CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-164/S-043

Name: Lovenox® (Enoxaparin Sodium) Injection

Sponsor: Aventis Pharmaceuticals, Inc.

Approval Date: January 23, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-043

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-043

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-164

Aventis Pharmaceuticals, Inc.
Attention: Joseph A. Carrado, M.Sc., R.Ph.,
Director and Regulatory Liaison
Global Drug Regulatory Affairs
200 Crossing Blvd., P.O. Box 6800
Bridgewater, NJ 08807-0800

Dear Mr. Carrado:

Please refer to your supplemental new drug application dated May 15, 2001, received May 16, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox (enoxaparin sodium) Injection, 300 mg/3.0 mL.

We acknowledge receipt of your submissions dated September 20, 2002 and January 17, 2003.

Your submission of September 20, 2002 constituted a complete response to our August 30, 2002, action letter.

This supplemental new drug application provides for a multiple-dose vial presentation of Lovenox Injection (300 mg/3 mL) at a concentration of 100 mg/mL and preserved with benzyl alcohol at 1.5% (m/v) level; a new contract manufacturing site, Catalytica Pharmaceuticals, Greenville, South Carolina, for the drug product; revised package insert labeling; and immediate container and carton labeling for he proposed multiple dose vial.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revision listed below.

In the **WARNINGS** section, **Pregnancy, Miscellaneous** subsection, in the first paragraph, third sentence, that reads, "Because benzyl alcohol may cross the placenta, Lovenox multiple-dose vials, preserved with benzyl alcohol, should be used with caution in pregnant women only if clearly needed (see **PRECAUTIONS, Pregnancy**)." insert the word "and" before the word "only" so that the sentence reads as follows:

"Because benzyl alcohol may cross the placenta, Lovenox multiple-dose vials, preserved with benzyl alcohol, should be used with caution in pregnant women and only if clearly needed (see **PRECAUTIONS, Pregnancy**)."

The final printed labeling (FPL) must be identical, and include the minor editorial revision indicated, to the submitted labeling (package insert submitted September 20, 2002 and immediate container and carton labels submitted September 20, 2002). This revision is a term of the approval of this application.

In addition, we recommend that you include multiple instructions for use in each multiple vial package.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-164/S-043." Approval of this submission by FDA is not required before the labeling is used.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

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

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Joyce Korvick
1/23/03 05:26:58 PM
for Dr.Robert Justice

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-043

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-164/S-043

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

Dear Mr. Carrado:

Please refer to your supplemental new drug application dated May 15, 2001, received May 16, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium) Injection, 30, 40, 60, 80 and 100 mg.

We acknowledge receipt of your submission dated May 1, 2002. Your submission of May 1, 2002 constituted a complete response to our September 14, 2001 action letter.

This supplement proposes the following changes:

1. A multiple dose vial presentation of lovenox Injection (300 mg/3mL) at a concentration of 100 mg/mL and preserved with benzyl alcohol at 1.5% (m/v) level, and

2. A new contract manufacturing site, Catalytica Pharmaceuticals, Greenville, South Carolina, for the drug product.

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

<u>300 mg/mL Immediate Container and Carton Labeling</u>

1. Include the dosage form "Injection" in the established name as "Enoxaparin Sodium Injection" for the 300 mg/3mL immediate container and carton labeling.

2. Increase the prominence of the established name so that it is at least half as large as the proprietary name on the carton labeling [see 21 CFR 202.1(b) (2)].

4. Revise the 300 mg/mL immediate container and 300 mg/mL carton labeling to express the net quantity statement in terms of volume (i.e., 3 mL) and not total drug concentration.

5. Delete the terminal zeros in "3.0 mL" from the 300 mg/mL immediate container and 300 mg/mL carton labeling because the amount could be misinterpreted as "30 mL."

6. Delete [redacted]

We remind you to incorporate the current number of reports of epidural or spinal hematoma formation in the labeling text of the package insert (PI) in the **ADVERSE REACTIONS** section, **Adverse Events in Lovenox Injection Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction** subsection, in the third paragraph, first sentence that begins, "Ongoing Safety Surveillance: Since 1993 . . ."

In addition, all previous revisions as reflected in the most recently approved labeling, specifically Supplement-046, approved January 9, 2002, which provided for revisions to the **PRECAUTIONS** section, **Pregnancy** subsection of the PI, 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.

APPEARS THIS WAY
ON ORIGINAL

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

Joyce Korvick
8/30/02 04:09:00 PM
for Victor Raczkowski

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-043

LABELING

ID number:	**50060724**
Version:	**G**
Country:	**USA**
Date:	**9-6-02**
Operator:	**DM**
Product Desc.	**Carton, Lovenox, 300mg, Multidose**
Supplier:	**Catalytica**

Artwork created in: Adobe Illustrator 9.0, Mac format

Fonts used: OceanSans AV Bold, Light, Light Italic, Zapf Dingbats

Minimum point size of text: 5 pt.

Colors Used:

Reflex Blue **PMS 186** No Varnish

Proofreading: **Date:** _____

Signature: _____

Date: _____

Signature: _____

Regulatory: **Date:** _____

Signature: _____

Functional: **Date:** _____

Signature: _____

ID number:	**50060723**
Version:	**D/Aventis Graphics**
Country:	**USA**
Date:	**9-6-02**
Operator:	**DM**
Product Desc.	**Label, Lovenox Multidose, Vial**
Supplier:	**Catalytica**

Artwork created in: Adobe Illustrator 9.0, Mac format

Fonts used: OceanSansAV, Bold, Zapf Dingbats

Minimum point size of text: 5 pt.

Colors Used:

PMS 186 **Black**

Proofreading: **Date:** _____

Signature: _____

Date: _____

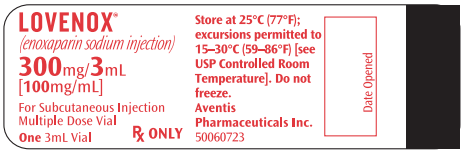
Signature: _____

Regulatory: **Date:** _____

Signature: _____

Functional: **Date:** _____

Signature: _____



LOVENOX®
(enoxaparin sodium injection)

Rx only
Rev. March 2003

SPINAL / EPIDURAL HEMATOMAS

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

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

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

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

DESCRIPTION

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

Lovenox Injection is available in two concentrations:

1. 100 mg per mL

-Prefilled Syringes	30 mg / 0.3 mL, 40 mg / 0.4 mL
-Graduated Prefilled Syringes	60 mg / 0.6 mL, 80 mg / 0.8 mL, 100 mg / 1 mL
-Ampules	30 mg / 0.3 mL
-Multiple-Dose Vials	300 mg / 3.0 mL

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

2. 150 mg per mL

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

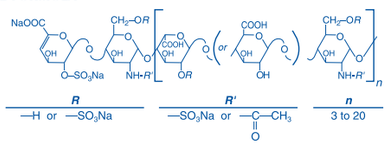
Lovenox Injection 150 mg/mL Concentration contains 15 mg enoxaparin sodium (appropriate anti-Factor Xa activity of 1500 IU [with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard]) per 0.1 mL Water for Injection.

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

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

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

STRUCTURAL FORMULA



CLINICAL PHARMACOLOGY

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

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

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

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

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

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

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

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

CLINICAL TRIALS

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

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

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

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

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

In a second double-blind, parallel group study, Lovenox Injection 40 mg SC once a day was compared to heparin 5000 U every 8 hours SC in patients undergoing colorectal surgery (one-third with cancer). A total of 1347 patients were randomized in the study and all patients were treated. Patients ranged in age from 18 to 92 years (mean age 50.1 years) with 54.2% men and 45.8% women. Treatment was initiated approximately 2 hours prior to surgery and continued for approximately 7 to 10 days after surgery. The efficacy data are provided below.

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

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

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

LOVENOX®
(enoxaparin sodium injection)

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery: Lovenox Injection has been shown to reduce the risk of post-operative deep vein thrombosis (DVT) following hip or knee replacement surgery.

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

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

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

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

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

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

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

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

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

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

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

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

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

Extended Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery: In a study of extended prophylaxis for patients undergoing hip replacement surgery, patients were treated, while hospitalized, with Lovenox Injection 40 mg SC, initiated up to 12 hours prior to surgery for the prophylaxis of post-operative DVT. At the end of the peri-operative period, all patients underwent bilateral venography. In a double-blind design, those patients with no venous thromboembolic disease were randomized to a post-discharge regimen of either Lovenox Injection 40 mg (n = 90) once a day SC or to placebo (n = 89) for 3 weeks. A total of 179 patients were randomized in the double-blind phase of the study and all patients were treated. Patients ranged in age from 47 to 87 years (mean age 69.4 years) with 57% men and 43% women. In this population of patients, the incidence of DVT during extended prophylaxis was significantly lower for Lovenox Injection compared to placebo. The efficacy data are provided below.

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

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

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

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

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

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

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

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

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

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

LOVENOX®
(enoxaparin sodium injection)

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

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

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

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

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

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

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

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

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

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

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

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

Similarly, in a multicenter, open-label, parallel group study, patients with acute proximal DVT were randomized to Lovenox Injection or heparin. Patients who could not receive outpatient therapy were excluded from entering the study. Outpatient exclusion criteria included the following: inability to receive outpatient heparin therapy because of associated co-morbid conditions or potential for non-compliance and inability to attend follow-up visits as an outpatient because of geographic inaccessibility. Eligible patients could be treated in the hospital, but ONLY Lovenox Injection patients were permitted to go home on therapy (72%). A total of 501 patients were randomized in the study and all patients were treated. Patients ranged in age from 19 to 96 years (mean age 57.8 years) with 60.5% men and 39.5% women. Patients were randomized to either Lovenox Injection 1 mg/kg every 12 hours SC or heparin i.v. bolus (5000 IU) followed by a continuous infusion administered to achieve an aPTT of 60 to 85 seconds (in-patient treatment). All patients also received warfarin sodium as described in the previous study. Lovenox Injection or standard heparin therapy was administered for a minimum of 5 days. Lovenox Injection was equivalent to standard heparin therapy in reducing the risk of recurrent venous thromboembolism. The efficacy data are provided below.

Efficacy of Lovenox Injection in Treatment of Deep Vein Thrombosis

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

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

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

Lovenox Injection is contraindicated in patients with active major bleeding, in patients with thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of enoxaparin sodium, or in patients with hypersensitivity to enoxaparin sodium.

Patients with known hypersensitivity to heparin or pork products should not be treated with Lovenox Injection or any of its constituents.

WARNINGS

Lovenox Injection is not intended for intramuscular administration.

Lovenox Injection cannot be used interchangeably (unit for unit) with heparin or other low molecular weight heparins as they differ in manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units, and dosage. Each of these medicines has its own instructions for use.

Lovenox Injection should be used with extreme caution in patients with a history of heparin-induced thrombocytopenia.

Hemorrhage: Lovenox Injection, like other anticoagulants, should be used with extreme caution in conditions with increased risk of hemorrhage, such as bacterial endocarditis, congenital or acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disease, hemorrhagic stroke, or shortly after brain, spinal, or ophthalmological surgery, or in patients treated concomitantly with platelet inhibitors.

Cases of epidural or spinal hematomas have been reported with the associated use of Lovenox Injection and spinal/epidural anesthesia or spinal puncture resulting in long-term or permanent paralysis. The risk of these events is higher with the use of post-operative indwelling epidural catheters or by the concomitant use of additional drugs affecting hemostasis such as NSAIDs (see boxed WARNING; ADVERSE REACTIONS, Ongoing Safety Surveillance; and PRECAUTIONS, Drug Interactions).

Major hemorrhages including retroperitoneal and intracranial bleeding have been reported. Some of these cases have been fatal.

Bleeding can occur at any site during therapy with Lovenox Injection. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

Thrombocytopenia: Thrombocytopenia can occur with the administration of Lovenox Injection.

Moderate thrombocytopenia (platelet counts between 100,000/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.

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

Miscellaneous: Lovenox multiple-dose vials contain benzyl alcohol as a preservative. The administration of medications containing benzyl alcohol as a preservative to premature neonates has been associated with a fatal "Gasping Syndrome". Because benzyl alcohol may cross the placenta, Lovenox multiple-dose vials, preserved with benzyl alcohol, should be used with caution in pregnant women and only if clearly needed (see **PRECAUTIONS, Pregnancy**).

PRECAUTIONS

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

Laboratory Tests: Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with Lovenox Injection. When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of Lovenox Injection activity and, therefore, unsuitable for monitoring. Anti-Factor Xa may be used to monitor the anticoagulant effect of Lovenox Injection in patients with significant renal impairment. If during Lovenox Injection therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa levels may be used to monitor the anticoagulant effects of Lovenox Injection (see **CLINICAL PHARMACOLOGY: Pharmacodynamics**).

Drug Interactions: Unless really needed, agents which may enhance the risk of hemorrhage should be discontinued prior to initiation of Lovenox Injection therapy. These agents include medications such as: anticoagulants, platelet inhibitors including acetylsalicylic acid, salicylates, NSAIDs (including ketorolac tromethamine), dipyridamole, or sulfinpyrazone. If co-administration is essential, conduct close clinical and laboratory monitoring (see **PRECAUTIONS: Laboratory Tests**).

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of enoxaparin. Enoxaparin was not mutagenic in *in vitro* tests, including the Ames test, mouse lymphoma cell forward mutation test, and human lymphocyte chromosomal aberration test, and the *in vivo* rat bone marrow chromosomal aberration test. Enoxaparin was found to have no effect on fertility or reproductive performance of male and female rats at SC doses up to 20 mg/kg/day or 141 mg/m^2/day. The maximum human dose in clinical trials was 2.0 mg/kg/day or 78 mg/m^2/day (for an average body weight of 70 kg, height of 170 cm, and body surface area of 1.8 m^2).

Pregnancy: *Teratogenic Effects:* Pregnancy Category B: Teratology studies have been conducted in pregnant rats and rabbits at SC doses of enoxaparin up to 30 mg/kg/day or 211 mg/m^2/day and 410 mg/m^2/day, respectively. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
There have been reports of congenital anomalies in infants born to women who received enoxaparin during pregnancy including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia, and cardiac defect. A cause and effect relationship has not been established nor has the incidence been shown to be higher than in the general population.
Non-teratogenic Effects: There have been post-marketing reports of fetal death when pregnant women received Lovenox Injection. Causality for these cases has not been determined. Pregnant women receiving anti-coagulants, including enoxaparin, are at increased risk for bleeding. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women receiving enoxaparin should be carefully monitored. Pregnant women and women of child-bearing potential should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.
In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 7 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. There are postmarketing reports of prosthetic valve thrombosis in pregnant women with prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. These events resulted in maternal death or surgical interventions. The use of Lovenox Injection is not recommended for thromboprophylaxis in pregnant women with prosthetic heart valves (see **WARNINGS: Prosthetic Heart Valves**).
Cases of "Gasping Syndrome" have occurred in premature infants when large amounts of benzyl alcohol have been administered (99-405 mg/kg/day). The multiple-dose vial of Lovenox solution contains 15 mg / 1.0 mL benzyl alcohol as a preservative (see **WARNINGS, Miscellaneous**).

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

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

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

ADVERSE REACTIONS

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

Major Bleeding Episodes Following Abdominal and Colorectal Surgery[1]

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

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

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

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

[1] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major. In the knee replacement surgery trials, intraocular hemorrhages were also considered major hemorrhages.
[2] Lovenox Injection 30 mg every 12 hours SC initiated 12 to 24 hours after surgery and continued for up to 14 days after surgery.
[3] Lovenox Injection 40 mg SC once a day initiated up to 12 hours prior to surgery and continued for up to 7 days after surgery.
[4] Lovenox Injection 40 mg SC once a day for up to 21 days after discharge.

NOTE: At no time point were the 40 mg once a day pre-operative and the 30 mg every 12 hours post-operative hip replacement surgery prophylactic regimens compared in clinical trials.
Injection site hematomas during the extended prophylaxis period after hip replacement surgery occurred in 9% of the Lovenox Injection patients versus 1.8% of the placebo patients.

Major Bleeding Episodes in Medical Patients With Severely Restricted Mobility During Acute Illness[1]

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

[1] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, (2) if the hemorrhage caused a decrease in hemoglobin of ≥2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major although none were reported during the trial.
[2] The rates represent major bleeding on study medication up to 24 hours after last dose.

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

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

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

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

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

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

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

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

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

[1] Excluding unrelated adverse events.

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

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

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

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

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

[1]Excluding unrelated and unlikely adverse events.

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

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

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

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

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

[1] Excluding unrelated adverse events.

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

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

Note: Lovenox Injection is available in two concentrations:

1. 100 mg/mL Concentration: 30 mg / 0.3 mL ampules, 30 mg / 0.3 mL and 40 mg / 0.4 mL prefilled single-dose syringes, 60 mg / 0.6 mL, 80 mg / 0.8 mL, and 100 mg / 1 mL prefilled, graduated, single-dose syringes, 300 mg / 3.0 mL multiple-dose vials.
2. 150 mg/mL Concentration: 120 mg / 0.8 mL and 150 mg / 1 mL prefilled, graduated, single-dose syringes.

Adult Dosage:
Abdominal Surgery: In patients undergoing abdominal surgery who are at risk for thromboembolic complications, the recommended dose of Lovenox Injection is **40 mg once a day** administered by SC injection with the initial dose given 2 hours prior to surgery. The usual duration of administration is 7 to 10 days; up to 12 days administration has been well tolerated in clinical trials.
Hip or Knee Replacement Surgery: In patients undergoing hip or knee replacement surgery, the recommended dose of Lovenox Injection is **30 mg every 12 hours** administered by SC injection. Provided that hemostasis has been established, the initial dose should be given 12 to 24 hours after surgery. For hip replacement surgery, a dose of

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

Directions for use of One Point Cut (OPC) ampules for Lovenox Injection:
Use aseptic technique throughout the process. Prior to starting, gently tap the top of the ampule to assist the flow of the solution from the upper portion of the ampule to the lower portion.
1. Locate the yellow dot on the upper portion of the ampule. Below this dot is a small score on the neck of the ampule. Hold the ampule with the yellow dot **facing away from you.** *Do not try to break the ampule at the colored rings,* which are identification marks used only in manufacturing.
2. Cover yellow dot with your index finger and position your thumb opposite yellow dot.
3. Apply pressure to the top and bottom portions of the ampule to snap the ampule open away from you.

HOW SUPPLIED

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

100 mg/mL Concentration

Dosage Unit / Strength[1]	**Anti-Xa Activity**[2]	**Package Size (per carton)**	**Label Color**	**NDC # 0075-**
Ampules				
30 mg / 0.3 mL	3000 IU	10 ampules	Medium Blue	0624-03
Prefilled Syringes[3]				
30 mg / 0.3 mL	3000 IU	10 syringes	Medium Blue	0624-30
40 mg / 0.4 mL	4000 IU	10 syringes	Yellow	0620-40
Graduated Prefilled Syringes[3]				
60 mg / 0.6 mL	6000 IU	10 syringes	Orange	0621-60
80 mg / 0.8 mL	8000 IU	10 syringes	Brown	0622-80
100 mg / 1 mL	10,000 IU	10 syringes	Black	0623-00
Multiple-Dose Vial[4]				
300 mg / 3.0 mL	30,000 IU	1 vial	Red	0626-03

[1] Strength represents the number of milligrams of enoxaparin sodium in Water for Injection. **Lovenox Injection** ampules, 30 and 40 mg prefilled syringes, and 60, 80, and 100 mg graduated prefilled syringes each contain **10 mg enoxaparin sodium per 0.1 mL Water for Injection**.
[2] Approximate anti-Factor Xa activity based on reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard.
[3] Each **Lovenox Injection** syringe is affixed with a 27 gauge x 1/2 inch needle.
[4] Each Lovenox multiple-dose vial contains 15 mg / 1.0 mL of benzyl alcohol as a preservative.

