(b) (2).

This submission contains an application form FDA 356h, both an archival copy and 2 review copies. The archival copy contains 2 diskettes of a Word 6.0 version of the Unannotated Labeling provided in Item 2.2.

If you have any questions concerning this submission please contact the undersigned or Connie Gombatz, (Manager, CMC) at (610)454-5430.

Sincerely,

Dennis Jurgens
Associate Director, CMC Conformance
Regulatory Affairs
Rhône-Poulenc Rorer Pharmaceuticals Inc.
Phone: (610) 454-3364
FAX: (610) 454-2949

Attachments:
Word 6.0 Diskettes (2)

NDA 20-164/S-030

Aventis
Attention: Mr. Dennis Jurgens
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

JAN 18 2000

Dear Mr. Jurgens:

We acknowledge receipt on December 29, 1999 of your December 29, 1999 resubmission to your supplemental new drug application for Lovenox® (enoxaparin sodium) Injection.

This resubmission contains additional Chemistry, Manufacturing and Controls, Clinical Pharmacology and Biopharmaceutics, nomenclature, and labeling information submitted in response to our December 13, 1999 action letter.

With this amendment, we have received a complete response to our December 13, 1999 action letter.

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

Sincerely,

Karen Oliver, RN, MSN
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-030

HFD-180/Div. Files

HFD-180/K.Oliver

HFD-180/L.Talarico

HFD-180/K.Robie-Suh

HFD-180/L.Zhou

HFD-180/J.Sieczkowski

HFD-870/S.Doddapaneni

HFD-870/S.Al-Fayoumi

DISTRICT OFFICE

Drafted by: KO/January 18, 2000

K.Oliver 01/18/00

final: KO/01/18/00/c:\data\mydocuments\NDA20164-S-030-01-18-00-ackfullresponse.doc

RESUBMISSION ACKNOWLEDGEMENT (AC)



NDA 20-164/S-020, 030, 034,
S-036, 037

INFORMATION REQUEST LETTER

Aventis Pharmaceuticals Inc.
C/O Quintiles, Inc.
Attention: Ms. Michelle Kliever
P.O. Box 9708 (Dock 6, F3-M3026)
Kansas City, MO 64134-0708

Dear Ms. Kliever:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium) Injection as follows:

Supplement 020, submitted November 24, 1998, approved August 3, 2000, provides for: changes to the CLINICAL TRIALS section, the "Unstable Angina and Non-Q-Wave Myocardial Infarction" subsection, regarding the one year follow-up period.

Supplement 030, submitted July 6, 1999, approved June 2, 2000, provides for: qualification of a new concentration of Lovenox® (enoxaparin sodium) Injection, 150mg/mL solution of enoxaparin sodium in Water for Injection, to supply 90 mg/0.6mL, 120 mg/0.8mL, and 150 mg/1mL pre-filled syringes.

Supplement 034, submitted November 3, 1999, approved May 30, 2000, provides for: in the PRECAUTIONS section of the package insert, the addition of a "Geriatric use" subsection, in response to the final rule entitled "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs' Addition of "Geriatric Use" Subsection in the Labeling, published in August 27, 1997 Federal Register (62 FR 45313-45326).

Supplement 036, submitted December 19, 1999, approved November 17, 2000, provides for: Lovenox Injection is indicated for the thromboprophylaxis of deep vein thrombosis, which may lead to pulmonary embolism, in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

Supplement 037, submitted March 14, 2000, approved September 13, 2000, provides for: (1) in the ADVERSE REACTIONS section: (a) in the "Ongoing Safety Surveillance" subsection, updating the number of neuraxial hematoma cases, and (b) after the "Ongoing Safety Surveillance" subsection, in the paragraph titled "Other reports include", adding the phrase "thrombocytopenia with thrombosis"; (2) in the WARNINGS section: (a) in the "Hemorrhage" subsection, expanding the description of major bleeding focusing on retroperitoneal hemorrhage and intracranial hemorrhage, and (b) in the "Thrombocytopenia" subsection, adding specific language identifying the potential outcomes of thrombocytopenia with thrombosis; and (3) in the DOSAGE AND ADMINISTRATION section, revising the second paragraph to clarify appropriate selection/training/monitoring of patients for home therapy.

