

# CENTER FOR DRUG EVALUATION AND RESEARCH

## **Approval Package for:**

***APPLICATION NUMBER:***

**NDA 20-164/S-050**

***Name:*** Lovenox® (Enoxaparin Sodium) Injection

***Sponsor:*** Aventis Pharmaceuticals Products, Inc.

***Approval Date:*** July 1, 2003

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***  
**NDA 20-164/S-050**

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**CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***

**NDA 20-164/S-050**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 20-164/S-050

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

Dear Dr. Smith:

Please refer to your supplemental new drug application dated October 25, 2002, received October 29, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox<sup>®</sup> (enoxaparin sodium injection).

We acknowledge receipt of your submission dated May 9, 2003.

Your submission of May 9, 2003, constituted a complete response to our April 23, 2003, action letter.

This supplemental new drug application provides for revisions to the **WARNINGS** section of the Lovenox package insert (PI) regarding mechanical prosthetic heart valves.

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 revisions listed below.

1. In the **WARNINGS** section, ninth paragraph, sixth sentence that begins "Women with mechanical prosthetic heart valves . . ." the term "still birth" should be presented as one word "stillbirth" so that the sentence reads "Women with mechanical prosthetic heart valves may be at higher risk for thromboembolism during pregnancy, and, when pregnant, have a higher rate of fetal loss from stillbirth, spontaneous abortion and premature delivery."
2. In the **HOW SUPPLIED** section, in the third paragraph, delete the redundant period at the end of the first sentence that reads "**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.."

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted labeling (package insert submitted May 9, 2003). These revisions are terms of the approval of this application.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-164/S-050." Approval of this submission by FDA is not required before the labeling is used.

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

MEDWATCH, HFD-410  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

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

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

Sincerely,

{See appended electronic signature page}

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

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/s/

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Joyce Korvick  
7/1/03 12:45:53 PM  
for Dr. Robert Justice

# **CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***

**NDA 20-164/S-050**

**APPROVABLE LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 20-164/S-050

Aventis Pharmaceuticals  
Attention: Joseph A. Carrado, M.Sc., R.Ph.  
Director, Global Drug Regulatory Liaison  
200 Crossing Boulevard  
P.O. Box 6890  
Bridgewater, NJ 08807-0890

Dear Mr. Carrado:

Please refer to your supplemental new drug application dated October 25, 2002, received October 29, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox<sup>®</sup> (enoxaparin sodium injection).

This supplemental new drug application provides for revisions to the **WARNINGS** section of the Lovenox package insert (PI) regarding mechanical prosthetic heart valves.

We completed our review of this application and it is approvable. Before this application may be approved, however, you must submit final printed labeling revised as follows. Additions are denoted by single underlining. Deletions are denoted by ~~strikeouts~~.

Package Insert

1. Revise the **WARNINGS** section of the PI as follows:

**“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<sup>3</sup> and 50,000/mm<sup>3</sup>) 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<sup>3</sup> 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<sup>3</sup>, Lovenox Injection should be discontinued. Cases of heparin-induced thrombocytopenia with thrombosis have also been observed in clinical practice. Some of these cases were complicated by organ infarction, limb ischemia, or death.

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

2. Revise the **PRECAUTIONS** section of the labeling as follows:

#### **“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.

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

**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<sup>2</sup>/day. The maximum human dose in clinical trials was 2.0 mg/kg/day or 78 mg/m<sup>2</sup>/day (for an average body weight of 70 kg, height of 170 cm, and body surface area of 1.8 m<sup>2</sup>).

**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<sup>2</sup>/day and 410 mg/m<sup>2</sup>/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.

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

#### Fetal Risk Summary

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

#### Clinical Considerations

Pregnancy alone confers an increased risk for thromboembolism, that is even higher for women with thromboembolic disease and certain high risk pregnancy conditions. While not adequately studied, pregnant women with mechanical prosthetic heart valves may be at even higher risk for thrombosis.

(see WARNINGS: Pregnant Women with Mechanical Prosthetic Heart Valves and PRECAUTIONS: Mechanical Prosthetic Heart Valves).

Pregnant women with thromboembolic disease, including those with prosthetic heart valves, and those with inherited or acquired thrombophilias, also have an increased risk of other maternal complications and fetal loss regardless of the type of anticoagulant used.

All patients receiving anticoagulants such as enoxaparin, including pregnant women, are at risk for bleeding. Pregnant women receiving enoxaparin should be carefully monitored for evidence of bleeding or excessive anticoagulation. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.

Consideration for use of a shorter acting agent should be specifically addressed as delivery approaches.

#### Data

- Human Data-

There are no adequate and well-controlled studies in pregnant women.

A retrospective study — 604 women who used enoxaparin during pregnancy. A total of 624 pregnancies resulted in 693 live births. There were 72 hemorrhagic events (11 serious) in 63 women. There were 14 cases of neonatal hemorrhage. Major congenital anomalies in live births occurred at rates (2.5%) similar to background rates.

There have been postmarketing reports of fetal death when pregnant women received Lovenox injection. Causality for these cases has not been determined. The evaluation of these cases is complicated by insufficient data, the underlying disease, and the possibility of inadequate anticoagulation.

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**).

See **WARNINGS: Pregnant Women with Mechanical Prosthetic Heart Valves** for a clinical study of pregnant women with mechanical prosthetic heart valves.

- Animal Data – Teratology studies have been conducted in pregnant rats and rabbits at SC doses of enoxaparin up to 30 mg/kg/day or 211 mg/m<sup>2</sup>/day and 410 mg/m<sup>2</sup>/day, respectively. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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

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

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

Please submit the final printed labeling (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 but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material.