150 mg/mL Concentration

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

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

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].
Keep out of the reach of children.

Lovenox Injection prefilled and graduated prefilled syringes manufactured in France.
Lovenox Injection ampules manufactured in England.
Lovenox multiple-dose vial manufactured for Aventis Pharmaceuticals Products Inc. by DSM Pharmaceuticals, Inc. Greenville, NC 27835.
Aventis Pharmaceuticals Products Inc.
BRIDGEWATER, NJ 08807

Prescribing information as of March 2003

50069638

50069650
Rev. March 2003

LOVENOX®
(enoxaparin sodium injection)™

LOVENOX®
(enoxaparin sodium injection)

Rx only
Rev. March 2003

SPINAL / EPIDURAL HEMATOMAS

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

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

Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurologic compromise is noted, urgent treatment is necessary. The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (see also **WARNINGS, Hemorrhage,** and **PRECAUTIONS, Drug Interactions**).

DESCRIPTION

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

Lovenox Injection is available in two concentrations:

1. 100 mg per mL

-Prefilled Syringes	30 mg / 0.3 mL, 40 mg / 0.4 mL
-Graduated Prefilled Syringes	60 mg / 0.6 mL, 80 mg / 0.8 mL, 100 mg / 1 mL
-Ampules	30 mg / 0.3 mL
-Multiple-Dose Vials	300 mg / 3.0 mL

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

2. 150 mg per mL

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

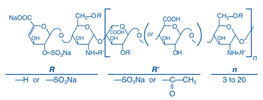
Lovenox Injection 150 mg/mL Concentration contains 15 mg enoxaparin sodium (appropriate anti-Factor Xa activity of 1500 IU [with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard]) per 0.1 mL Water for Injection.

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

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

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

STRUCTURAL FORMULA



LOVENOX®
(enoxaparin sodium injection)

CLINICAL PHARMACOLOGY

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

Pharmacodynamics (conducted using 100 mg / mL concentration): Maximum anti-Factor Xa and anti-thrombin (anti-Factor IIa) activities occur 3 to 5 hours after SC injection of enoxaparin. Mean peak anti-Factor Xa activity was 0.16 IU/mL (1.58 µg/mL) and 0.38 IU/mL (3.83 µg/mL) after the 20 mg and the 40 mg clinically tested SC doses, respectively. Mean (n = 46) peak anti-Factor Xa activity was 1.1 IU/mL at steady state in patients with unstable angina receiving 1mg/kg SC every 12 hours for 14 days. Mean absolute bioavailability of enoxaparin, given SC, based on anti-Factor Xa activity is 92% in healthy volunteers. The volume of distribution of anti-Factor Xa activity is about 6 L. Following intravenous (i.v.) dosing, the total body clearance of enoxaparin is 26 mL/min. After i.v. dosing of enoxaparin labeled with the gamma-emitter, ^{99m}Tc, 40% of radioactivity and 8 to 20% of anti-Factor Xa activity were recovered in urine in 24 hours. Elimination half-life based on anti-Factor Xa activity was 4.5 hours after SC administration. Following a 40 mg SC once a day dose, significant anti-Factor Xa activity persists in plasma for about 12 hours. Following SC dosing, the apparent clearance (CL/F) of enoxaparin is approximately 15 mL/min. Apparent clearance and A_{max} derived from anti-Factor Xa values following single SC dosing (40 mg and 60 mg) were slightly higher in males than in females. The source of the gender difference in these parameters has not been conclusively identified, however, body weight may be a contributing factor.

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

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

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

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

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

CLINICAL TRIALS

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

In a double-blind, parallel group study of patients undergoing elective cancer surgery of the gastrointestinal, urological, or gynecological tract, a total of 1116 patients were enrolled in the study, and 1115 patients were treated. Patients ranged in age from

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32 to 97 years (mean age 67 years) with 52.7% men and 47.3% women. Patients were 98% Caucasian, 1.1% Black, 0.4% Oriental, and 0.4% others. Lovenox Injection 40 mg SC, administered once a day, beginning 2 hours prior to surgery and continuing for a maximum of 12 days after surgery, was comparable to heparin 5000 U every 8 hours SC in reducing the risk of deep vein thrombosis (DVT). The efficacy data are provided below.

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

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

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

In a second double-blind, parallel group study, Lovenox Injection 40 mg SC once a day was compared to heparin 5000 U every 8 hours SC in patients undergoing colorectal surgery (one-third with cancer). A total of 1347 patients were randomized in the study and all patients were treated. Patients ranged in age from 18 to 92 years (mean age 50.1 years) with 54.2% men and 45.8% women. Treatment was initiated approximately 2 hours prior to surgery and continued for approximately 7 to 10 days after surgery. The efficacy data are provided below.

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

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

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

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery: Lovenox Injection has been shown to reduce the risk of post-operative deep vein thrombosis (DVT) following hip or knee replacement surgery.

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

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

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

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

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

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

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

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

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

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

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

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

Additionally, in an open-label, parallel group, randomized clinical study, Lovenox Injection 30 mg every 12 hours SC in patients undergoing elective knee replacement surgery was compared to heparin 5000 U every 8 hours SC. A total of 453 patients were randomized in the study and all were treated. Patients ranged in age from 38 to 90 years (mean age 68.5 years) with 43.7% men and 56.3% women. Patients were 92.5% Caucasian, 5.3% Black, 0.2% Oriental, and 0.4% others. Treatment was initiated after surgery and continued up to 14 days. The incidence of deep vein thrombosis was significantly lower for Lovenox Injection compared to heparin. *Extended Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery:* In a study of extended prophylaxis for patients undergoing hip replacement surgery, patients were treated, while hospitalized, with Lovenox Injection 40 mg SC, initiated up to 12 hours prior to surgery for the prophylaxis of post-operative DVT. At the end of the peri-operative period, all patients underwent bilateral venography. In a double-blind design, those patients with no venous thromboembolic disease were randomized to a post-discharge regimen of either Lovenox Injection 40 mg (n = 90) once a day SC or to placebo (n = 89) for 3 weeks. A total of 179 patients were randomized in the double-blind phase of the study and all patients were treated. Patients ranged in age from 47 to 87 years (mean age 69.4 years) with 57% men and 43% women. In this population of patients, the incidence of DVT during extended prophylaxis was significantly lower for Lovenox Injection compared to placebo. The efficacy data are provided below.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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Similarly, in a multicenter, open-label, parallel group study, patients with acute proximal DVT were randomized to Lovenox Injection or heparin. Patients who could not receive outpatient therapy were excluded from entering the study. Outpatient exclusion criteria included the following: inability to receive outpatient heparin therapy because of associated co-morbid conditions or potential for non-compliance and inability to attend follow-up visits as an outpatient because of geographic inaccessibility. Eligible patients could be treated in the hospital, but ONLY Lovenox Injection patients were permitted to go home on therapy (72%). A total of 501 patients were randomized in the study and all patients were treated. Patients ranged in age from 19 to 96 years (mean age 57.8 years) with 60.5% men and 39.5% women. Patients were randomized to either Lovenox Injection 1 mg/kg every 12 hours SC or heparin i.v. bolus (5000 IU) followed by a continuous infusion administered to achieve an aPTT of 60 to 85 seconds (in-patient treatment). All patients also received warfarin sodium as described in the previous study. Lovenox Injection or standard heparin therapy was administered for a minimum of 5 days. Lovenox Injection was equivalent to standard heparin therapy in reducing the risk of recurrent venous thromboembolism. The efficacy data are provided below.

Efficacy of Lovenox Injection in Treatment of Deep Vein Thrombosis

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

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

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

Lovenox Injection is contraindicated in patients with active major bleeding, in patients with thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of enoxaparin sodium, or in patients with hypersensitivity to enoxaparin sodium.

Patients with known hypersensitivity to heparin or pork products should not be treated with Lovenox Injection or any of its constituents.

WARNINGS

Lovenox Injection is not intended for intramuscular administration.

Lovenox Injection cannot be used interchangeably (unit for unit) with heparin or other low molecular weight heparins as they differ in manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units, and dosage. Each of these medicines has its own instructions for use.

Lovenox Injection should be used with extreme caution in patients with a history of heparin-induced thrombocytopenia.

Hemorrhage: Lovenox Injection, like other anticoagulants, should be used with extreme caution in conditions with increased risk of hemorrhage, such as bacterial endocarditis, congenital or acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disease, hemorrhagic stroke, or shortly after brain, spinal, or ophthalmological surgery, or in patients treated concomitantly with platelet inhibitors.

Cases of epidural or spinal hematomas have been reported with the associated use of Lovenox Injection and spinal/epidural anesthesia or spinal puncture resulting in long-term or permanent paralysis. The risk of these events is higher with the use of post-operative indwelling epidural catheters or by the concomitant use of additional drugs affecting hemostasis such as NSAIDs (see boxed WARNING; ADVERSE REACTIONS, Ongoing Safety Surveillance; and PRECAUTIONS, Drug Interactions).

Major hemorrhages including retroperitoneal and intracranial bleeding have been reported. Some of these cases have been fatal.

Bleeding can occur at any site during therapy with Lovenox Injection. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

Thrombocytopenia: Thrombocytopenia can occur with the administration of Lovenox Injection.

Moderate thrombocytopenia (platelet counts between 100,000/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.

Prosthetic Heart Valves: The use of Lovenox Injection is not recommended for thromboprophylaxis in patients with prosthetic heart valves. Cases of prosthetic heart valve thrombosis have been reported in patients with prosthetic valves who have received enoxaparin for thromboprophylaxis. Some of these cases were

ID number: 50069650
Version: B
Country: USA
Date: 4-1-03
Operator: DM
Logo version: USA A2
Product Desc. Insert, Lovenox, Ampoule
Supplier: LeTrait
Artwork created in: QuarkXpress 4.0, Mac format
Fonts used: OceanSansAV Light, Bold, Light Italic
Minimum point size of text: 5 pt.

Colors Used:
Reflex Blue

Proofreading: Date: _____
Signature: _____
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Regulatory: Date: _____
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Functional: Date: _____
Signature: _____

pregnant women in whom thrombosis led to maternal deaths and fetal deaths. Pregnant women with prosthetic heart valves may be at higher risk for thromboembolism (see **PRECAUTIONS: Pregnancy**).
Miscellaneous: Lovenox multiple-dose vials contain benzyl alcohol as a preservative. The administration of medications containing benzyl alcohol as a preservative to premature neonates has been associated with a fatal "Gasping Syndrome". Because benzyl alcohol may cross the placenta, Lovenox multiple-dose vials, preserved with benzyl alcohol, should be used with caution in pregnant women and only if clearly needed (see **PRECAUTIONS, Pregnancy**).

PRECAUTIONS

General: Lovenox Injection should not be mixed with other injections or infusions. Lovenox Injection should be used with care in patients with a bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration, diabetic retinopathy, and hemorrhage. Elderly patients and patients with renal insufficiency may show delayed elimination of enoxaparin. Lovenox Injection should be used with care in these patients. Adjustment of enoxaparin sodium dose may be considered for low weight (<45 kg) patients and/or for patients with severe renal impairment (creatinine clearance <30 mL/min).
If thromboembolic events occur despite Lovenox Injection prophylaxis, appropriate therapy should be initiated.
Laboratory Tests: Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with Lovenox Injection. When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of Lovenox Injection activity and, therefore, unsuitable for monitoring. Anti-Factor Xa may be used to monitor the anticoagulant effect of Lovenox Injection in patients with significant renal impairment. If during Lovenox Injection therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa levels may be used to monitor the anticoagulant effects of Lovenox Injection (see **CLINICAL PHARMACOLOGY: Pharmacodynamics**).
Drug Interactions: Unless really needed, agents which may enhance the risk of hemorrhage should be discontinued prior to initiation of Lovenox Injection therapy. These agents include medications such as: anticoagulants, platelet inhibitors including acetylsalicylic acid, salicylates, NSAIDs (including ketorolac tromethamine), dipyridamole, or sulfinpyrazone. If co-administration is essential, conduct close clinical and laboratory monitoring (see **PRECAUTIONS: Laboratory Tests**).
Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of enoxaparin. Enoxaparin was not mutagenic in *in vitro* tests, including the Ames test, mouse lymphoma cell forward mutation test, and human lymphocyte chromosomal aberration test, and the *in vivo* rat bone marrow chromosomal aberration test. Enoxaparin was found to have no effect on fertility or reproductive performance of male and female rats at SC doses up to 20 mg/kg/day or 141 mg/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.
There have been reports of congenital anomalies in infants born to women who received enoxaparin during pregnancy including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia, and cardiac defect. A cause and effect relationship has not been established nor has the incidence been shown to be higher than in the general population.
Non-teratogenic Effects: There have been post-marketing reports of fetal death when pregnant women received Lovenox Injection. Causality for these cases has not been determined. Pregnant women receiving anti-coagulants, including enoxaparin, are at increased risk for bleeding. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women receiving enoxaparin should be carefully monitored. Pregnant women and women of child-bearing potential should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.
In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 7 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. There are postmarketing reports of prosthetic valve thrombosis in pregnant women with prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. These events resulted in maternal death or surgical interventions. The use of Lovenox Injection is not recommended for thromboprophylaxis in pregnant women with prosthetic heart valves (see **WARNINGS: Prosthetic Heart Valves**).
Cases of "Gasping Syndrome" have occurred in premature infants when large amounts of benzyl alcohol have been administered (99-405 mg/kg/day). The multiple-dose vial of Lovenox solution contains 15 mg / 1.0 mL benzyl alcohol as a preservative (see **WARNINGS, Miscellaneous**).
Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Lovenox Injection is administered to nursing women.
Pediatric Use: Safety and effectiveness of Lovenox Injection in pediatric patients have not been established.
Geriatric Use: Over 2800 patients, 65 years and older, have received Lovenox Injection in pivotal clinical trials. The efficacy of Lovenox Injection in the elderly (≥65 years) was similar to that seen in younger patients (<65 years). The incidence of bleeding complications was similar between elderly and younger patients when 30 mg every 12 hours or 40 mg once a day doses of Lovenox Injection were employed. The incidence of bleeding complications was higher in elderly patients as compared to younger patients when Lovenox Injection was administered at doses of 1.5 mg/kg once a day or 1 mg/kg every 12 hours. The risk of Lovenox Injection-associated bleeding increased with age. Serious adverse events increased with age for patients receiving Lovenox Injection. Other clinical experience (including postmarketing surveillance and literature reports) has not revealed additional differences in the safety of Lovenox Injection between elderly and younger patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised. Monitoring of geriatric patients with low body weight (<45 kg) and those predisposed to decreased renal function should be considered. (see **CLINICAL PHARMACOLOGY** and **General** and **Laboratory Tests** subsections of **PRECAUTIONS**)

ADVERSE REACTIONS

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

Major Bleeding Episodes Following Abdominal and Colorectal Surgery[1]

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

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

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

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

[1] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major. In the knee replacement surgery trials, intraocular hemorrhages were also considered major hemorrhages.
[2] Lovenox Injection 30 mg every 12 hours SC initiated 12 to 24 hours after surgery and continued for up to 14 days after surgery.
[3] Lovenox Injection 40 mg SC once a day initiated up to 12 hours prior to surgery and continued for up to 7 days after surgery.
[4] Lovenox Injection 40 mg SC once a day for up to 21 days after discharge.

NOTE: At no time point were the 40 mg once a day pre-operative and the 30 mg every 12 hours post-operative hip replacement surgery prophylactic regimens compared in clinical trials.
Injection site hematomas during the extended prophylaxis period after hip replacement surgery occurred in 9% of the Lovenox Injection patients versus 1.8% of the placebo patients.

Major Bleeding Episodes in Medical Patients With Severely Restricted Mobility During Acute Illness[1]

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

[1] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, (2) if the hemorrhage caused a decrease in hemoglobin of ≥2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major although none were reported during the trial.
[2] The rates represent major bleeding on study medication up to 24 hours after last dose.

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

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

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

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

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

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

Thrombocytopenia: see **WARNINGS: Thrombocytopenia**.
Elevations of Serum Aminotransferases: Asymptomatic increases in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels greater than three times the upper limit of normal of the laboratory reference range have been reported in up to 6.1% and 5.9% of patients, respectively, during treatment with Lovenox Injection. Similar significant increases in aminotransferase levels have also been observed in patients and healthy volunteers treated with heparin and other low molecular weight heparins. Such elevations are fully reversible and are rarely associated with increases in bilirubin.
Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, elevations that might be caused by drugs like Lovenox Injection should be interpreted with caution.

Local Reactions: Mild local irritation, pain, hematoma, ecchymosis, and erythema may follow SC injection of Lovenox Injection.
Other: Other adverse effects that were thought to be possibly or probably related to treatment with Lovenox Injection, heparin, or placebo in clinical trials with patients undergoing hip or knee replacement surgery, abdominal or colorectal surgery, or treatment for DVT and that occurred at a rate of at least 2% in the Lovenox Injection group, are provided below.

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

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

[1] Excluding unrelated adverse events.

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

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

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

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

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

[1] Excluding unrelated and unlikely adverse events.

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

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

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

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

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

[1] Excluding unrelated adverse events.

Ongoing Safety Surveillance: Since 1993, there have been over 80 reports of epidural or spinal hematoma formation with concurrent use of Lovenox Injection and spinal/epidural anesthesia or spinal puncture. The majority of patients had a post-operative indwelling epidural catheter placed for analgesia or received additional drugs affecting hemostasis such as NSAIDs. Many of the epidural or spinal hematomas caused neurologic injury, including long-term or permanent paralysis. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.
Other Ongoing Safety Surveillance Reports: local reactions at the injection site (i.e., skin necrosis, nodules, inflammation, oozing), systemic allergic reactions (i.e., pruritus, urticaria, anaphylactoid reactions), vesiculobullous rash, purpura, thrombocytopenia, 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, 300 mg / 3.0 mL multiple-dose vials.
2. 150 mg/mL Concentration: 120 mg / 0.8 mL and 150 mg / 1 mL prefilled, graduated, single-dose syringes.

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

Directions for use of One Point Cut (OPC) ampules for Lovenox Injection:
Use aseptic technique throughout the process. Prior to starting, gently tap the top of the ampule to assist the flow of the solution from the upper portion of the ampule to the lower portion.
1. Locate the yellow dot on the upper portion of the ampule. Below this dot is a small score on the neck of the ampule. Hold the ampule with the yellow dot **facing away from you.** *Do not try to break the ampule at the colored rings*, which are identification marks used only in manufacturing.
2. Cover yellow dot with your index finger and position your thumb opposite yellow dot.
3. Apply pressure to the top and bottom portions of the ampule to snap the ampule open away from you.