We also refer to your submissions dated December 5, 2000 (received December 6, 2000) to the identified supplements, containing the final printed labeling (FPL) for the respective supplements.

We have reviewed the labeling that you have submitted. We request that you resubmit final printed labeling for the package inserts, and the immediate container labels, blisters, and cartons for the 90 mg/0.6 mL, 120 mg/0.8 mL, and the 150 mg/1mL strengths, modified as follows:

PACKAGE INSERTS (Supplements 020, 030, 034, 036, 037)

1. Due to the size of the package insert, and the multiple column lay-out (Maisons-Alfort package insert with 8 columns and Dagenham package insert with 6 columns), provide page numbers at the bottom of each column, as the package insert will be folded vertically on the column margin.
2. Provide the running head, "Lovenox® (enoxaparin sodium) Injection", at the top of each column of the package inserts as required under 21 CFR 201.10(g)(1).
3. In the CLINICAL TRIALS section, the "Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery" subsection, the "Efficacy of Lovenox Injection in Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery" table, within the body of the table, delete the phrase "Lovenox Dosing Regimen", and replace with the phrase "Dosing Regimen". This change will provide consistency in table text.
4. In the Maisons-Alfort package insert, in the CLINICAL TRIALS section, the "Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery" subsection, the "Efficacy of Lovenox Injection In the Prophylaxis of Deep Vein Thrombosis Following Total Knee Replacement Surgery" table (located on side 1, at the bottom of column 2, and on side 2, at the top of column 3) should be re-located such that the table appears intact.

5. In the Maisons-Alfort package insert, in the CLINICAL TRIALS section, the “Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction” subsection, the “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)” table (located at the bottom of side 2, column 2, and the top of side 2, column 3) should be re-located such that the table appears intact.
6. In the Maisons-Alfort Package Insert, in the ADVERSE REACTIONS section, the “Other” subsection, the “Adverse Events Occurring at $\geq 2\%$ Incidence in Lovenox Injection Treated Patients Undergoing Hip or Knee Replacement Surgery” table (located at the bottom of side 4, column 6, and the top of side 5, column 7) should be re-located such that the table appears intact.
7. In the HOW SUPPLIED section, in the “100 mg/mL Concentration” table, the following number display should be changed, to facilitate clarity and easy readability, as follows:

from:

10 000 IU

to:

10,000 IU

8. In the HOW SUPPLIED section, the “100 mg/mL Concentration” table, the following number display should be changed to facilitate clarity and easy readability, as follows:

from:

12 000 IU

to:

12,000 IU

from:

15 000 IU

to:

15,000 IU

IMMEDIATE CONTAINER LABELS (Supplement 030)

9. Provide the immediate container label for the 90 mg/0.6 mL graduated prefilled syringe, or alternatively, delete the packaging configuration from the DOSAGE AND ADMINISTRATION and the HOW SUPPLIED sections of the package insert as required under 21 CFR 201.57(k).

10. Based on the submitted color mock-ups, the colors of the immediate container labels are not accurately identified in the HOW SUPPLIED section of the package insert. Revise the HOW SUPPLIED section of the package insert to accurately identify the colors "Purple" (120 mg/0.8 mL) and "Blue" (150 mg/1.0 mL). Further, the 30 mg ampules and 30 mg/0.3 mL prefilled syringes are identified in the HOW SUPPLIED section as "Medium Blue". Provide more distinctive colors for the visual differentiation of the two strengths (30 mg/0.3 mL and 150 mg/1.0 mL).

BLISTER LABELS (Supplement 030)

11. Provide identical color (as much as possible) across a specific package line. Hence, if the colors are changed (as requested in 10. above), the blister colors should change accordingly.

CARTONS (Supplement 030)

12. The mock up cartons are different in size and shape than those submitted December 29, 1999 (and currently approved for other strengths). Please re-submit the cartons, similar to those submitted December 29, 1999, and revise according to the June 2, 2000 approval letter, or alternatively, provide an explanation of the change in the carton size and configuration, and a side-by-side comparison of the texts of the carton mock-ups.
13. Provide identical color (as much as possible) across a specific package line. Hence, if the colors are changed (as requested in 10. above), the carton colors should change accordingly.