HOW SUPPLIED

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

100 mg/mL Concentration

Dosage Unit / Strength[1]	Anti-Xa Activity[2]	Package Size (per carton)	Label Color	NDC # 0075-
Ampules 30 mg / 0.3 mL	3000 IU	10 ampules	Medium Blue	0624-03
Prefilled Syringes[3] 30 mg / 0.3 mL	3000 IU	10 syringes	Medium Blue	0624-30
40 mg / 0.4 mL	4000 IU	10 syringes	Yellow	0620-40
Graduated Prefilled Syringes[3] 60 mg / 0.6 mL	6000 IU	10 syringes	Orange	0621-60
80 mg / 0.8 mL	8000 IU	10 syringes	Brown	0622-80
100 mg / 1 mL	10,000 IU	10 syringes	Black	0623-00
Multiple-Dose Vial[4] 300 mg / 3.0 mL	30,000 IU	1 vial	Red	0626-03

[1] Strength represents the number of milligrams of enoxaparin sodium in Water for Injection. **Lovenox Injection** ampules, 30 and 40 mg prefilled syringes, and 60, 80, and 100 mg graduated prefilled syringes each contain **10 mg enoxaparin sodium per 0.1 mL Water for Injection**.
[2] Approximate anti-Factor Xa activity based on reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard.
[3] Each **Lovenox Injection** syringe is affixed with a 27 gauge x 1/2 inch needle.
[4] Each Lovenox multiple-dose vial contains 15 mg / 1.0 mL of benzyl alcohol as a preservative.

150 mg/mL Concentration

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

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

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].
Keep out of the reach of children.

Lovenox Injection prefilled and graduated prefilled syringes manufactured in France.
Lovenox Injection ampules manufactured in England.
Lovenox multiple-dose vial manufactured for Aventis Pharmaceuticals Products Inc. by DSM Pharmaceuticals, Inc. Greenville, NC 27835.
Aventis Pharmaceuticals Products Inc.
BRIDGEWATER, NJ 08807

Prescribing information as of March 2003

50069650

50069639
Rev. March 2003

LOVENOX® (enoxaparin sodium injection)

Aventis

50069639

LOVENOX®
(enoxaparin sodium injection)

Rx only
Rev. March 2003

SPINAL / EPIDURAL HEMATOMAS

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

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

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

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

DESCRIPTION

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

Lovenox Injection is available in two concentrations:

1. 100 mg per mL

-Prefilled Syringes	30 mg / 0.3 mL, 40 mg / 0.4 mL
-Graduated Prefilled Syringes	60 mg / 0.6 mL, 80 mg / 0.8 mL, 100 mg / 1 mL
-Ampules	30 mg / 0.3 mL
-Multiple-Dose Vials	300 mg / 3.0 mL

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

2. 150 mg per mL

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

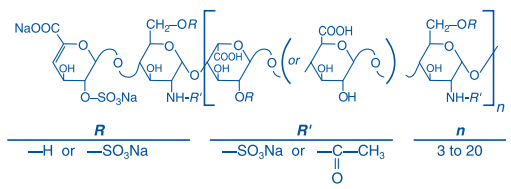
Lovenox Injection 150 mg/mL Concentration contains 15 mg enoxaparin sodium (appropriate anti-Factor Xa activity of 1500 IU [with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard]) per 0.1 mL Water for Injection.

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

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

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

STRUCTURAL FORMULA



CLINICAL PHARMACOLOGY

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

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.

LOVENOX®
(enoxaparin sodium injection)

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

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

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

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

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

CLINICAL TRIALS

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

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

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

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

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

In a second double-blind, parallel group study, Lovenox Injection 40 mg SC once a day was compared to heparin 5000 U every 8 hours SC in patients undergoing colorectal surgery (one-third with cancer). A total of 1347 patients were randomized in the study and all patients were treated. Patients ranged in age from 18 to 92 years (mean age 50.1 years) with 54.2% men and 45.8% women. Treatment was initiated approximately 2 hours prior to surgery and continued for approximately 7 to 10 days after surgery. The efficacy data are provided below.

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

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

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

ID number:	**50069639**
Version:	**B**
Country:	**USA**
Date:	**4-1-03**
Operator:	**DM**
Logo version:	**USA SCV A3**
Product Desc.	**Insert, Lovenox Preventis**
Supplier:	**LeTrait**
Artwork created in:	**QuarkXpress 4.0, Mac format**
Fonts used:	**OceanSansAV Light, Bold, Light Italic**
Minimum point size of text:	**5 pt.**
Colors Used:	
Reflex Blue	

Aventis

Proofreading: **Date:** _____
Signature: _____
Date: _____
Signature: _____

Regulatory: **Date:** _____
Signature: _____

Functional: **Date:** _____
Signature: _____

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery: Lovenox Injection has been shown to reduce the risk of post-operative deep vein thrombosis (DVT) following hip or knee replacement surgery.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Efficacy of Lovenox Injection in Treatment of Deep Vein Thrombosis

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

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

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS

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

Miscellaneous: Lovenox multiple-dose vials contain benzyl alcohol as a preservative. The administration of medications containing benzyl alcohol as a preservative to premature neonates has been associated with a fatal "Gasping Syndrome". Because benzyl alcohol may cross the placenta, Lovenox multiple-dose vials, preserved with benzyl alcohol, should be used with caution in pregnant women and only if clearly needed (see **PRECAUTIONS, Pregnancy**).

PRECAUTIONS

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

Laboratory Tests: Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with Lovenox Injection. When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of Lovenox Injection activity and, therefore, unsuitable for monitoring. Anti-Factor Xa may be used to monitor the anticoagulant effect of Lovenox Injection in patients with significant renal impairment. If during Lovenox Injection therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa levels may be used to monitor the anticoagulant effects of Lovenox Injection (see **CLINICAL PHARMACOLOGY: Pharmacodynamics**).

Drug Interactions: Unless really needed, agents which may enhance the risk of hemorrhage should be discontinued prior to initiation of Lovenox Injection therapy. These agents include medications such as: anticoagulants, platelet inhibitors including acetylsalicylic acid, salicylates, NSAIDs (including ketorolac tromethamine), dipyridamole, or sulfinpyrazone. If co-administration is essential, conduct close clinical and laboratory monitoring (see **PRECAUTIONS: Laboratory Tests**).

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of enoxaparin. Enoxaparin was not mutagenic in *in vitro* tests, including the Ames test, mouse lymphoma cell forward mutation test, and human lymphocyte chromosomal aberration test, and the *in vivo* rat bone marrow chromosomal aberration test. Enoxaparin was found to have no effect on fertility or reproductive performance of male and female rats at SC doses up to 20 mg/kg/day or 141 mg/m^2/day. The maximum human dose in clinical trials was 2.0 mg/kg/day or 78 mg/m^2/day (for an average body weight of 70 kg, height of 170 cm, and body surface area of 1.8 m^2).

Pregnancy: *Teratogenic Effects:* Pregnancy Category B: Teratology studies have been conducted in pregnant rats and rabbits at SC doses of enoxaparin up to 30 mg/kg/day or 211 mg/m^2/day and 410 mg/m^2/day, respectively. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
There have been reports of congenital anomalies in infants born to women who received enoxaparin during pregnancy including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia, and cardiac defect. A cause and effect relationship has not been established nor has the incidence been shown to be higher than in the general population.
Non-teratogenic Effects: There have been post-marketing reports of fetal death when pregnant women received Lovenox Injection. Causality for these cases has not been determined. Pregnant women receiving anti-coagulants, including enoxaparin, are at increased risk for bleeding. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women receiving enoxaparin should be carefully monitored. Pregnant women and women of child-bearing potential should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.
In a clinical study of pregnant women with prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 7 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. There are postmarketing reports of prosthetic valve thrombosis in pregnant women with prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. These events resulted in maternal death or surgical interventions. The use of Lovenox Injection is not recommended for thromboprophylaxis in pregnant women with prosthetic heart valves (see **WARNINGS: Prosthetic Heart Valves**).
Cases of "Gasping Syndrome" have occurred in premature infants when large amounts of benzyl alcohol have been administered (99-405 mg/kg/day). The multiple-dose vial of Lovenox solution contains 15 mg / 1.0 mL benzyl alcohol as a preservative (see **WARNINGS, Miscellaneous**).

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

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

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

ADVERSE REACTIONS

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

Major Bleeding Episodes Following Abdominal and Colorectal Surgery[1]

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

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

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

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

[1] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major. In the knee replacement surgery trials, intraocular hemorrhages were also considered major hemorrhages.
[2] Lovenox Injection 30 mg every 12 hours SC initiated 12 to 24 hours after surgery and continued for up to 14 days after surgery.
[3] Lovenox Injection 40 mg SC once a day initiated up to 12 hours prior to surgery and continued for up to 7 days after surgery.
[4] Lovenox Injection 40 mg SC once a day for up to 21 days after discharge.

NOTE: At no time point were the 40 mg once a day pre-operative and the 30 mg every 12 hours post-operative hip replacement surgery prophylactic regimens compared in clinical trials.
Injection site hematomas during the extended prophylaxis period after hip replacement surgery occurred in 9% of the Lovenox Injection patients versus 1.8% of the placebo patients.

Major Bleeding Episodes in Medical Patients With Severely Restricted Mobility During Acute Illness[1]

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

[1] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, (2) if the hemorrhage caused a decrease in hemoglobin of ≥2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major although none were reported during the trial.
[2] The rates represent major bleeding on study medication up to 24 hours after last dose.

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

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

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

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

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

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

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

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

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

[1] Excluding unrelated adverse events.

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

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

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

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

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

[1]Excluding unrelated and unlikely adverse events.

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

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

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

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

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

[1] Excluding unrelated adverse events.

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

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

Note: Lovenox Injection is available in two concentrations:

1. **100 mg/mL Concentration:** 30 mg / 0.3 mL ampules, 30 mg / 0.3 mL and 40 mg / 0.4 mL prefilled single-dose syringes, 60 mg / 0.6 mL, 80 mg / 0.8 mL, and 100 mg / 1 mL prefilled, graduated, single-dose syringes, 300 mg / 3.0 mL multiple-dose vials.
2. **150 mg/mL Concentration:** 120 mg / 0.8 mL and 150 mg / 1 mL prefilled, graduated, single-dose syringes.

Adult Dosage:
Abdominal Surgery: In patients undergoing abdominal surgery who are at risk for thromboembolic complications, the recommended dose of Lovenox Injection is **40 mg once a day** administered by SC injection with the initial dose given 2 hours prior to surgery. The usual duration of administration is 7 to 10 days; up to 12 days administration has been well tolerated in clinical trials.
Hip or Knee Replacement Surgery: In patients undergoing hip or knee replacement surgery, the recommended dose of Lovenox Injection is **30 mg every 12 hours** administered by SC injection. Provided that hemostasis has been established, the initial dose should be given 12 to 24 hours after surgery. For hip replacement surgery, a dose of **40 mg once a day** SC, given initially 12 (±3) hours prior to surgery, may be considered. Following the initial phase of thromboprophylaxis in hip replacement surgery patients, continued prophylaxis with Lovenox Injection 40 mg once a day administered by SC injection for 3 weeks is recommended. The usual duration of administration is 7 to 10 days; up to 14 days administration has been well tolerated in clinical trials.
Medical Patients During Acute Illness: In medical patients at risk for thromboembolic complications due to severely restricted mobility during acute illness, the recommended

dose of Lovenox Injection is **40 mg once a day** administered by SC injection. The usual duration of administration is 6 to 11 days; up to 14 days of Lovenox Injection has been well tolerated in the controlled clinical trial.

Unstable Angina and Non-Q-Wave Myocardial Infarction: In patients with unstable angina or non-Q-wave myocardial infarction, the recommended dose of Lovenox Injection is **1 mg/kg** administered SC **every 12 hours** in conjunction with oral aspirin therapy (100 to 325 mg once daily). Treatment with Lovenox Injection should be prescribed for a minimum of 2 days and continued until clinical stabilization. To minimize the risk of bleeding following vascular instrumentation during the treatment of unstable angina, adhere precisely to the intervals recommended between Lovenox Injection doses. The vascular access sheath for instrumentation should remain in place for 6 to 8 hours following a dose of Lovenox Injection. The next scheduled dose should be given no sooner than 6 to 8 hours after sheath removal. The site of the procedure should be observed for signs of bleeding or hematoma formation. The usual duration of treatment is 2 to 8 days; up to 12.5 days of Lovenox Injection has been well tolerated in clinical trials.

Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism: In **outpatient treatment**, patients with acute deep vein thrombosis without pulmonary embolism who can be treated at home, the recommended dose of Lovenox Injection is **1 mg/kg every 12 hours** administered SC. In **inpatient (hospital) treatment**, patients with acute deep vein thrombosis with pulmonary embolism or patients with acute deep vein thrombosis without pulmonary embolism (who are not candidates for outpatient treatment), the recommended dose of Lovenox Injection is **1 mg/kg every 12 hours** administered SC **or 1.5 mg/kg once a day** administered SC at the same time every day. In both outpatient and inpatient (hospital) treatments, warfarin sodium therapy should be initiated when appropriate (usually within 72 hours of Lovenox Injection). Lovenox Injection should be continued for a minimum of 5 days and until a therapeutic oral anticoagulant effect has been achieved (International Normalization Ratio 2.0 to 3.0). The average duration of administration is 7 days; up to 17 days of Lovenox Injection administration has been well tolerated in controlled clinical trials.

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

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

Lovenox Injection is administered by SC injection. It must not be administered by intramuscular injection. Lovenox Injection is intended for use under the guidance of a physician. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up, as necessary. Proper training in subcutaneous injection technique (with or without the assistance of an injection device) should be provided.

Subcutaneous Injection Technique: Patients should be lying down and Lovenox Injection administered by deep SC injection. To avoid the loss of drug when using the 30 and 40 mg prefilled syringes, do not expel the air bubble from the syringe before the injection. Administration should be alternated between the left and right anterolateral and left and right posterolateral abdominal wall. The whole length of the needle should be introduced into a skin fold held between the thumb and forefinger; the skin fold should be held throughout the injection. To minimize bruising, do not rub the injection site after completion of the injection. 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.

Directions for use of One Point Cut (OPC) ampules for Lovenox Injection:
Use aseptic technique throughout the process. Prior to starting, gently tap the top of the ampule to assist the flow of the solution from the upper portion of the ampule to the lower portion.

1. Locate the yellow dot on the upper portion of the ampule. Below this dot is a small score on the neck of the ampule. Hold the ampule with the yellow dot **facing away from you.** *Do not try to break the ampule at the colored rings,* which are identification marks used only in manufacturing.
2. Cover yellow dot with your index finger and position your thumb opposite yellow dot.
3. Apply pressure to the top and bottom portions of the ampule to snap the ampule open away from you.

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

100 mg/mL Concentration

Dosage Unit / Strength[1]	Anti-Xa Activity[2]	Package Size (per carton)	Label Color	NDC # 0075-
Ampules				
30 mg / 0.3 mL	3000 IU	10 ampules	Medium Blue	0624-03
Prefilled Syringes[3]				
30 mg / 0.3 mL	3000 IU	10 syringes	Medium Blue	0624-30
40 mg / 0.4 mL	4000 IU	10 syringes	Yellow	0620-40
Graduated Prefilled Syringes[3]				
60 mg / 0.6 mL	6000 IU	10 syringes	Orange	0621-60
80 mg / 0.8 mL	8000 IU	10 syringes	Brown	0622-80
100 mg / 1 mL	10,000 IU	10 syringes	Black	0623-00
Multiple-Dose Vial[4]				
300 mg / 3.0 mL	30,000 IU	1 vial	Red	0626-03

[1] Strength represents the number of milligrams of enoxaparin sodium in Water for Injection. **Lovenox Injection** ampules, 30 and 40 mg prefilled syringes, and 60, 80, and 100 mg graduated prefilled syringes each contain **10 mg enoxaparin sodium per 0.1 mL Water for Injection**.
[2] Approximate anti-Factor Xa activity based on reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard.
[3] Each **Lovenox Injection** syringe is affixed with a 27 gauge x 1/2 inch needle.
[4] Each Lovenox multiple-dose vial contains 15 mg / 1.0 mL of benzyl alcohol as a preservative.

150 mg/mL Concentration

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

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

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].
Keep out of the reach of children.

Lovenox Injection prefilled and graduated prefilled syringes manufactured in France.
Lovenox Injection ampules manufactured in England.
Lovenox multiple-dose vial manufactured for Aventis Pharmaceuticals Products Inc. by DSM Pharmaceuticals, Inc. Greenville, NC 27835.
Aventis Pharmaceuticals Products Inc.
BRIDGEWATER, NJ 08807

Prescribing information as of March 2003

50069639

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-043

LABELING REVIEWS

Division of Gastrointestinal and Coagulation Drug Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application Number: NDA 20-164/SCM-043

Name of Drug: Lovenox® Injection (enoxaparin sodium)

Sponsor: Aventis Pharmaceuticals Inc.

Materials Reviewed: Package Insert dated May 1, 2002 and immediate container labeling (300 mg/3.0 mL Ampule).

Submission Date: May 1, 2002
Receipt Date: May 2, 2002

Background and Summary

Background: This prior approval chemistry, manufacturing and controls (CMC) supplement with labeling (SCM-043) was originally submitted on May 15, 2001, to provide for a multiple-dose vial presentation of Lovenox Injection (300 mg/3mL) at a concentration of 100 mg/mL and preserved with benzyl alcohol at 1.5% (m/v) level; a new contract manufacturing site, Catalytica Pharmaceuticals, Greenville, South Carolina, for the drug product; revised package insert labeling; and immediate container and carton labeling for the proposed multiple dose vial. On September 14, 2001, the Division sent a non-approval letter to the sponsor for SCM-043. The letter summarized the deficiencies as follows: "During recent inspections of the manufacturing facilities *for* [sic] your supplement, Catalytica Pharmaceuticals, Greenville, South Carolina, a number of deficiencies were noted and conveyed to you or your suppliers by the investigator. Satisfactory inspections will be required before this application may be approved."

On May 1, 2002, Aventis Pharmaceuticals submitted a resubmission to SCM–043. The sponsor noted that the manufacturing site was recently re-inspected by the FDA in which a FDA Form 483 with observations was issued. (The Form 483 is the document sent from the FDA Office of Compliance delineating results found during an inspection. A "Withhold" recommendation was made by the Office of Compliance on September 14, 2001, based on significant deviations with the firm's sterile production operations, insufficient quality assurance oversight, inadequate environmental monitoring, deficient facilities for ——— processing and deviations involving general procedures and practices). The sponsor further noted that the manufacturing site had made a voluntary corrective action plan in the sterile manufacturing operations area which was accepted by the Atlanta District Office. The chemistry review of the submission notes that the Catalytica Pharmaceuticals site has had a satisfactory clinical good manufacturing practices (CGMP) inspection result. The overall recommendation by Establishment Evaluation System (EES) was acceptable on February 12, 2002 (see Chemist's review #3 dated May 16, 2002). Also noted in the chemist's review #3 is that the statement, "Nitrogen is used in the headspace to inhibit oxidation" was deleted from the package insert and that this sentence should be retained.

13 Pages Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

✓ § 552(b)(5) Deliberative Process

LABELING REVIEW COMPLETED 8/23/02

[ ]

5. [ ] **This is in violation of the "Guidance for Industry, Product name Placement, Size, and Prominence in Advertising and Promotional Labeling," April 1996, which refer to the regulations provided under 21 CFR 201.10(g)(1) and 202.1(b)(1) in that the established name shall be placed in direct conjunction with the proprietary name or designation and there should be no intervening matter that in any way would detract, obfuscate, or de-emphasize the established or proper name of the product. The Medical Officer and chemistry reviewer should review this proposed tradename.**

CONCLUSIONS

1. **The following items are acceptable: I. A. 1., - 7., A. 9. - 10., I. B., I. C., I. J. 1. - 2., I. K. 1. - 18.**

2. **The following items are not acceptable: I. A., 8.**

3. **The sponsor should be requested to update the proposed labeling submitted to SCM-043 to incorporate the revised wording approved in SLR-046 in the following items: Section I. D., I. F. 1., I. G., I. H. 1. – 5., I. I.**

4. **The Medical Officer needs to comment on the following items: I. E., I. F. 2., I. H. 6., I. J. 3., III. A. 4.**

5. **The Chemistry reviewer needs to review and comment on the following items: II and III. A. 1., III. A. 3., III. A. 4. and III. A. 5.**

6. **In addition, the sponsor should be requested to revise the labeling in items III. A. 2.**

7. **This labeling supplement should be approvable pending comments from the Medical Officer and chemistry reviewer.**

Cc:
Archival NDA 20-164/S-043
HFD-180/Div. Files
HFD-180/D.Moore

HFD-180/R.He/K.Robie-Suh/J.Sieczkowski/L.Zhou
HFD-180/V.Raczkowski/J.Korvick
Drafted by: dm/8/12/02
Initialed by: J.Dubeau 8.19.02/L.Zhou 8.20.02/K.Robie-Suh 8.21.02
Final: August 23, 2002
Filename:N20164S43Lblrev2.doc
RPM LABELING REVIEW

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

/s/

Diane V. Moore
8/23/02 10:19:15 AM
CSO

Julieann DuBeau
8/23/02 02:52:19 PM
CSO

Division of Gastrointestinal and Coagulation Drug Products

ADDENDUM TO REGULATORY PROJECT MANAGER LABELING REVIEW

Application Number: NDA 20-164/SCM-043

Name of Drug: Lovenox® Injection (enoxaparin sodium), 30, 40, 60, 80 and 100 mg

Sponsor: Aventis Pharmaceuticals

Materials Reviewed: Package Insert dated May 1, 2002 and immediate container labeling (300 mg/3.0 mL Ampule).

Submission Date: May 1, 2002
Receipt Date: May 2, 2002

Background and Summary

Background: This prior approval chemistry, manufacturing and controls (CMC) supplement with labeling (SCM-043) was originally submitted on May 15, 2001, to provide for a multiple-dose vial presentation of Lovenox Injection (300 mg/3mL) at a concentration of 100 mg/mL and preserved with benzyl alcohol at 1.5% (m/v) level; a new contract manufacturing site, Catalytica Pharmaceuticals, Greenville, South Carolina, for the drug product; revised package insert labeling; and immediate container and carton labeling for the proposed multiple dose vial. On September 14, 2001, the Division sent a not-approval letter to the sponsor for SCM-043. The letter summarized the deficiencies as follows: "During recent inspections of the manufacturing facilities *for* [sic] your supplement, Catalytica Pharmaceuticals, Greenville, South Carolina, a number of deficiencies were noted and conveyed to you or your suppliers by the investigator. Satisfactory inspections will be required before this application may be approved."

On May 1, 2002, Aventis Pharmaceuticals submitted a resubmission to SCM–043. The sponsor noted that the manufacturing site was recently re-inspected by the FDA in which a FDA Form 483 with observations was issued. (The Form 483 is the document sent from the FDA Office of Compliance delineating results found during an inspection. A "Withhold" recommendation was made by the Office of Compliance on September 14, 2001, based on significant deviations with the firm's sterile production operations, insufficient quality assurance oversight, inadequate environmental monitoring, deficient facilities for ——— processing and deviations involving general procedures and practices). The sponsor further noted that the manufacturing site had made a voluntary corrective action plan in the sterile manufacturing operations area which was accepted by the Atlanta District Office.

A consult was sent to the Division of Medication Errors and Technical Support (DMETS) in the Office of Drug Safety on May 1, 2002, SCM-043 to review the proposed proprietary name ——— for a multiple-dose vial to determine the potential for confusion with approved

proprietary and established names. The consult was completed on July 29, 2002. Currently, the tradename for this product is "Lovenox." Although there are seven pre-filled syringe strengths and one ampule strength approved, only two of the strengths of Lovenox have [redacted].

Regulatory Project Manager (RPM) Labeling Review dated August 23, 2002, was performed on the May 1, 2002, resubmission to NDA 20-164/SCM-043. The RPM Labeling Review made reference to comments contained in Chemistry Review #3 (dated May 16, 2002) recommending the supplement be approved for the manufacture of the new Lovenox Injection multi-dose formulation (300mg/3mL with benzyl alcohol preservative) at Catalytica Pharmaceuticals. The chemistry review further recommended that the approval letter should not be issued until the Division has received a response from the consult sent to DMETS on May 1, 2002 for NDA 20-164/SCM-043. The only chemistry issue with the labeling is the sponsor's proposal to remove the statement, "Nitrogen is used in the headspace to inhibit oxidation" in the package insert (PI). According to the chemistry review #3, this statement should be retained. (See RPM labeling review dated August 23, 2002, sections I. **PACKAGE INSERT LABELING**, A. **DESCRIPTION** section, items 1. – 10. and J. **DOSAGE AND ADMINISTRATION** section, items 1. - 2. and K. **HOW SUPPLIED** section, items 1. – 18).

Chemistry Review #3 was drafted but never finalized in the Division File System (DFS). Chemistry Review #4 was finalized on August 27, 2002, with the following conclusion:

> "From a chemistry viewpoint, the supplement should be approved for the manufacture of the new Lovenox Injection multi-dose formulation (300 mg/3mL with benzyl alcohol preservative) at Catalytica Pharmaceuticals."

The recommendation from Chemistry Review #4 is as follows:

> "The approval letter should not be issued until a response is received concerning the labeling issues noted in the RPM Labeling Review of 21-AUG-2002 (see also DMETS Consult Review; #02-115/29-JUL-2002) and the only chemistry labeling issue."

The only remaining chemistry issue is concerned with the firm's proposal to remove the following statement: "Nitrogen is used in the headspace to inhibit oxidation" from the PI. The outcome of a discussion between, Dr. Joseph Sieczkowski, chemistry reviewer and Dr. Liang Zhou, Chemistry Team Leader was that the nitrogen statement does not need to be retained in the labeling. However, it is noted as being a specific requirement in the drug product manufacturing section under the CMC section of the supplement.

Review

1. Items I.E., I. F. 2., I. H. 6., I. J. 3., and IIIL. A. 4. in the RPM Labeling Review dated August 23, 2002, are acceptable (see Medical Officer Review dated August 26, 2002, by Dr. Ruyi He).

2. The items referenced in the RPM review dated August 23, 2002, (I. **PACKAGE INSERT LABELING**, A. **DESCRIPTION** section, items 1. – 10. and J. **DOSAGE AND ADMINISTRATION** section, items 1. - 2. and K. **HOW SUPPLIED** section, items 1. – 18) are acceptable according to Dr. Liang Zhou, Chemistry Team Leader in oral comment to Diane Moore, RPM, on August 28, 2002.

3. The outcome of a discussion between the Chemistry Reviewer, Dr. Joseph Sieczkowski, and the Chemistry Team Leader, Dr. Liang Zhou was that Item 2. in the **CONCLUSIONS** section of the August 23, 2002, RPM Labeling Review that states that item I.A.8 is not acceptable, is now acceptable (see Chemistry Review #4 dated August 27, 2002.)

Conclusions

1. **The labeling supplement should be approvable.**

2. **The fifth sentence in the DESCRIPTION section that reads, "Nitrogen is used in the headspace to inhibit oxidation." does not need to be retained in the PI.**

3. **The sponsor should submit draft labeling revised according to the recommendations described in the RPM Labeling Review dated August 23, 2002, under III. CARTON LABELING A. COMMENTS 1. – 5.**

4. **The sponsor should be requested to update the proposed labeling submitted to SCM-043 to incorporate the revised wording approved in SLR-046 in the following items outlined in the RPM Labeling Review dated August 23, 2002: Section I. D., I. F. 1., I. G., I. H. 1. – 5., I. I.**

Diane Moore, B.S.
Regulatory Health Project Manager

Supervisory Comment/Concurrence:

Julieann DuBeau, MSN, RN
Chief, Project Management Staff

Liang Zhou, Ph.D.
Chemistry Team Leader

Drafted: dm/August 28, 2002
Revised/Initialed: LZ 8.28.02/A.Kacuba 8.28.02
Finalized: August 28, 2002
Filename: N20164S43add.doc

RPM LABELING REVIEW

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

/s/

Diane V. Moore
8/28/02 04:23:34 PM
CSO

Alice Kacuba
8/28/02 04:36:09 PM
CSO
Signed for Julieann DuBeau

Liang Zhou
8/28/02 05:26:07 PM
CHEMIST

Division of Gastrointestinal and Coagulation Drug Products
(DGICDP)

REGULATORY PROJECT MANAGER LABELING REVIEW

Application Number: NDA 20-164/SCM-043 (Cycle 3)

Name of Drug: Lovenox® (enoxaparin sodium) Injection

Sponsor: Aventis Pharmaceuticals Inc.

Materials Reviewed: Package Insert (PI) dated September 20, 2002
Immediate container labeling (300 mg/3.0 mL Ampule) dated September 20, 2002

Submission Date: September 20, 2002
Receipt Date: September 23, 2002
Amendment Date: January 17, 2003
Receipt Date: January 21, 2003

Background and Summary

Background: Lovenox was approved March 29, 1993. It is approved for the following indications:

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

This prior approval chemistry, manufacturing and controls (CMC) supplement with labeling (SCM-043) was originally submitted on May 15, 2001, to provide for a multiple-dose vial presentation of Lovenox Injection (300 mg/3mL) at a concentration of 100 mg/mL and preserved with benzyl alcohol at 1.5% (m/v) level; a new contract manufacturing site, Catalytica Pharmaceuticals, Greenville, South Carolina, for the drug product; revised package insert labeling; and immediate container and carton labeling for the proposed multiple dose vial. On September 14, 2001, the Division sent a not approval letter to the sponsor for SCM-043. The letter summarized the deficiencies as follows: "During recent inspections of the manufacturing facilities *for* [sic] your supplement, Catalytica Pharmaceuticals, Greenville, South Carolina, a

number of deficiencies were noted and conveyed to you or your suppliers by the investigator. Satisfactory inspections will be required before this application may be approved."

On May 1, 2002, Aventis Pharmaceuticals submitted a full response to the September 14, 2001, not approvable letter. The sponsor noted that the manufacturing site was recently re-inspected by the FDA in which a FDA Form 483 with observations was issued. (The Form 483 is the document sent from the FDA Office of Compliance delineating results found during an inspection. A "Withhold" recommendation was made by the Office of Compliance on September 14, 2001, based on significant deviations with the firm's sterile production operations, insufficient quality assurance oversight, inadequate environmental monitoring, deficient facilities for ——— processing and deviations involving general procedures and practices). The sponsor further noted that the manufacturing site had made a voluntary corrective action plan in the sterile manufacturing operations area which was accepted by the Atlanta District Office. The chemistry review of the submission notes that the Catalytica Pharmaceuticals site has had a satisfactory clinical good manufacturing practices (CGMP) inspection result. The overall recommendation by the Establishment Evaluation System (EES) was acceptable on February 12, 2002 (see Chemist's review #3 dated May 16, 2002). Also noted in the chemist's review #3 is that the statement, "Nitrogen is used in the headspace to inhibit oxidation" was deleted from the package insert and that this sentence should be retained. Chemistry Review #3 was drafted, but not finalized. Chemistry Review #4 was finalized on August 27, 2002, with the following conclusion:

> "From a chemistry viewpoint, the supplement should be approved for the manufacture of the new Lovenox Injection multi-dose formulation (300 mg/3mL with benzyl alcohol preservative) at Catalytica Pharmaceuticals."

The recommendation from Chemistry Review #4 is as follows:

> "The approval letter should not be issued until a response is received concerning the labeling issues noted in the RPM Labeling Review of 21-AUG-2002 (see also DMETS Consult Review; #02-115/29-JUL-2002) and the only chemistry labeling issue."

The only remaining chemistry issue was concerned with the firm's proposal to remove the following statement: "Nitrogen is used in the headspace to inhibit oxidation" from the PI. The outcome of a discussion between Dr. Joseph Sieczkowski, chemistry reviewer, and Dr. Liang Zhou, Chemistry Team Leader, was that the nitrogen statement does not need to be retained in the labeling. However, it is noted as being a specific requirement in the drug product manufacturing section under the Chemistry, Manufacturing and Control (CMC) section of the supplement (see Addendum to RPM Labeling Review dated August 28, 2002).

A consult was sent to the Division of Medication Errors and Technical Support (DMETS) in the Office of Drug Safety on May 1, 2002, for NDA 20-164/SCM-043 to review the proposed proprietary name ——— for a multiple-dose vial and determine the potential for confusion with approved proprietary and established names. DMETS Consult # 02-0115 was completed on July 29, 2002. DMETS does not recommend the use of the proprietary name

[redacted] for the multi-dose vial. DMETS has no objection to the use of the proprietary name Lovenox for the multi-dose vial. Currently, the proprietary name for this product is "Lovenox." Although there are seven prefilled syringe strengths and one ampule strength approved, only two of the strengths of Lovenox have [redacted]

An approvable letter was sent to the sponsor on August 30, 2002, with the following recommendations:

300 mg/mL Immediate Container and Carton Labeling

1. Include the dosage form "Injection" in the established name as "Enoxaparin Sodium Injection" for the 300 mg/3mL immediate container and carton labeling.

2. Increase the prominence of the established name so that it is at least half as large as the proprietary name on the carton labeling [see 21 CFR 202.1(b) (2)].

4. Revise the 300 mg/mL immediate container and 300 mg/mL carton labeling to express the net quantity statement in terms of volume (i.e., 3 mL) and not total drug concentration.

5. Delete the terminal zeros in "3.0 mL" from the 300 mg/mL immediate container and 300 mg/mL carton labeling because the amount could be misinterpreted as "30 mL."

6. [redacted]

7. Incorporate the current number of reports of epidural or spinal hematoma formation in the labeling text of the package insert (PI) in the **ADVERSE REACTIONS** section, **Adverse Events in Lovenox Injection Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction** subsection, in the third paragraph, first sentence that begins, "Ongoing Safety Surveillance: Since 1993 . . ."

8. In addition, all previous revisions as reflected in the most recently approved labeling, specifically Supplement-046, approved January 9, 2002, which provided for revisions to the **PRECAUTIONS** section, **Pregnancy** subsection of the PI, must be included.

The sponsor submitted electronic draft labeling on September 20, 2002 (received September 23, 2002), in response to the Agency's approvable letter dated August 30, 2002. The revisions reflected in the approved labeling to SLR-046 (approved January 9, 2002) have been incorporated into the revised draft labeling for S-043. Specifically, the tradename "Lovenox injection" has replaced the term "enoxaparin" in the **CLINICAL TRIALS**, **WARNINGS** and **PRECAUTIONS** and **ADVERSE REACTIONS** sections of the labeling (see RPM review of S-043 dated August 23, 2002). The sponsor also included the paragraph added to the

2 Pages Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

✓ § 552(b)(5) Deliberative Process

LABELING REVIEW COMPLETED 1/23/03

[ ]

Review

I. PACKAGE INSERT

The PI submitted on September 20, 2002, (no identifier) was compared to approved PI from Supplement SLR-046 dated August 14, 2001, approved January 9, 2002, coded 50063316.

A. **DESCRIPTON** section

1. The sponsor proposes to add the term "aqueous" following the term, "sterile" in the first sentence so that the sentence reads:

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

   The sponsor proposed this addition in the May 1, 2002, submission (received May 2, 2002). It was found to be acceptable (see CMC review #4 dated August 28, 2002 and RPM Labeling Review dated August 23, 2002, and Addendum to the RPM review dated August 28, 2002).

2. In the second sentence that reads, "Lovenox Injection is available in two concentrations: **1 100mg per mL of Water for Injection**," the sponsor proposes to add a period after the number "1" and delete the phrase, "of Water for Injection" so that the sentence reads:

   "Lovenox Injection is available in two concentrations:
   1. 100 mg per mL"

   The sponsor proposed this addition in the May 1, 2002, submission (received May 2, 2002). It was found to be acceptable (see CMC review #4 dated August 28, 2002 and RPM Labeling Review dated August 23, 2002, and Addendum to the RPM review dated August 28, 2002).

3. In the third paragraph, the sponsor proposes to add "*Multiple-Dose Vials* 300 mg/3.0 mL" to the list of available syringes and ampules.

The sponsor proposed this addition in the May 1, 2002, submission (received May 2, 2002). It was found to be acceptable (see CMC review #4 dated August 28, 2002 and RPM Labeling Review dated August 23, 2002, and Addendum to the RPM review dated August 28, 2002).

4. In the fifth paragraph that reads, "**2 150 mg per mL of Water for Injection,**" the sponsor proposes to add a period after the number "2" and delete the phrase "**of Water for Injection.**"

   The sponsor proposed this addition in the May 1, 2002, submission (received May 2, 2002). It was found to be acceptable (see CMC review #4 dated August 28, 2002, RPM Labeling Review dated August 23, 2002, and Addendum to the RPM review dated August 28, 2002).

5. In the first sentence, sixth paragraph that begins, "The solutions are preservative-free . . . ." the sponsor proposes to delete the term "solutions" and add the phrase, "Lovenox prefilled syringes, graduated prefilled syringes, and ampules" so that the sentence reads:

   "The Lovenox prefilled syringes, graduated prefilled syringes, and ampules are preservative-free and intended for use only as a single-dose injection."

   The sponsor proposed this addition in the May 1, 2002, submission (received May 2, 2002). It was found to be acceptable (see CMC review #4 dated August 28, 2002, RPM Labeling Review dated August 23, 2002, and Addendum to the RPM review dated August 28, 2002).

6. In the sixth paragraph, the sponsor proposes to add a second sentence that reads, "The multiple-dose vial contains 15 mg/1.0 mL benzyl alcohol as a preservative."

   The sponsor proposed this addition in the May 1, 2002, submission (received May 2, 2002). It was found to be acceptable (see CMC review #4 dated August 28, 2002, RPM Labeling Review dated August 23, 2002, and Addendum to the RPM review dated August 28, 2002).

7. In the sixth paragraph, the sponsor proposes to delete the fifth sentence that reads, "Nitrogen is used in the headspace to inhibit oxidation."