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

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, RN, MSN
Chief, Project Management Staff
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

/s/

Julie DuBeau
3/20/01 03:52:39 PM

**APPEARS THIS WAY
ON ORIGINAL**



Quintiles, Inc.
Post Office Box 9708
Kansas City, MO 64134-0708
(816) 767-6000

May 23, 2001

ORIGINAL



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

Subject: **NDA 20-164/S-030**
Lovenox® (enoxaparin sodium) Injection

**Submission of Final Printed
Labeling and Labels**

SCF-30-FIT

Dear Dr. Talarico:

Quintiles, Inc., as the US Agent for Aventis Pharmaceuticals Inc., has been authorized to communicate with the Agency for the above referenced NDA. On their behalf, the following information is being submitted in duplicate as an amendment to the above-reference NDA pursuant to 21 CFR 314.50. A complete desk copy of this submission is enclosed for Karen Oliver, Project Manager for the Division of Gastrointestinal and Coagulation Drug Products.

As requested by the Agency, we are providing 20 copies of the final printed labeling in the two formats requested (Maisons-Alfort and Dagenham). Of these copies, 10 of each format have been individually mounted for submission. The text of the labeling is identical to that received from the Agency by fax on November 17, 2000, with the S-036 approval letter and the additional changes requested in the Agency fax of March 26, 2001. Additionally, 20 mock-up copies of the syringe label, blisterfoil, carton labels and plunger for the 120 mg and 150 mg packaging are being provided.

For the Agency's reference and in response to items 9 - 12 in the March 26, 2001 fax, the Sponsor is providing a mock-up copy for all strengths of all Lovenox labels in this submission. This is to allow the review of the colors for the product. The sponsor is providing a mock-up copy of all labels for marketed product and a plunger. These examples are provided to:

- assure that the Sponsor has provided distinctive colors as requested
- assure there is visual differentiation of the colors
- assure identical color across a specific package line.

In the June 2, 2000 approval letter, the Agency advised that the phrase "NEW CONCENTRATION" on the 120 mg/0.8mL and 150 mg/1mL cartons should be deleted after 6 months. The Sponsor has not yet launched the product; the six-month period has not expired. Therefore, this wording is still presented on the label copy and the Sponsor intends to launch with this statement present. The Sponsor will comply with the six-month timeframe.

The Sponsor no longer plans to market the 90 mg dosage strength and it has been deleted from the labeling.

Identical labeling is also being supplied to supplements 020, 034, 036, and 037.

NDA 20-164/S-030
Lovenox ® (enoxaparin sodium) Inj.

May 23, 2001
Submission of Final Printed Labeling and Labels

Please let me know if you need additional information.

Sincerely,

Michelle Kliewer

Michelle Kliewer
Associate Director, Regulatory and Technical Services
Quintiles, Inc.
Phone: 816-767-6671
Fax: 816-767-7373

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-164/S-020, 030, 034
S-036, 037

Aventis Pharmaceuticals Products Inc.
C/O Quintiles, Inc.
Attention: Ms. Michelle Kliewer
P.O. Box 9708 (Dock 6, F3-M3026)
Kansas City, MO 64134-0708

Dear Ms. Kliewer:

We acknowledge the receipt of your May 23, 2001 submission containing final printed labeling in response to our August 30, 2000 (S-020), June 2, 2000 (S-030), May 30, 2000 (S-034), November 17, 2000 (S-036), and September 13, 2000 (S-037) letters approving your supplemental drug applications as follows:

Supplement 020, submitted November 24, 1998, approved August 3, 2000, provides for: changes to the CLINICAL TRIALS section, the "Unstable Angina and Non-Q-Wave Myocardial Infarction" subsection, regarding the one year follow-up period.

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We have reviewed the labeling (package inserts, immediate container vial labels, and cartons) that you submitted in accordance with our approval letters, and we find it acceptable.

We request that you consider implementing the following changes to the running head: (1) enlarge the print size; (2) use bolded letters; and (3) center the words at the top of each column.

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

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

/s/

Lilia Talarico
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