   This deletion is acceptable (see CMC review #4 dated August 28, 2002 and Addendum to RPM Labeling Review dated August 28, 2002).

8. In the sixth paragraph, sixth sentence that begins, "Enoxaparin is obtained by . . .," the sponsor has added the term "sodium" after "Enoxaparin" so that the sentence reads, "Enoxaparin sodium is obtained by alkaline degradation of heparin benzyl ester derived from porcine intestinal mucosa."

The sponsor proposed this addition in the May 1, 2002, submission (received May 2, 2002). It was found to be acceptable (see CMC review #4 dated August 28, 200, RPM Labeling Review dated August 23, 2002, and Addendum to the RPM review dated August 28, 2002).

9. In the sixth paragraph, the eighth sentence that begins, "The substance is the sodium . . ." The term "drug" has been added so that the sentence reads, "The drug substance is the sodium salt."

   The sponsor proposed this addition in the May 1, 2002, submission (received May 2, 2002). It was found to be acceptable (see CMC review #4 dated August 28, 2002 , RPM Labeling Review dated August 23, 2002, and Addendum to the RPM review dated August 28, 2002).

B. **CLINICAL TRIALS** section

The sponsor replaced the term "enoxaparin" with the term "Lovenox Injection" in the following places:

1. **CLINICAL TRIALS** section, **Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery** subsection, third paragraph, sixth sentence that reads, "The incidence of proximal and total DVT after surgery was significantly lower for enoxaparin compared to placebo."

2. **CLINICAL TRIALS** section, **Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery** subsection, fourth paragraph, sixth sentence that reads, "The incidence of deep vein thrombosis was significantly lower for enoxaparin compared to heparin."

3. **CLINICAL TRIALS** section, **Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery** subsection, *Extended Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery* subsection, the first paragraph, first sentence that reads, "In a study of extended prophylaxis for patients undergoing hip replacement surgery, patients were treated, while hospitalized, with enoxaparin 40 mg SC, initiated up to 12 hours prior to surgery for the prophylaxis of post-operative DVT."

4. **CLINICAL TRIALS** section, **Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery** subsection, *Extended Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery* subsection, the first paragraph, third sentence that reads, "In a double-blind design, those patients with no venous thromboembolic disease were randomized to a post-discharge regimen of either enoxaparin 40 mg (n=90) once a day SC or to a placebo (n=89) for 3 weeks."

5. **CLINICAL TRIALS** section, **Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery** subsection, *Extended Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery* subsection, the first paragraph, sixth sentence that reads, "In this population of patients, the incidence of DVT during extended prophylaxis was significantly lower for enoxaparin compared to placebo."

6. **CLINICAL TRIALS** section, **Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction subsection**, in the third paragraph, the first sentence that reads, "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 enoxaparin versus heparin (32.0% vs 35.7%).

   The above revisions are in compliance with the Agency's request in the August 30, 2002, approvable letter to S-043 to include the revisions to the PI that were approved in S-046 into the PI for S-043. The replacement of enoxaparin with Lovenox Injection in the above sections is acceptable.

C. **CONTRAINDICATIONS** section

In the second paragraph, first sentence that begins, "Patients with known hypersensitivity . . ." the sponsor proposes to add the phrase, "or any of its constituents" so that the sentence reads, "Patients with known hypersensitivity to heparin or pork products should not be treated with Lovenox Injection or any of its constituents."

This change is acceptable. See Medical Officer (M.O.) review dated August 26, 2002.

D. **WARNINGS** section:

1. In the approvable letter to S-043 dated August 30, 2002, the sponsor was reminded to include the revisions approved in SLR-046. In S-046, the sponsor replaced the term "enoxaparin" with the term "Lovenox Injection" in the following places:

   a. **WARNINGS** section, fifth paragraph, the first sentence that reads, "**Cases of epidural or spinal hematomas have been reported with the associated use of enoxaparin and spinal/epidural anesthesia or spinal puncture resulting in long-term or permanent paralysis.**"

   b. **WARNINGS** section, seventh paragraph, in the first sentence that reads, "Bleeding can occur at any site during therapy with enoxaparin.

   c. **WARNINGS** section, tenth paragraph, second sentence that reads, "If the platelet count falls below 100,000/mm3, enoxaparin should be discontinued."

The revisions are in compliance with the Agency's request in the August 30, 2002, approvable letter to S-043 to include the revisions to the PI that were approved in S-046 on January 9, 2002, into the PI for S-043. The revisions are acceptable.

2. In the approvable letter to S-043 dated August 30, 2002, the sponsor was reminded to include the **Prosthetic Heart Valves** subsection that was added to the **WARNINGS** section in S-046 (approved January 9, 2002) into the **WARNINGS** section of the labeling for S-043. The sponsor included this section in the amended proposed labeling for S-043. The section reads as follows:

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

   The addition is in compliance with the Agency's request in the August 30, 2002, approvable letter to S-043 to include the revisions made to the PI that were approved on January 9, 2002 in S-046 into the PI for S-043. The addition is acceptable.

3. The sponsor proposes to add a new **Miscellaneous** subsection following the **Thrombocytopenia** subsection. The Paragraph reads as follows:

   "**Miscellaneous:** Lovenox multiple-dose vials contain benzyl alcohol as a preservative. The administration of medications containing benzyl alcohol as a preservative to premature neonates has been associated with a fatal "Gasping Syndrome". Because benzyl alcohol may cross the placenta, Lovenox multiple-dose vials, preserved with benzyl alcohol, should be used with caution in pregnant women only if clearly needed (see **PRECAUTIONS, Pregnancy**)."

   The Medical Officer, Dr. Ruyi He, found this addition to be acceptable (see M.O. review dated August 26, 2002). Note: The third sentence would read clearer if the word "and" was inserted before the word "only" so that the sentence reads, "Because benzyl alcohol may cross the placenta, Lovenox multiple-dose vials, preserved with benzyl alcohol, should be used with caution in pregnant women and only if clearly needed (see PRECATIONS, Pregnancy)." The sponsor could be requested to make the revision at the next printing.

E. **PRECAUTIONS** section

1. In the approvable letter to S-043 dated August 30, 2002, the sponsor was reminded to include the revisions approved in SLR-046. In S-046, the sponsor replaced the term "enoxaparin" with the term "Lovenox Injection" in the following places:

   a. In the **PRECAUTIONS** section, **General** subsection, in the second paragraph, third sentence that reads, "Enoxaparin should be used with care in these patients."

   b. In the **PRECAUTIONS** section, **General** subsection, in the third paragraph, the first sentence that reads, "If thromboembolic events occcur despite enoxaparin prophylaxis, appropriate therapy should be initiated."

   c. In the **PRECAUTIONS** section, **Pregnancy** subsection, Non-teratogenic Effects subsection, the first sentence that reads, "There have been a few spontaneous post-marketing reports of fetal death when pregnant women received enoxaparin."

   d. In the **PRECAUTIONS** section, **Nursing Mothers** subsection, the second sentence that reads, "Because many drugs are excreted in human milk, caution should be exercised when enoxaparin is administered to nursing women."

   e. In the **PRECAUTIONS** section, **Pediatric Use** subsection, the first sentence that reads, "Safety and effectiveness of enoxaparin in pediatric patients have not been established."

   f. In the **PRECAUTIONS** section, **Geriatric Use** subsection, the first sentence that reads, "Over 2800 patients, 65 years and older, have received enoxaparin sodium in pivotal clinical trials."

   The revisions are in compliance with the Agency's request in the August 30, 2002, approvable letter to S-043 to include the revisions made to the PI that were approved in S-046 into the PI for S-043. The revisions are acceptable.

2. In the Approvable letter to S-043 dated August 30, 2002, the sponsor was reminded to include the second paragraph of the **PRECAUTIONS** section, **Pregnancy** subsection, *Teratogenic Effects* subsection that was added in the approved labeling to S-046 into the final printed labeling for S-043.

   The sponsor added the following paragraph into the **PRECAUTIONS** section, **Pregnancy** subsection, *Teratogenic Effects* subsection of the proposed final printed labeling for S-043:

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

The addition is in compliance with the Agency's request in the August 30, 2002, Approvable letter to S-043 to include the revisions to the PI that were approved in S-046 into the PI for S-043. The addition is acceptable.

3. In the **PRECAUTIONS** section, **Pregnancy** subsection, *Non-teratogenic Effects* subsection, in the first sentence that begins, "There have been post-marketing reports . . .", the sponsor has deleted the proposed phrase, "a few spontaneous" after the word "been" so that the sentence reads, "There have been post-marketing reports of fetal death when pregnant women received Lovenox Injection."

   The revision is in accordance with the labeling revision made in S-046 and requested in the August 30, 2002, approvable letter to S-043. The revision is acceptable.

4. In the **PRECAUTIONS** section, **Pregnancy** subsection, *Non-teratogenic Effects* subsection, in the first paragraph, the second sentence that begins, "Causality for these cases," the sponsor has replaced the phrase "of the cases" with the phrase "for these cases" as revised and approved in S-046 so that the sentence reads "Causality for these cases has not been determined."

   The revision is in accordance with the labeling revision approved in S-046 (January 9, 2002) and requested in the August 30, 2002, approvable letter to S-043. The revision is acceptable.

5. In the **PRECAUTIONS** section, **Pregnancy** subsection, *Non-teratogenic Effects* subsection, the sponsor has deleted the previously-proposed third and fourth sentences that read,

   [redacted]

   The revision is in accordance with the labeling revisions approved in S-046 (January 9, 2002). The removal of the two sentences was requested in the August 30, 2002, approvable letter to S-043. The revision is acceptable.

6. The sponsor has added the following four sentences to the first paragraph of the **PRECAUTIONS** section, **Pregnancy** subsection, *Non-teratogenic Effects* subsection: "Pregnant women receiving anti-coagulants, including enoxaparin, are at increased risk for bleeding. Hemorrhage can occur at any site and may lead to death

of mother and/or fetus. Pregnant women receiving enoxaparin should be carefully monitored. Pregnant women and women of child-bearing potential should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnacy."

The sponsor was requested to add the four sentences in the August 30, 2002, Approvable letter to S-043 so that the wording would be the same as the approved wording in S-046 (approved January 9, 2002). The addition is acceptable.

7. The sponsor has added the following paragraph to the end of the **PRECAUTIONS** section, **Pregnancy** subsection, *Non-teratogenic Effects* subsection:

   "Cases of "Gasping Syndrome" have occurred in premature infants when large amounts of benzyl alcohol have been administered (99-405 mg/kg/day). The multiple-dose vial of Lovenox solution contains 15 mg/1.0 mL benzyl alcohol as a preservative (see **WARNINGS, Miscellaneous**)."

   This paragraph was proposed in the May 1, 2002, submission. The revision is acceptable (see MO review dated August 26, 2002 by Dr. Ruyi He).

F. In the **ADVERSE REACTIONS** section, **Adverse Events in Lovenox Injection Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction** subsection, in the third paragraph, first sentence that begins, "**Ongoing Safety Surveillance: Since 1993**, . . " the sponsor has updated the number of reports of epidural or spinal hematoma formation to 80 as in the approved labeling to S-046 and replaced the term "enoxaparin" with "Lovenox Injection."

These revisions were requested in the August 26, 2002, approvable letter to S-043. The revisions are acceptable.

G. **DOSAGE AND ADMINISTRATION** section

1. In the third paragraph, first sentence that begins, "**1 100 mg/mL Concentration**: 30 mg/0.3 mL ampules, . . ." the sponsor has added a period after the "1" and "300 mg/3.0 mL multiple-dose vials" at the end of the first item.

   This addition of the period is editorial and acceptable. The addition of the 300 mg/3.0 mL multiple-dose vials is acceptable (see CMC review #4 and Addendum to the RPM Labeling review dated August 28, 2002).

2. In the fourth paragraph that reads, "**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." The sponsor has added a period after the number "2." The sponsor has also deleted the previous 90 mg/0.6 mL strength.

The 90 mg/0.6 mL strength is not included in the currently approved labeling (S-046, approved January 9, 2002). The deletion was found to be acceptable by the chemistry reviewer (see CMC review #4). (Also see August 23, 2002 RPM review and Addendum to the RPM review dated August 28, 2002).
The addition of the period after the "2" is editorial and acceptable.

3. In the **Adult Dosage** subsection, **Administration** subsection, in the paragraph that begins, "Lovenox Injection is a clear, colorless . . ." the sponsor proposes to revise the second sentence that reads as follows:

   "When using Lovenox Injection ampules to assure withdrawal of the appropriate volume of drug, the use of a tuberculin syringe or equivalent is recommended."

   The proposed sentence reads as follows:

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

   The proposed revision is acceptable (see M.O. review by Dr. Ruyi He dated August 26, 2002).

4. After the **Adult Dosage** subsection, **Administration** subsection, The sponsor has added a new subsection entitled **"Directions for use of One Point Cut (OPC) ampules for Lovenox Injection:"** The section reads as follows:

   "Use aseptic technique throughout the process. Prior to starting, gently tap the top of the ampule to assist the flow of the solution from the upper portion of the ampule to the lower portion.
   1. Locate the yellow dot on the upper portion of the ampule. Below this dot is a small score on the neck of the ampule. Hold the ampule with the yellow dot **facing away from you** . *Do not try to break the ampule at the colored rings*, which are identification marks used only in manufacturing.
   2. Cover yellow dot with your index finger and position your thumb opposite yellow dot.
   3. Apply pressure to the top and bottom portions of the ampule to snap the ampule open away from you."

The wording in this section is identical to the wording proposed and accepted in ——— (see RPM Labeling Review to——— dated August 5, 2002). In an August 5, 2002, approvable letter for ——— to the sponsor, the Division recommended that to assure safe use of the OPC ampules, the sponsor should do the following:

1. [redacted]

2.

3.

Since the proposed wording for the DOSAGE AND ADMINISTRATION section, Administration subsection, "Directions for use of One Point Cut (OPC) ampules for Lovenox Injection:" subsection is identical to the wording proposed in ——— and that wording is acceptable (see Memorandum by Dr. Kathy Robie-Suh dated July 29, 2002), the proposed wording is acceptable for S-043. The sponsor adequately addressed the above items from the August 5, 2002 approvable letter in the January 17, 2003, correspondence per Dr. Ruyi He, Medical Officer in an oral comment to Diane Moore, RPM on January 17, 2003. This section is acceptable.

H. **HOW SUPPLIED** section

1. In the first line, the sponsor has deleted the right parenthesis after the word "sodium" and inserted a right parenthesis after the word "injection." The word "injection" has been changed from a capitalized word to all lower case lettering so that the sentence reads, "Lovenox® (enoxaparin sodium injection) is available in two concentrations."

   The term "Injection" refers to the route of administration and the phrase "enoxaparin sodium" is the established name for Lovenox. The proposed inclusion of the word "injection" in the parenthesis is a minor editorial change and is acceptable.

2. In the table entitled, "100 mg/mL Concentration," the sponsor has made the following revisions:

   a. In the fourth column, first row, the sponsor proposes to delete the term "syringe."

      The term is redundant and does not fit all of the categories of containers in the column. The deletion is acceptable.

   b. In the second column, fourth row, the sponsor has included the comma in the number "10,000"

This is the same as the approved labeling in S-046 (January 9, 2002). It is acceptable.

c. In the first column, fifth row, the sponsor has added the title, "**Multiple-Dose Vial**. 300 mg/3.0 mL."

The addition denotes the new 300 multiple dose vial. The addition is acceptable. (See chemistry review #4 by Dr. Joseph Sieczkowski, dated August 28, 2002).

d. In the second column, fifth row, the sponsor has added "30,000 IU."

The addition denotes the new 300 multiple dose vial. The addition is acceptable. (See chemistry review #4 by Dr. Joseph Sieczkowski, dated August 28, 2002).

e. In the third column, fifth row, the sponsor has added "1 vial."

The addition denotes the new 300 multiple dose vial. The addition is acceptable. (See chemistry #4 by Dr. Joseph Sieczkowski, dated August 28, 2002).

f. In the fourth column, fifth row, the sponsor has added the term "Red."

The addition denotes the new 300 multiple dose vial. The addition is acceptable. (See chemistry review #4 by Dr. Joseph Sieczkowski, dated August 28, 2002).

g. In the fifth column, fifth row, the sponsor has added "0626-03."

The addition denotes the new 300 multiple dose vial. The addition is acceptable. (See chemistry review #4 by Dr. Joseph Sieczkowski, dated August 28, 2002).

h. In the second sentence of the first footnote, the sponsor has added the word "and" after "80" so that the footnote reads, "Strength represents the number of milligrams of enoxaparin sodium in Water for Injection. **Lovenox Injection** ampules, 30 and 40 mg prefilled syringes, and 60, 80 and 100 mg graduated prefilled syringes each contain **10 mg enoxaparin sodium per 0.1 mL Water for Injection**."

The addition is editorial and acceptable.

i. The sponsor has added a footnote that reads, "[4] Each Lovenox multiple-dose vial contains 15 mg/1.0 mL of benzyl alcohol as a preservative."

The labeling notes benzyl alcohol in the multiple-dose vial in the sixth paragraph of the DESCRIPTION section. That section was found to be acceptable (See CMC review #4 dated August 28, 2002). The Medical Officer found this acceptable in an oral comment to Diane Moore, RPM, on January 13, 2003.

3. In the table entitled, "150 mg/mL Concentration," the sponsor has proposed the following revisions:

   a. The sponsor has deleted the contents of the second row that included, "90 mg/0.6 mL, 9000 IU, 10 syringes, Hot Pink and 2909-01." as in the approved labeling from S-021, S-022 and S-023.

      The deletions are editorial and acceptable as this strength is not being marketed.

   b. In the second column, third row, the sponsor has revised the number "12000 IU" to "12,000 IU"as in the approved labeling in S-046.

      The revision is editorial and acceptable.

   c. In the fourth column, second row, the sponsor has revised "Lavender" to "Purple" as in the approved labeling from S-046.

      The revision is editorial and acceptable.

   d. In the fourth column, second row, the sponsor has revised the number "15000 IU" to "15,000 IU." as in the approved labeling from S-046.

      The revision is editorial and acceptable.

   e. Footnote #1 which begins, "Strength represents the number . . ." the sponsor has deleted the 90 mg strength as in the approved labeling to S-046.

      The revision is acceptable.

4. In the first paragraph after the table entitled, "150 mg/mL Concentration," the sponsor proposes to revise the phrase, "Store at Controlled Room Temperature 15-25°C (59-77°F) [see USP]" to "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [see USP Controlled Room Temperature]."

   The revision is in accordance to USP 24 monograph General notices, page 11 under "Controlled room Temperature" and is therefore acceptable.

5. The sponsor proposes to add a fifth sentence that reads, "Lovenox multiple-dose vial manufactured for Aventis Pharmaceuticals Products Inc. by DSM Pharmaceuticals, Inc. Greenville, NC 27835."

   The revision is editorial. The manufacturing site was approved (see CMC review #4 dated August 28, 2002).

6. The sponsor's COLLEGEVILLE, PA 19426 address has been replaced by the BRIDGEWATER, NJ 08807 address. This revision is already in the approved labeling. The date for the Prescribing information as of "November 2000" has been deleted. The sponsor has added a new line that reads, "©2002 Aventis Pharmaceuticals, Inc." The name designates the owner of the product.

   These revisions are editorial and are acceptable.

II. IMMEDIATE CONTAINER

The proposed immediate container label for the Lovenox 300 mg/3.0 mL multiple dose vial is consistent with previously approved Lovenox immediate container syringe labels. The Lovenox 300 mg/3.0 mL vial labeling is coded 50060723. The [redacted] has been removed as requested in the Approvable letter to S-043 dated August 30, 2002.

The proposed labeling for the 300 mg/3.0 mL multiple dose vial immediate container label is acceptable.

III. CARTON

The sponsor's proposed carton labeling for the 300mg/3.0 mL multiple dose vial carton is consistent with previously approved cartons for LOVENOX prefilled syringe products. The proposed carton labeling for the 300 mg/3 mL multiple dose vial is coded 50060724.

The sponsor has removed the [redacted] on the carton labeling. The sponsor has included the other recommendations from the August 30, 2002, approvable letter to S-043 and has included the dosage form (injection) in the established name, increased the prominence of the established name so that it is at least half as large as the proprietary name, included a quantity statement expressed in terms of volume (300mg/3mL) [100 mg/mL] and deleted the terminal zero in "3.0 mL."

The proposed labeling for the 300 mg/3.0 mL multiple dose vial carton is acceptable.

CONCLUSIONS

1. **The following items are acceptable: I. A. 1.-9, I. B., 1.-6., I. C., I. D., 1.-3., I. E. 1.-7., I.F., I.G. 1-4., I. H. 1., I. H. 2. a.-h., I. H. 3. a.-.e., I. H. 4.-6., II. And III.**

2. **Item I. H. 2. i. is acceptable per the Medical Officer.**

3. **This CMC supplement with labeling should be approved.**

4. **An approval letter should be sent to the sponsor with a request to add the word "and" before the word "only" in the third sentence of the first paragraph in the PRECAUTIONS section, Miscellaneous subsection of the PI, at the next printing, as stated in item I. D. 3.**

5. **The approval letter should also contain a recommendation to include multiple instructions for use in each multiple vial package as recommenced by DMETS (see page 4 of this RPM Review).**

Diane Moore, B.S.
Regulatory Health Project Manager

Julieann DuBeau, MSN, RN
Chief, Project Management Staff

Ruyi He, M.D.
Medical Officer

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

Cc:

Archival NDA 20-164/S-043
HFD-180/Div. Files
HFD-180/D.Moore
HFD-180/R.He/K.Robie-Suh/L.Zhou/A.Al-Hakim
HFD-180/RJustice/J.Korvick
Drafted by: dm/1/17/03
Initialed by: J.DuBeau 1.21.03/R.He, K.Robie-Suh 1.22.03
Final: January 23, 2003
Filename:N20164S43LblrevCycle3Final.doc
RPM LABELING REVIEW

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/s/

Diane V. Moore
1/23/03 10:23:45 AM
CSO

Julieann DuBeau
1/23/03 12:42:23 PM
CSO

Ruyi He
1/23/03 01:02:25 PM
MEDICAL OFFICER

Kathy Robie-Suh
1/23/03 01:43:31 PM
MEDICAL OFFICER

Division of Gastrointestinal and Coagulation Drug Products (DGICDP)

REGULATORY PROJECT MANAGER LABELING REVIEW

Application Number: NDA 20-164/SCM-043 Final Printed Labeling (FPL)

Name of Drug: Lovenox® (enoxaparin sodium injection)

Sponsor: Aventis Pharmaceuticals Inc.

Materials Reviewed: Package Insert (PI) submitted April 11, 2003, and Carton and Immediate Container Labeling submitted June 2, 2003.

Submission Date:	February 27, 2003
Receipt Date:	February 28, 2003
Amendment Date:	April 11, 2003
Receipt Date:	April 14, 2003
Amendment Date	June 2, 2003
Receipt Date:	June 14, 2003

Background and Summary

Background: Lovenox was approved March 29, 1993. It is approved for the following indications:

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

The prior approval chemistry, manufacturing and controls (CMC) supplement with labeling (SCM-043) was originally submitted on May 15, 2001 (received May 16, 2001). The supplement provides for a multiple-dose vial presentation of Lovenox Injection (300 mg/3 mL) at a concentration of 100 mg/mL and preserved with benzyl alcohol at 1.5% (m/v) level; a new contract manufacturing site, Catalytica Pharmaceuticals, Greenville, South Carolina, for the drug product; revised package insert labeling; and immediate container and carton labeling for the proposed multiple dose vial.

On September 14, 2001, the Agency sent the sponsor a not approvable letter. On May 1, 2002 (received May 2, 2002), Aventis Pharmaceuticals submitted a full response to the September 14, 2001, not approvable letter. An approvable letter was sent to the sponsor on August 30, 2002. The sponsor submitted electronic draft labeling on September 20, 2002 (received September 23, 2002), in response to the Agency's approvable letter dated August 30, 2002. The sponsor amended the labeling on January 17, 2003 (received January 21, 2003). Supplement-043 was approved on draft January 23, 2003.

The sponsor submitted FPL on February 27, 2003 (received February 28, 2003). This labeling included labeling revisions to include instructions on the use of the automatic safety device provided in the "Changes Being Effected" (CBE) S-051 (submitted December 19, 2002 (received December 20, 2002). These proposed revisions were not included in the approved labeling for Supplement S-043. Since S-051 was a CBE, the sponsor implemented the labeling submitted to S-051 prior to the approval of S-043. Supplement-043 was approved January 23, 2003, whereas S-051 was approved after additional revisions on June 20, 2003. The labeling submitted as FPL on February 27, 2003 (received February 28, 2003), was not similar to any approved labeling (neither S-043 nor S-051). Diane Moore, Regulatory Project Manager (RPM), contacted the sponsor and requested revised labeling for FPL for S-043 that was identical to the approved labeling for S-043. On April 11, 2003, the sponsor submitted revised FPL for S-043. This submission did not include the immediate container and carton labeling from S-043. On May 15, 2003, Diane Moore, RPM, contacted the sponsor and requested the immediate container and carton labeling FPL for S-043. On June 2, 2003, the sponsor submitted the immediate container and carton labeling FPL for S-043.

Review

The electronic final printed PI submitted on April 11, 2003 (received April 14, 2003) identifier codes "50069638," "50069639," and "50069650" and the WORD version (no identifier) were compared to the PI submitted September 20, 2002 (received September 23, 2002), (no identifier). The PIs are identical except for the following:

I. Package Insert

A. **DESCRIPTON** section

In the fifth paragraph that begins "**Lovenox Injection 150 mg/mL Concentration**" the sponsor deleted the word "or" after the term "enoxaparin sodium" so that the sentence reads "**Lovenox Injection 150 mg/mL Concentration** contains 15 mg enoxaparin sodium (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 editorial deletion of the word "or" corrects the sentence so that it makes a definite statement of concentration. The deletion is acceptable.

B. WARNINGS section

In the **Miscellaneous** subsection, third sentence that begins "Because benzyl alcohol may cross . . ." the sponsor added the word "and" after the word "women" so that the sentence reads "Because benzyl alcohol may cross the placenta, Lovenox multiple-dose vials, preserved with benzyl alcohol, should be used with caution in pregnant women and only if clearly needed (see **PRECAUTIONS, Pregnancy**)."

The Agency requested the addition of the word "and" in the above sentence in the January 23, 2003 approval letter for NDA 20-164/S-043. The addition is editorial and acceptable.

C. **HOW SUPPLIED** section

1. In the table entitled "**100 mg/mL Concentration**," the sponsor has added lines between the following concentrations in the table:

   a. the 30 mg/0.3 mL and 40 mg/0.4 mL prefilled syringes;

   b. the 60 mg/0.6 mL and the 80 mg/0.8 mL graduated prefilled syringes; and

   c. the 80 mg/0.8 mL and the 100 mg/1 mL graduated prefilled syringes.

The additional lines separate the different dosage strengths more efficiently. The additions are editorial and acceptable.

2. In the table entitled "**150 mg/mL Concentration**," the sponsor has added lines between the 120 mg/0.8 mL and the 150 mg/1 mL graduated prefilled syringes.

The additional lines separate the different dosage strengths more efficiently. The additions are editorial and acceptable.

Immediate Container Label

The immediate container label FPL submitted on June 2, 2003 (received June 3, 2003) identifier code "50060723" was compared to the immediate container label FPL submitted September 20, 2002 (received September 23, 2002, approved January 23, 2003) identified as "50060723." The immediate container labels are identical.

Carton Container Labeling

The carton FPL submitted on June 2, 2003 (received June 3, 2003) identifier code "50060724" was compared to the carton container FPL submitted September 20, 2002 (received September 23, 2002, approved January 23, 2003) identified as "50060724." The carton container labeling are identical.

CONCLUSIONS

1. The PI FPL for NDA 20-164/S-043 submitted April 11, 2003 (received April 14, 2003) is acceptable.

2. The carton and immediate container labeling submitted June 2, 2003 (received June 3, 2003) is acceptable.

3. An "acknowledgement and retain" letter should be sent to the sponsor for the FPL for S-043.

Diane Moore, B.S.
Regulatory Health Project Manager

Cc:
Archival NDA 20-164/S-043
HFD-180/Div. Files
HFD-180/D.Moore
HFD-180/R.He/K.Robie-Suh
HFD-180/RJustice/J.Korvick
Drafted by: dm/5/09/03
Final: October 6, 2003
Filename:N20164S43FARPMrev.doc
RPM LABELING REVIEW

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/s/

Diane V. Moore
10/6/03 04:27:48 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-043

MEDICAL REVIEW

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

NDA:	NDA 20-164/SCM-043-BZ
Sponsor:	AVENTIS PHARMACEUTICAL PRODUCTS, INC 300 Somerset Corporate Boulevard Bridgewater, NJ 08807-2854 USA
Drug name:	**Lovenox** (enoxaparin sodium)
Subject:	Package Insert update and review
Date submitted:	May 1, 2002
Date received:	May 2, 2002
Date assigned:	May 20, 2002
Review completed:	August 26, 2002
Reviewer:	Ruyi He, M.D.

BACKGROUND:

The supplement 043 was originally submitted on May 15, 2001 for a multiple-dose vial presentation of Lovenox Injection (300 mg/3mL) preserved with benzyl alcohol at 1.5% (m/v) level; a new contract manufacturing site; revised package insert labeling; and immediate container and carton labels for the proposed multiple dose vial. On September 14, 2001, the Division sent a non-approval letter to the sponsor for S-043, because inspections of the manufacturing facilities were failed.

In this submission, the sponsor resubmitted Supplement-034, after the manufacturing site was recently re-inspected by the FDA and was accepted by the Atlanta District Office. The sponsor did not update proposed package insert from the previous May 15, 2001 submission. Thus the package insert dose not incorporate the updated information of supplement 046 labeling approved January 9, 2002. Wording in approved labeling from S-046 is newest version. In the following section, I will provide my comments for clinical related labeling changes. For other changes, please see FDA Regulatory Project Manager Labeling Review dated August 23, 2002 and FDA Chemist's review #3 for this submission dated May 16, 2002.

PACKAGE INSERT LABELING CHANGES

1. **CONTRAINDICATIONS** section

In the second paragraph, first sentence that begins, "Patients with known hypersensitivity . . ." the sponsor proposes to add the phrase, "or any of its constituents." so that the sentence reads, "Patients with known hypersensitivity to heparin or pork products should not be treated with Lovenox Injection or any of its constituents."

This change is acceptable.

2. The sponsor proposes to add a new **Miscellaneous** subsection in the section of **WARNINGS,** following the Thrombocytopenia subsection. The Paragraph reads as follows:

"**Miscellaneous:** Lovenox multiple-dose vials contain benzyl alcohol as a preservative. The administration of medications containing benzyl alcohol as a preservative to premature neonates has been associated with a fatal "Gasping Syndrome". Because benzyl alcohol may cross the placenta, Lovenox multiple-dose vials, preserved with benzyl alcohol, should be used with caution in pregnant women only if clearly needed (see **PRECAUTIONS, Pregnancy**)."

This change is acceptable.

3. The sponsor proposes to add a new paragraph under **PRECAUTIONS** section, **Pregnancy** subsection, *Non-teratogenic Effects* subsection:

Cases of "Gasping Syndrome" have occurred in premature infants when large amounts of benzyl alcohol have been administered (99-405 mg/kg/day). The multiple-dose vial of Lovenox solution contains 15 mg/1.0 mL benzyl alcohol as a preservative (see WARNINGS, Miscellaneous)."

This change is acceptable.

4. In the **Adult Dosage** subsection, **Administration** subsection, in the paragraph that begins, "Enoxaparin injection is a clear, colorless . . ." the sponsor proposes to revise the second sentence that reads as follows:

"When using Lovenox Injection ampules to assure withdrawal of the appropriate volume of drug, the use of a tuberculin syringe or equivalent is recommended."

The proposed sentence reads as follows:

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

The proposed change is acceptable.

CONCLUSIONS

From the clinical standpoint, the changes #1 to #4 listed above are acceptable.

For other changes, please see FDA Regulatory Project Manager Labeling Review dated August 23, 2002 and FDA Chemist's review #3 for this submission dated May 16, 2002.

From the clinical standpoint, I recommend that this labeling supplement be approved.

Ruyi He, MD

IND: NDA 20-164/S-043
HFD-180/Div. Files
HFD-180/V. Raczkowski
HFD-180/J. Korvick
HFD-180/K.Robie-Suh
HFD-180/R.He
HFD-180/L.Zhou
HFD-180/J. Choudary
HFD-180/T. Permutt
HFD-181/D. Moore
f/t 8/26/02 rh
N/20164/S043.RH

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/s/

Ruyi He
8/26/02 11:11:22 AM
MEDICAL OFFICER

Kathy Robie-Suh
8/26/02 01:16:45 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-043

CHEMISTRY REVIEWS

CHEMIST'S REVIEW #1	1. Organization: HFD-180	2. NDA Number: 20-164
3. Name and Address of Applicant (City & State): Aventis Pharmaceutical Products 10236 Marion Park Drive, PO Box 9720 Kansas City, MO 64134		4. AF Number: Supplement(s)
6. Name of Drug: Lovenox Injection	7. Nonproprietary Name: enoxaparin sodium injection	Number(s) / Date(s) SCM-043 15-MAY-2001 BC 24-MAY-2001 BC 23-Aug-2001
8. The supplement provides for: (1) A Lovenox Injection multi-dose vial (300mg/3 mL enoxaparin sodium) preserved with benzyl alcohol (1.5% m/v). (2) A new contract manufacturer, Catalytica Pharmaceuticals, Greenville, South Carolina.		9. Amendments and Other (Reports, etc.) Dates:
10. Pharmacological Category: Anti-thrombotic	11. How Dispensed: Rx-XXX OTC –	12. Related DMF(s): DMF DMF DMF DMF14141 DSM Catalytica Pharm.
13. Dosage Form: Injection (multi-dose vial)	14. Potency: 100mg/1.0mL	
15. Chemical Name and Structure: See USP Dictionary (2001)		16. Records and Reports: Current Yes No Reviewed Yes No
17. Comments: See Review Notes. cc: NDA 20-164 HFD-180/Div File HFD-181/CSO/KOliver HFD-180/Jsieczkowski HFD-180/LZhou		
18. Conclusions and Recommendations: Conclusion: From a chemistry viewpoint, the supplement should be approved. Recommendations: Before the issuance of a letter to Aventis concerning the approvability of this supplement: 1.the recommendations stated in the Microbiologist's Review and in the CDER CGMP compliance report (present facility status is OAI ALERT) should be taken into account. 2. Other consult reviews requested by the Medical Division may be pending and those also should be considered in the evaluation of this supplement and the issuance of a letter. At present, this is a chemistry supplement review and therefore, any letter issued should be under the chemistry Team Leader's signature.		
19. Reviewer		
Name: Joseph Sieczkowski, PhD	Signature	Date Completed: August 27, 2001

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15 Pages Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

CHEMISTRY REVIEW #1

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/s/

Joe Sieczkowski
8/28/01 05:53:13 AM
CHEMIST

Liang Zhou
8/28/01 04:36:30 PM
CHEMIST

CHEMIST'S REVIEW #2	1. Organization: HFD-180	2. NDA Number: 20-164
3. Name and Address of Applicant (City & State): Aventis Pharmaceutical Products 10236 Marion Park Drive, PO Box 9720 Kansas City, MO 64134		4. AF Number: Supplement(s)
6. Name of Drug: Lovenox Injection	7. Nonproprietary Name: enoxaparin sodium injection	Number(s) / Date(s) SCM-043 — 15-MAY-2001 BC — 24-MAY-2001 BC — 23-Aug-2001
8. The supplement provides for: (1) A Lovenox Injection multi-dose vial (300mg/3 mL enoxaparin sodium) preserved with benzyl alcohol (1.5% m/v). (2) A new contract manufacturer, Catalytica Pharmaceuticals, Greenville, South Carolina.		9. Amendments and Other (Reports, etc.) Dates:
10. Pharmacological Category: Anti-thrombotic	11. How Dispensed: Rx-XXX OTC	12. Related DMF(s): DMF [redacted] DMF DMF DMF14141 DSM Catalytica Pharm.
13. Dosage Form: Injection (multi-dose vial)	14. Potency: 100mg/1.0mL	
15. Chemical Name and Structure: See USP Dictionary (2001)		16. Records and Reports: Current Yes No Reviewed Yes No

17. Comments: The Clinical Pharm. and Biopharm. Review (9/14/01) concludes that the proposed drug product is bioequivalent. Pharmacology will review the status of benzyl alcohol, as it will be clinically addressed in the final printed labeling. All outstanding consult issues have been reviewed or satisfactorily resolved and chemistry agrees with the conclusions of the consult reviews.

cc: NDA 20-164
HFD-180/Div File
HFD-181/CSO/KOliver
HFD-180/Jsieczkowski
HFD-180/LZhou

18. Conclusions and Recommendations:
Recommendations: Office of Compliance recommends "Withhold" (14-Sep-2001). It is recommended that on the basis of the Office of Compliance's Recommendation, the supplement should not be approved. The CSO should prepare a not approveable letter for the Division Director's signature.

19. Reviewer

Name: Joseph Sieczkowski, PhD	Signature	Date Completed: 14-Sep-2001

Form FDH 2266 (7/75) ALT R

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/s/

Joe Sieczkowski
9/14/01 12:22:55 PM
CHEMIST

Liang Zhou
9/14/01 12:48:33 PM
CHEMIST

Note:

Chemistry Review #3 was not finalized prior to Chemistry Review #4 being finalized. Thus, there is no Chemistry Review #3 in this package.

CHEMIST'S REVIEW #4	1. Organization: HFD-180	2. NDA Number: 20-164
3. Name and Address of Applicant (City & State): Aventis Pharmaceutical Products 10236 Marion Park Drive, PO Box 9720 Kansas City, MO 64134		4. AF Number:

6. Name of Drug: Lovenox Injection	7. Nonproprietary Name: enoxaparin sodium injection	Supplement(s) Number(s)	Date(s)
		SCM-043	15-MAY-2001
		BC	24-MAY-2001
		BC	23-Aug-2001
		AZ	01-MAY-2002

8. The supplement provides for: (1) A new Lovenox Injection multi-dose vial (300mg/3mL enoxaparin sodium) preserved with benzyl alcohol (1.5% m/v). (2) A new contract manufacturer, Catalytica Pharmaceuticals, Greenville, SC.	9. Amendments and Other (Reports, etc.) Dates:

10. Pharmacological Category: Anti-thrombotic	11. How Dispensed: Rx-XXX OTC	12. Related DMF(s): DMF [redacted] DMF DMF DMF14141 DSM Catalytica Pharm.
13. Dosage Form: Injection (syringes) (100mg/mL multi-dose vial/S-043)	14. Potency: 100mg/1.0mL 150mg/1.0mL	

15. Chemical Name and Structure: See USP Dictionary (2002)	16. Records and Reports: Current Yes No Reviewed Yes No

17. Comments: Chemistry Review #4 is for the AZ Amendment that is Aventis' response to the Division's Not Approvable letter of 14-SEP-2001

cc: NDA 20-164
HFD-180/Div File
HFD-181/CSO/DMoore
HFD-180/JSieczkowski

18. Conclusions and Recommendations:

Conclusion: From a chemistry viewpoint, the supplement should be approved for the manufacture of the new Lovenox Injection multi-dose formulation (300mg/3mL with benzyl alcohol preservative) at Catalytica Pharmaceuticals.

Recommendation: The approval letter should not be issued until a response is received concerning the labeling issues noted in the RPM Labeling Review of 21-AUG-2002 (see also DMETS Consult Review: #02-115/29-JUL-2002) and the only chemistry labeling issue (see below). The only chemistry issue is concerned with the removal of the statement, "Nitrogen is used in the headspace to inhibit oxidation" from the package insert. After a discussion with the Team Leader, the nitrogen statement does not need to be in the labeling but is noted as being a specific requirement in the drug product manufacturing section under the CMC section submitted in the supplement.

19. Reviewer

Name: Joseph Sieczkowski, PhD	Signature	Date Completed: 27-AUG-2002

Review Notes

Chemistry Review # 3 Comment (May 12, 2002)

DMETS: The DMETS group should review the appropriateness of the drug product name ———— Injection as it will be included in the Lovenox Injection package insert with other Lovenox Injection products. **(Consult Request)**

Chemistry Review #4

This chemistry review is concerned with comments in the RPM LABELING REVIEW that references DMETS Consult Review (#02-115 dated July 29, 2002) of the drug product labeling. The chemistry review was triggered by the "Conclusions" section in the RPM Labeling Review. The following sections are reproduced from the RPM Review followed by the Chemistry Comment:

Comment and bullet items from the RPM review, that are noted by the RPM as the domain of the chemist, are provided below:

II. IMMEDIATE CONTAINER LABELING

The proposed labeling is consistent with previously approved labeling for Lovenox immediate containers except for the ———— A consult was sent to the DMETS to assess the appropriateness of the ———— on May 20, 2002. In the DMETS Consult # 02-0115, completed July 29, 2002, DMETS does not recommend the use of the proprietary name ———— for the multi-dose vial. DMETS has no objection to the use of the proprietary name Lovenox for the multi-dose vial. The Chemistry reviewer should review and comment on this immediate container labeling.

III.CARTON LABELING

The labeling is consistent with previously approved labeling for LOVENOX except for the———— A consult was sent to the DMETS to assess the appropriateness of the ———— on May 20, 2002. In the DMETS Consult # 02-0115, completed July 29, 2002, DMETS does not recommend the use of the proprietary name ———— for the multi-dose vial. DMETS has no objection to the use of the proprietary name Lovenox for the multi-dose vial.

The DMETS consult provided the additional recommendations regarding the immediate container and carton labeling:

- **Include the dosage form "Injection" in the established name (i.e, Enoxaparin Sodium Injection) for the 300 mg per 3 mL container.**
- **Increase the prominence of the established name so that it is at least half as large as the proprietary name.**
- **The net quantity statement should be expressed in terms of volume (i.e., 3 mL) and not total drug concentration. Revise accordingly.**

- **The terminal zeros in '3.0 mL' should be deleted since they could be misinterpreted as '30 mL.'**

- **Delete** [ ]

Chemistry Comment:
DMETS comments and proposals for the immediate container labeling and the carton labeling appear acceptable on the basis of the regulations and their concerns for the printed information layouts in the labeling. One item of potential concern is the proposed change to the expression of the drug product volume. Scientifically the measured volume should be expressed to indicate the level of significance for the volume fill which in this case is plus or minus one-tenth, the last significant place for the volume as in"3.0 mL" not "3 mL" as proposed by DMETS. However, from a safety point of view, DMETS comment appears to be valid. Because DMETS was consulted for their expertise in evaluating the labeling from a safety standpoint as well as a regulatory point of view, the chemistry reviewer defers to DMETS opinion in this regard.

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/s/

Joe Sieczkowski
8/27/02 02:44:58 PM
CHEMIST

Liang Zhou
8/28/02 09:48:15 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-043

MICROBIOLOGY REVIEW

REVIEW TO HFD-180
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF/HFD-805
MICROBIOLOGY REVIEW #1 OF NDA

7 September 2001

A. 1. NDA: 20-164/SCM-043

2. TYPE OF SUPPLEMENT: Prior Approval

3. SUPPLEMENT PROVIDES FOR: A multiple dose vial, addition of a preservative, and a new manufacturing facility

4. APPLICANT/SPONSOR: Aventis Pharmaceuticals
399 Interpace Parkway
Parsippany, NJ 07054

5. MANUFACTURING SITE: Catalytica Pharmceuticals
Greenville, NC

6. DRUG PRODUCT NAME:
Proprietary: LOVENOX
Nonproprietary: enoxaparin sodium
Drug Priority Classification: P

7. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile preserved solution in a 5 mL glass vial, 100mg/mL, for subcutaneous administration

8. METHOD(S) OF STERILIZATION: ———

9. PHARMACOLOGICAL CATEGORY: Anti-Coagulant

B. 1. DOCUMENT/LETTER DATE: May 15, 2001
2. RECEIPT DATE: May 16, 2001
3. CONSULT DATE: May 30, 2001
4. DATE OF AMENDMENT: N/A
5. ASSIGNED FOR REVIEW: June 15, 2001
6. SUPPORTING/RELATED DOCUMENTS: DMF 14141

C. REMARKS: This submission references a DMF (#14141, Catalytica) for information regarding the manufacturing facility and manufacturing process.

D. CONCLUSIONS: This submission is recommended for approval from the standpoint of product quality microbiology.

Bryan S. Riley, Ph.D.
Microbiology Reviewer

cc.: Original NDA 20-164
HFD 180/Division File
HFD 180/Project Manager
HFD 180/Chemist
HFD 805/Consult File
HFD 805/ B. Riley

Drafted by: Bryan Riley, Ph.D.
R/D initialed by: Peter Cooney, Ph.D.

filename: C:\Data\Data\Word\NDA\S\20164s43.doc

APPEARS THIS WAY
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4 Pages Withheld

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_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

MICROBIOLOGY REVIEW # 1

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/s/

Bryan Riley
9/11/01 07:35:10 AM
MICROBIOLOGIST

Peter Cooney
9/12/01 09:39:50 AM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-043

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-164 / SCM-043 **Stamp Date**: 5/16/01

Trade Name: Lovenox® SC Injection

Active Ingredient: Enoxaparin sodium

Sponsor: Aventis Pharmaceuticals Inc.

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Type of Submission: Prior Approval Supplement

Background

Lovenox® (Enoxaparin sodium) injection is a low molecular weight heparin first approved for marketing in the US on 3/29/93 for prevention of deep vein thrombosis (DVT). Currently, Lovenox® injection is additionally approved for treatment of DVT as well as prevention of ischemic complications of unstable angina and non-Q-wave myocardial infarction when concurrently administered with aspirin. It is administered by subcutaneous (SC) injection, 30 mg BID or 40 mg QD in patients undergoing hip or knee surgery, 40 mg QD in patients undergoing abdominal surgery and may be at risk of thromboembolic complications, 1 mg/kg BID or 1.5 mg/kg QD in patients with acute deep vein thrombosis with or without pulmonary embolism and 1 mg/kg BID in patients with unstable angina or non-Q-wave myocardial infarction.

Lovenox® is currently only approved as single-dose pre-filled syringes containing 100 mg/ml or 150 mg/ml aqueous solution of enoxaparin sodium. The current study supplement is submitted in support of a multiple dose formulation of Lovenox® which also contains 1.5% benzyl alcohol as a preservative.

The current submission includes the final report for Study **RP54563Q-134** entitled,

"A PHASE 1, OPEN, RANDOMIZED, THREE-PERIOD CROSS-OVER STUDY COMPARING THE PHARMACOKINETIC PROFILE OF TWO FORMULATIONS OF RP 54563 (Enoxaparin: prefilled syringe and multidose vial, freshly opened or 7 days following opening) AFTER SINGLE 40 mg S.C. DOSE ADMINISTERED IN HEALTHY MALE AND FEMALE SUBJECTS"

Primary Review Issue

- **Is the multiple dose formulation of Lovenox® bioequivalent to the single dose pre-filled formulation ?**

Objectives

- To compare the pharmacokinetic parameters of enoxaparin sodium administered as single S.C. 40 mg dose from 2 different formulations: prefilled syringe and multi-dose vial.
- To verify that conservation of opened multi-dose vial for 7 days does not modify the biological properties of enoxaparin sodium administered as single S.C. 40 mg dose.

Study Design

Open, randomized, three-period crossover study

Subjects	24 male and female subjects
Key Inclusion Criteria	Healthy elderly subjects, Age 18-45
Treatments	Subjects were randomized into 3 treatment periods of 40 mg enoxaparin sodium S.C. injection each: • **Treatment A: 40 mg prefilled syringe** • **Treatment B: 40 mg freshly opened multi-dose vial** • **Treatment C: 40 mg multi-dose vial 7 days after opening**
Wash-out Period	At least 14 days
PK/PD Sampling Times	For enoxaparin assay, plasma samples were collected at: 0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16 and 24 hrs post-dose

Pharmacokinetic (PK) Analysis

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), Heptest® and aPTT clotting times. Validated amidolytic methods were utilized to determine anti-Xa and anti-IIa activities.

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.

Limits of quantitation for anti-Xa and anti-IIa activities were 0.025 IU anti-Xa/ml and 0.025 IU anti-IIa/ml, respectively. The anti-Xa activity assay was linear over a range of 0-0.401 IU anti-Xa/ml, while anti-IIa activity assay was linear over a range of 0-0.388 IU anti-IIa/ml

The following pharmacokinetic parameters were determined for anti-Xa, anti-IIa activities and Heptest®: A_{max}, t_{max}, $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, **MRT and** $t_{1/2}$.

Results

Table 1. Summary of PK parameters of anti-Xa activity

Treatment		*tmax* (h)		*Amax* IUaXa/ml	*AUC(0-t)* h.IUaXa/ml	*AUC* h.aXa/ml	*MRT* h	*Vz/F* l	*Vss/F* l	*CL/F* l/h	*t1/2λz* h
A	mean		-	0.55	4.08	4.30	6.0	4.3	5.5	0.92	3.3
	SD		-	0.10	0.75	0.81	1.2	0.8	1.1	0.18	0.8
	CV%		-	18	18	19	20	19	19	19	24
	median	3.00		-	-	-	-	-	-	-	-
	range	1.50	-4.00	0.39-0.78	2.41-6.12	2.63-6.76	4.7-10.4	3.2-6.2	3.9-7.9	0.57-1.46	2.6-6.3
B	mean		-	0.53	3.90	4.09	5.9	4.9	6.1	1.04	3.3
	SD		-	0.11	0.74	0.73	0.8	1.0	1.2	0.21	0.6
	CV%		-	20	19	18	14	21	20	20	19
	median	2.50		-	-	-	-	-	-	-	-
	range	1.50	-3.50	0.36-0.79	2.27-5.32	2.46-5.48	4.6-7.5	3.2-6.9	4.0-8.8	0.75-1.67	2.4-4.8
C	mean		-	0.51	3.80	4.02	5.9	5.1	6.2	1.06	3.4
	SD		-	0.09	0.74	0.75	0.8	1.1	1.3	0.20	0.6
	CV%		-	18	20	19	14	21	21	19	18
	median	2.50		-	-	-	-	-	-	-	-
	range	1.00	-4.50	0.33-0.69	2.50-5.36	2.69-5.64	5.0-8.5	3.2-7.7	4.3-9.7	0.73-1.52	2.6-5.1

Table 2. Summary of PK parameters of anti-IIa activity

Treatment		tmax h		Amax IUaIIa/ml	AUC(0-t) h.IUaIIa/ml	CL/F* l/h
A	mean		-	0.07	0.25	4.44
	SD		-	0.02	0.12	1.70
	CV%		-	31	50	8
	median	3.50		-	-	-
	range	2.00	- 5.00	0.04-0.12	0.06-0.54	1.7-7.6
B	mean		-	0.10	0.23	3.78
	SD		-	0.11	0.11	2.30
	CV%		-	107	47	9
	median	3.00		-	-	-
	range	1.50	- 4.50	0.03-0.44	0.06-0.40	2.3-8.9
C	mean		-	0.07	0.23	3.81
	SD		-	0.02	0.12	1.90
	CV%		-	29	50	9
	median	2.50		-	-	-
	range	1.00	- 5.00	0.04-0.11	0.04-0.49	1.9-8.7

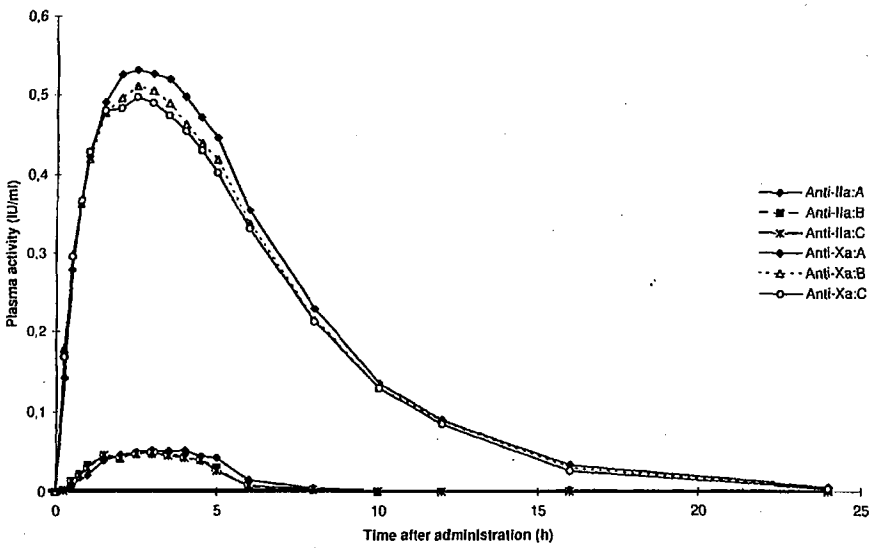

Fig. 1. Mean plasma anti-Xa and anti-IIa activities

Table 3. Summary of PK parameters of Heptest® clotting time prolongations

Treatment		tmax h	Amax s	AUC(0-t) h.s	AUC h.s	MRT h	t1/2λz h
A	mean	-	93.0	879.5	925.5	8.2	5.3
	SD	-	12.1	94.6	115.8	1.2	1.0
	CV%	-	13	11	13	15	19
	median	2.5	-	-	-	-	-
	range	1.0 -4.5	76.5-130.3	687.9-1050.5	700.9-1177.0	6.5-11.6	3.7-8.6
B	mean	-	93.0	854.9	909.1	8.3	5.5
	SD	-	11.0	82.4	99.3	1.5	1.1
	CV%	-	12	10	11	18	19
	median	1.8	-	-	-	-	-
	range	0.8 -4.0	76.2-123.8	719.0-1045.3	738.7-1153.1	5.8-11.3	3.8-7.7
C	mean	-	92.2	872.2	929.3	8.6	5.7
	SD	-	12.9	106.7	129.0	1.4	1.1
	CV%	-	14	12	14	17	19
	median	1.8	-	-	-	-	-
	range	0.8 -4.5	76.3-120.8	696.2-1133.5	729.1-1220.7	5.9-12.2	3.9-8.9

Table 4. Summary of PK parameters of aPTT clotting time prolongations

Treatment		*Baseline (s)*	*Amax (s)*	*A (Δ t)max (s)*	*tmax (h)*	
A	Mean	31.6	42.3	10.7		-
	SD	3.1	5.4	2.8		-
	CV%	10	13	27		-
	median	-	-	-	0.8	
	range	26.0-37.3	34.1-52.4	6.5-16.6	2.5	-5.0
B	Mean	31.7	41.6	9.9		-
	SD	2.8	4.2	2.4		-
	CV%	9	10	24		-
	median	-	-	-	0.5	
	range	25.9-36.9	34.5-49.3	6.8-14.6	2.3	-5.0
C	Mean	31.3	41.1	9.8		-
	SD	3.3	4.8	2.4		-
	CV%	11	12	24		-
	median	-	-	-	0.5	
	range	23.9-37.2	33.1-52.5	6.5-15.9	2.0	-6.0

Table 5. Geometric mean ratio and confidence intervals for anti-Xa

Parameter	Treatment comparison	Pr>|T|	estimate% α=0.10	lower C.I.% α=0.10	upper C.I.% α=0.10
Log Amax	A vs B	0.0085	95	92	98
	A vs C	0.0002	93	90	96
	B vs C	0.2200	98	95	101
Log AUC(0-t)	A vs B	0.0272	95	92	99
	A vs C	0.0011	93	90	96
	B vs C	0.2272	98	94	101
Log AUC	A vs B	0.0134	95	92	98
	A vs C	0.0010	93	90	96
	B vs C	0.3467	98	95	101

Overall, all three treatments were shown to be bioequivalent on AUC and A_{max} of anti-Xa activity (Table 5).

Reviewer's Recommendations

The current study report has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/Division of Pharmaceutical Evaluation II), and from the view point of OCPB, single-dose pre-filled syringe formulation and multiple dose vial formulation (both freshly opened and at 7 days after opening) are bioequivalent on anti-Xa activity. Bioequivalence on anti-IIa activity was not assessed as anti-IIa activity levels were too low to allow bioequivalence calculations.

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/s/

Suliman Alfayoumi
9/14/01 10:12:53 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
9/14/01 11:10:05 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-043

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-164/S-043

PRIOR APPROVAL SUPPLEMENT

Aventis Pharmaceuticals
Attention: Dhiren N. Shah, Ph.D.
Director, US Drug Regulatory Affairs
10236 Marion Park Drive
P.O. Box 9627
Kansas City, MO 64134-0627

Dear Dr. Shah:

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

Name of Drug Product: Lovenox® (enoxaparin sodium) Injection

NDA Number: 20-164

Supplement Number: S-043

Date of Supplement: May 15, 2001

Date of Receipt: May 16, 2001

This supplement proposes the following: (1) a multiple dose vial presentation of Lovenox Injection (300 mg/3mL) at a concentration of 100 mg/mL and preserved with benzyl alcohol at 1.5% (m/v) level; and (2) a new contract manufacturing site, Catalytica Pharmaceuticals, Greenville, South Carolina, for the drug product.

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 July 15, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be September 16, 2001 and the secondary user fee goal date will be November 16, 2001.

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

U.S. Postal/Courier/Overnight Mail:

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

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Karen Oliver
5/24/01 03:43:17 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-164/S-043

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

Dear Mr. Carrado:

Please refer to your supplemental new drug application dated May 15, 2001, received May 16, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium) Injection.

We acknowledge receipt of your submissions dated May 24, August 23, and September 10, 2001.

This supplement proposes the following changes: (1) a multiple dose vial presentation of Lovenox® Injection (300 mg/3mL) at a concentration of 100 mg/mL and preserved with benzyl alcohol at 1.5% (m/v) level; (2) a new contract manufacturing site, Catalytica Pharmaceuticals, Greenville, South Carolina, for the drug product; (3) revised package insert labeling; and (4) immediate container and carton labels for the proposed multiple dose vial.

We have completed our review and find the information presented is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

> During recent inspections of the manufacturing facilities your supplement, Catalytica Pharmaceuticals, Greenville, South Carolina, a number of deficiencies were noted and conveyed to you or your suppliers by the investigator. Satisfactory inspections will be required before this application may be approved.

Labeling comments will be provided when the supplement is otherwise approvable.

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 314.120. 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, call Karen Oliver, Regulatory Project Manager, at (301) 827-7457.

Sincerely,
{See appended electronic signature page}

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

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/s/

Lilia Talarico
9/14/01 03:02:13 PM

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Division of Medical Errors and Technical Support: Attention: Dr. Phillips
HFD-400 PKLN bldg Room 15B-03

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

DATE:	IND NO.:	NDA NO.:	TYPE OF DOCUMENT:	DATE OF DOCUMENT:
May 20, 2002		20-164	SCM-043 AZ	May 1, 2002

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
Lovenox® (enoxaparin sodium), Injection	Standard	anti-coagulant	June 20, 2002

NAME OF FIRM: Elkins-Sinn

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL	PRE--NDA MEETING	X RESPONSE TO DEFICIENCY LETTER
PROGRESS REPORT	END OF PHASE II MEETING	FINAL PRINTED LABELING
NEW CORRESPONDENCE	RESUBMISSION	X LABELING REVISION
DRUG ADVERTISING	SAFETY/EFFICACY	ORIGINAL NEW CORRESPONDENCE
ADVERSE REACTION REPORT	PAPER NDA	FORMULATIVE REVIEW
MANUFACTURING CHANGE/ADDITION	CONTROL SUPPLEMENT	OTHER *(SPECIFY BELOW)*:
MEETING PLANNED BY		X New name Lovenox 300 Injection

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

DISSOLUTION	X DEFICIENCY LETTER RESPONSE
BIOAVAILABILTY STUDIES	PROTOCOL-BIOPHARMACEUTICS
PHASE IV STUDIES	IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	SUMMARY OF ADVERSE EXPERIENCE
CASE REPORTS OF SPECIFIC REACTIONS (List below)	POISON RISK ANALYSIS
COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

CLINICAL	PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review the appropriateness of the drug product name [redacted] Injection as it will be included in the Lovenox Injection package insert with other Lovenox Injection products.

cc: Original NDA 20-164
HFD-180/Div. Files
HFD-180/Diane Moore

SIGNATURE OF REQUESTER:	METHOD OF DELIVERY (Check one): MAIL HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

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/s/

Diane V. Moore
5/20/02 02:04:32 PM

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: 05/20/02	**DUE DATE:** 07/20/02	**ODS CONSULT #:** 02-0115

TO:

Victor Raczkowski, M.D.
Acting Director, Division of Gastro-Intestinal and Coagulation Drug Products
HFD-180

THROUGH:

Diane Moore
Project Manager
HFD-180

PRODUCT NAME:	**NDA SPONSOR:** Aventis Pharmaceuticals
Lovenox (Enoxaparin Sodium Injection) 300 mg per 3 mL (100 mg per 1 mL) **NDA #:** 20-164/S-043	

SAFETY EVALUATOR: Denise P. Toyer, R.Ph.

SUMMARY: In response to a consult from the Division of Gastro-Intestinal and Coagulation Drug Products (HFD-180), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name ——— to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:

1. DMETS does not recommend use of the name ——— for the multi-dose vial.
2. DMETS has no objections to the use of the name Lovenox ———

Additionally, DMETS recommends revising the labels and labeling as outlined in Section III of this review.

Carol Holquist, R.Ph.
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-5161

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: July 25, 2002

NDA NUMBER: 20-164/S-043

NAME OF DRUG: **Lovenox**
(Enoxaparin Sodium Injection)
300 mg per 3 mL
(100 mg per 1 mL)

NDA HOLDER: Aventis Pharmaceuticals

I. EXECUTIVE SUMMARY

This consult was written in response to a request from the Division of Gastro-Intestinal and Coagulation Drug Products (HFD-180), for assessment of the tradename ———— regarding potential name confusion with other proprietary drug names. This supplement provides for a multiple dose vial containing 300 mg per 3 mL. The container labels, carton and insert labeling for ———— were reviewed for possible interventions in minimizing medication errors.

PRODUCT INFORMATION

Lovenox Injection is a sterile solution containing enoxaparin sodium, a low molecular weight heparin. Lovenox is available in concentrations of 100 mg/mL and 150 mg/mL. Table 1 and 2 illustrates the different packaging configurations for the 100 mg/mL and 150 mg/mL concentration, respectively:

Table 1

Dosage Unit / Strength	Anti-Xa Activity	Package Size (per carton)	Syringe Label Color	NDA Approval Date
Ampules			Medium Blue	
30 mg / 0.3 mL	3000 IU	10 ampules		03/29/93
Prefilled Syringes			Medium Blue	
30 mg / 0.3 mL	3000 IU	10 syringes		03/29/93
40 mg / 0.4 mL	4000 IU	10 syringes	Yellow	01/30/98
Graduated Prefilled Syringes				
60 mg / 0.6 mL	6000 IU	10 syringes	Orange	03/27/98
80 mg / 0.8 mL	8000 IU	10 syringes	Brown	03/27/98
100 mg / 1 mL	10,000 IU	10 syringes	Black	03/27/98

Table 2

Dosage Unit / Strength	Anti-Xa Activity	Package Size (per carton)	Syringe Label Color	
Graduated Prefilled Syringes				
120 mg / 0.8 mL	12,000 IU	10 syringes	Purple	06/02/00
150 mg / 1mL	15,000 IU	10 syringes	Navy Blue	06/02/00

Each Lovenox injection syringe in affixed with a 27 gauge x 1/2 inch needle. 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 also indicated for the prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin. Lovenox is indicated for the treatment of Deep Vein Thrombosis with or without Pulmonary Embolism. The recommended adult dosage in knee or hip replacement surgery is 30 mg administered subcutaneously every 12 hours, 40 mg administered subcutaneously once daily in patients undergoing abdominal surgery, 1 mg/kg administered subcutaneously every 12 hours in patients with unstable angina, Non-Q-Wave myocardial infarction, and treatment of Deep Vein Thrombosis with or without Pulmonary Embolism.

II. RISK ASSESSMENT:

A search was conducted of several standard published drug product reference texts[1,2,] as well as several FDA databases[3] for existing drug names which sound alike or look alike to ——— to a degree where potential confusion between drug names could occur under the usual clinical practice settings. Searches of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[4] and the Saegis[5] Pharma-In-Use database were also conducted.

The standard DMETS prescription analysis studies were not conducted because the proprietary name Lovenox was approved on March 28, 1993.

DMETS searched the FDA Adverse Event Reporting System (AERS) database in order to determine any post-marketing safety reports of medication errors associated with Lovenox. Additionally,

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[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/tmdb/index.html.

[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

AERS was searched for any reports relating to confusion between the proprietary name Lovenox and other currently marketed proprietary names.

A. REFERENCE SEARCH

The search of the reference texts and databases did not identify any sound-alike or look-alike names of concern.

B. AERS SEARCH

The Adverse Event Reporting System (AERS) was searched for all post-marketing safety reports of medication errors associated with Lovenox. The MEDDRA Preferred Terms (PT) "Medication Error" and "Overdose" and the drug names of "Lovenox," "Enoxaparin," "Enoxa%," and "Love%" were used as search criteria. The search identified 69 reports of medication errors. Only one case was related to name confusion between Lovenox and another currently marketed proprietary name, Levaquin. A brief description of the case is listed below.

- A patient with a diagnosis of pneumonia was ordered "Lovenox 500 mg QD.' Upon clarification, the order was for 'Levaquin 500 mg QD."

Additionally, seven cases were related to confusion with the label and labeling. One of the seven cases involved the occurrence of an actual error. The description of the *actual error* involved:

- A technician filling 5 ampules of Lovenox rather than one ampule on ten patients because the lidding did not indicate that it contained 5 ampules.

The remaining six cases involved *potential medication error reports*. A brief description of the seven cases is listed below.

1. 150 mg/mL syringe looks similar to the 30 mg/0.3mL syringe and the 120 mg/0.8 mL box is labeled 150 mg/mL.
2. 120 mg/0.8 mL label is also expressed as 150 mg/mL in red letters.
3. 60 mg and 80 mg packages are too close in color (orange vs. brown).
4. New 100 mg syringe box is similar to 30 mg syringe box.
5. 150 mg syringe label is similar to 30 mg syringe (navy blue vs. medium blue).
6. 60 mg, 80 mg and 100 mg syringes are graduated in fourths rather than fifths.

A detailed description of all eight cases can be found in Attachment A.

C. SAFETY EVALUATOR RISK ASSESSMENT

This supplement provides for the marketing of a Lovenox multiple dose vial that contains a total drug concentration of 300 mg per 3 mL (100 mg per mL). Aventis proposes using the proprietary name [redacted]
Aventis currently markets 30 mg ampules and prefilled syringes using the proprietary name 'Lovenox' in the following strengths: 30 mg, 40 mg, 60 mg, 80 mg, and 100 mg. These five strengths have a concentration of 100 mg per 1 mL (10 mg per 0.1 mL). Aventis also markets a more concentrated formulation of Lovenox. This formulation is available in prefilled syringes

[redacted]

III. COMMENTS TO THE SPONSOR:

The Division of Medication Errors and Technical Support does not recommend the use of the proprietary name [redacted].

[redacted]

In addition, DMETS conducted a review of the container label, carton, and insert labeling for Lovenox. We have identified areas of possible improvement, in the interest of minimizing potential user error.

A. CONTAINER LABEL (300 mg per 3 mL)

1. Include the dosage form "Injection" in the established name (i.e., Enoxaparin Sodium Injection).

2. Increase the prominence of the established name so that it is at least half as large as the proprietary name.

3. The net quantity statement should be expressed in terms of volume (i.e., 3 mL) and not total drug concentration. Revise accordingly.

4. The terminal zeros in '3.0 mL' should be deleted since they could be misinterpreted as '30 mL.'

5. Delete

B. CARTON LABELING (300 mg per 3 mL)

See comments A1 through A5.

IV. RECOMMENDATIONS:

1. DMETS does not recommend use of the proprietary name ———, for the multi-dose vial.
2. DMETS has no objection to the use of the proprietary name Lovenox for the multi-dose vial.

Additionally, DMETS recommends implementation of the label, labeling and packaging recommendations outlined in the review in order to further minimize the potential for medication errors detected through our post-marketing surveillance.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

Denise P. Toyer, Pharm.D.
Safety Evaluator Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

ATTACHMENT A

AERS Reports related to Name Confusion Between Lovenox and Other Currently Marketed Products			
AERS/DQRS/USP Number	**Date of Report**	**Actual/Potential**	**Narrative of Report**
3874947-9	02/27/2002	Potential	Patient had diagnosis of pneumonia. MD ordered Lovenox 500 mg QD for the patient. Pharmacist called the MD and clarified it to be Levaquin 500 mg QD.
AERS Reports related to Label and Labeling Confusion With Lovenox Products			
AERS/DQRS/USP Number	**Date of Report**	**Actual/Potential**	**Narrative of Report**
3222088-6	03/16/1999	Potential	Potential for error due the way the 60 mg/0.6 mL, 80 mg/0.8 mL and 100 mg/mL Lovenox syringes are graduated Lovenox is dosed at 1 mg/kg. When a 62 mg dose was ordered, nurses were confused on how to measure the dose because each graduation has subsections in fourths rather than fifths. The reporter is also concerned that because nurses are familiar with using syringes graduated in fifths, they may automatically assume that the hash mark after 0.5 would be 0.52, but it actually is 0.525.
3576963-3	09/21/2000	Potential	These two product packages are too close in color to each other. The 60 mg is orange and the 80 mg is brown. Since they are adjacent strengths in the range of available strengths, they are logically stored next to each other. I am not personally aware of any instances of patients receiving the wrong dose in my workplace, but I am aware of several dispensing errors that have been caught by the nursing staff. This has however resulted at times in wastage because the most common error is an 80 mg syringe being dispensed for a dose somewhat less than 60 mg. I suggest changing one of these package colors to bright -neon- green to better distinguish them from each other.
3693101-0	04/02/2001	Potential	The new box that the Lovenox 100 mg syringes are packaged in looks just like the Lovenox 30 mg box. The 100 mg syringes used to be packaged in flat, well marked, easy to read containers.
3850066-2	01/08/2002	Potential	I am concerned with the labeling of the new strengths of Lovenox. The original syringes were 100 mg/mL. The new 120 mg and 150 mg syringes are 150 mg/mL. Today we received the 120 mg syringe from our wholesaler and the billing technician asked me about the strength. The 120 mg/0.8 mL is white lettering on a purple background. Just below this in red letter is the new concentration, 150 mg/mL. The red lettering immediately attracts your attention and if you are not careful, you assume that the syringes are 150 mg. This can cause a problem because our wholesaler's invoice stated that were out of the 120 mg syringes and invoiced us for the 150 mg syringe. This is very poor choice of labeling because the red letters attract attention and it is easy to overlook the actual strength. I believe that there should be only one strength of Lovenox available and then there would be no need to have a separate concentration label.

AERS Reports related to Label and Labeling Confusion With Lovenox Products			
AERS/DQRS/USP Number	**Date of Report**	**Actual/Potential**	**Narrative of Report**
3850073-X	01/08/2002	Potential	Aventis has just come out with a couple of new sizes of Lovenox syringes-120 mg and 150mg. This is in addition to the 30, 40, 60, 80, and 100 mg sizes that were already marketed. The different size syringes have different color labels up till now there were all distinctly different in color. However, now the largest size (150 mg) syringe is NAVY blue and the smallest size (30mg) is MEDIUM blue. The concentration of the drug product in the two new ones is also higher than the others (0.15 mg/mL vs. 0.1 mg/mL). The syringes are somewhat different in size, but I'm thinking that to many people, blue is blue. It's unfortunate that Aventis couldn't have chosen another color, especially when it involves such a large difference in dose of a potent anticoagulant.
3862122-3	01/29/2002	Actual	In unit dose refill process, pharmacy technician filled 5 amps instead of one ampule to ten patients. Pharmacists changed the Quantity to one for all ten patients. Incident occurred due very poor labeling on package-see attached.
3879388-6	02/06/2002	Potential	Our nurses, pharmacists, and MDs are used to this standard concentration and we collectively feel that Aventis has made a poor choice in the labeling of the product, specifically, the 150 mg/mL syringe looks VERY similar to 30 mg/0.3 mL syringe. No where on the 150 mg/mL syringes is there anything about the "NEW CONCENTRATION" etc. Additionally, the 120 mg/0.8mL also is very confusing especially when the box is labeled 150 mg/mL.

APPEARS THIS WAY
ON ORIGINAL

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/s/

Carol Holquist
7/25/02 11:22:42 AM
PHARMACIST

Jerry Phillips
7/29/02 01:24:55 PM
DIRECTOR

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-164/S-043

Aventis Pharmaceuticals, Inc.
Attention: Joseph A. Carrado, M.Sc., R.Ph.
Director and Regulatory Liaison
Global Drug Regulatory Affairs
200 Crossing Boulevard
Bridgewater, NJ 08807-0890

Dear Mr. Carrado

We acknowledge receipt on September 23, 2002, of your September 20, 2002, resubmission to your supplemental new drug application for Lovenox® (enoxaparin sodium) Injection.

We consider this a complete response to our August 30, 2002, action letter. Therefore, the user fee goal date is March 23, 2003.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Diane V. Moore
12/18/02 04:04:27 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-164/S-043

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

Dear Dr. Smith:

We acknowledge receipt of your April 11 and June 2, 2003, submissions containing final printed labeling in response to our January 23, 2003, letter approving your supplemental new drug application for Lovenox® (enoxaparin sodium) injection.

We have reviewed the labeling that you submitted in accordance with our January 23, 2003, letter and we find it acceptable.

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

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Diane V. Moore
10/6/03 04:44:09 PM
For Dr. Robert L. Justice

Aventis Pharmaceuticals

April 11, 2003

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

NDA 20-164
Lovenox® (enoxaparin sodium injection)
Other: FPL for Approved
Supplement NDA 20-164/S-043

Dear Dr. Justice:

Reference is made to NDA 20-164, Lovenox® (enoxaparin sodium) Injection; to the Supplemental New Drug Application (Supplement 043) submitted May 15, 2001; to the Division's letter dated September 14, 2001, received September 20, 2001, advising that Supplement 043 was not approvable; to our October 25, 2001 letter, advising the Division of our intent to file an amendment to this supplement; to our May 1, 2002 amendment to Supplement 043; to the Division's letter dated August 30, 2002, advising that Supplement 043 was approvable; to our September 20, 2002 amendment to Supplement 043, which provided draft labeling (immediate container and carton) and updated Lovenox Prescribing Information; to our General Correspondence submission dated January 17, 2003 and to the Division's approval letter for Supplement 043 dated January 23, 2003.

On February 27, 2003 Aventis submitted Final Printed Labeling (FPL) for Supplement 043 in accordance with the Division's January 23, 2003 approval letter. In addition, the submitted FPL included instructions on the use of the automatic safety device, as provided in Supplement 051 and submitted to the Division on December 19, 2002 as a Changes Being Effected-0 supplement. Supplement 051 was implemented immediately and before the approval of Supplement 043 as it provided safety-related changes conforming to the November 6, 2000 Needlestick Safety and Prevention Act (Public Law 106-430), and to final rule by Occupational Safety and Health Administration (OSHA) amending the Blood Borne Pathogen (BBP) standard published in the January 18, 2001 Federal Register.

As discussed with Ms. Diane Moore, we are providing, for administrative purposes only, FPL which is identical to that reviewed for Supplement 043, including the minor editorial revision indicated. The FPL is being provided as an Electronic Regulatory Submission for Archive as current PDF files. Also, the FPL is being provided as an electronic review aid as running text. These files have been checked for viruses by Quintiles, Inc. using McAfee VirusScan v4.5.1 SP1, created on April 11, 2003. The size of contents is approximately 2 MB and is contained on one CD.

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

If you should have any questions or comments, please do not hesitate to contact the undersigned at 908-231-3103 or Steve Caffé, M.D. at 908-231-5863.

Sincerely,

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