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

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

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

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

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

**APPEARS THIS WAY  
ON ORIGINAL**

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

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/s/

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Robert Justice  
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# **CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***  
**NDA 20-164/S-050**

**LABELING**



Labeling: SLR 050 AL  
NDA No 20164 Rec'd 5-12-03  
Reviewed by: \_\_\_\_\_

AP Du 7/1/03



APPROVED  
JUL - 1 2003

Rx only  
Rev.XXXX

#### SPINAL / EPIDURAL HEMATOMAS

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

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

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

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

#### DESCRIPTION

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

Lovenox Injection is available in two concentrations:

##### 1. 100 mg per mL

-Prefilled Syringes	30 mg / 0.3 mL, 40 mg / 0.4 mL
-Graduated Prefilled Syringes	60 mg / 0.6 mL, 80 mg / 0.8 mL, 100 mg / 1 mL
-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
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**Lovenox Injection 150 mg/mL Concentration** contains 15 mg enoxaparin sodium (approximate anti-Factor Xa activity of 1500 IU [with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard]) per 0.1 mL Water for Injection.

The Lovenox prefilled syringes, 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

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 to 8000 daltons       $\geq 68\%$

>8000 daltons                      ≤18%

[illegible]

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).

Following SC dosing, the apparent clearance (CL/F) of enoxaparin is approximately 15 mL/min. Apparent clearance and A<sub>max</sub> 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
<b>A<sub>max</sub></b> (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%	
<b>t<sub>max</sub>**</b> (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)
<b>AUC</b> (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**

<b>Indication</b>	<b>Dosing Regimen</b>	
	<b><u>Lovenox Inj.</u></b> 40 mg q.d. SC n (%)	<b><u>Heparin</u></b> 5000 U q8h SC n (%)
All Treated Abdominal Surgery Patients	555 (100)	560 (100)
Treatment Failures Total VTE <sup>1</sup> (%)	56 (10.1) (95% CI <sup>2</sup> : 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)

<sup>1</sup> VTE = Venous thromboembolic events which included DVT, PE, and death considered to be thromboembolic in origin.

<sup>2</sup> 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**

<b>Indication</b>	<b>Dosing Regimen</b>	
	<b><u>Lovenox Inj.</u></b> 40 mg q.d. SC n (%)	<b><u>Heparin</u></b> 5000 U q8h SC n (%)
All Treated Colorectal Surgery Patients	673 (100)	674 (100)
Treatment Failures Total VTE <sup>1</sup> (%)	48 (7.1) (95% CI <sup>2</sup> : 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)

<sup>1</sup> VTE = Venous thromboembolic events which included DVT, PE, and death considered to be thromboembolic in origin.

<sup>2</sup> 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**

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

<sup>1</sup> p value versus placebo = 0.0002

<sup>2</sup> 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**

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

<sup>1</sup> p value versus Lovenox 10 mg once a day = 0.0008

<sup>2</sup> 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**

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

<sup>1</sup> p value versus placebo = 0.0001

<sup>2</sup> CI = Confidence Interval

<sup>3</sup> p value versus placebo = 0.013

<sup>4</sup> 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**

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

<sup>1</sup> p value versus placebo = 0.008

<sup>2</sup> CI= Confidence Interval

<sup>3</sup> 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**

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

<sup>1</sup> Treatment failures during therapy, between Days 1 and 14.

<sup>2</sup> VTE = Venous thromboembolic events which included DVT, PE, and death considered to be thromboembolic in origin.

<sup>3</sup> CI = Confidence Interval

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

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



**Efficacy of Lovenox Injection in the Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction**

**(Combined Endpoint of Death, Myocardial Infarction, or Recurrent Angina)**

Indication	Dosing Regimen <sup>1</sup>		Reduction (%)	p Value
	<u>Lovenox Inj.</u> 1 mg/kg q12h SC n (%)	<u>Heparin</u> aPTT Adjusted i.v. Therapy n (%)		
All Treated Unstable Angina and Non-Q-Wave MI Patients	1578 (100)	1529 (100)		
Timepoint <sup>2</sup>				
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

<sup>1</sup> All patients were also treated with aspirin 100 to 325 mg per day.

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

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

**Efficacy of Lovenox Injection in the Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction**

**(Combined Endpoint of Death or Myocardial Infarction)**

Indication	Dosing Regimen <sup>1</sup>		Reduction (%)	p Value
	<u>Lovenox Inj.</u> 1 mg/kg q12h SC n (%)	<u>Heparin</u> aPTT Adjusted i.v. Therapy n (%)		
All Treated Unstable Angina and Non-Q-Wave MI Patients	1578 (100)	1529 (100)		
Timepoint <sup>2</sup>				
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

<sup>1</sup> All patients were also treated with aspirin 100 to 325 mg per day.

<sup>2</sup> 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**

	<b>Dosing Regimen<sup>1</sup></b>		
	<b>Lovenox Inj. 1.5 mg/kg q.d. SC</b>	<b>Lovenox Inj. 1 mg/kg q12h SC</b>	<b>Heparin aPTT Adjusted i.v. Therapy</b>
<b>Indication</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>
All Treated DVT Patients with or without PE	298 (100)	312 (100)	290 (100)
Patient Outcome			
Total VTE <sup>2</sup> (%)	13 (4.4) <sup>3</sup>	9 (2.9) <sup>3</sup>	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)

<sup>1</sup> All patients were also treated with warfarin sodium commencing within 72 hours of Lovenox Injection or standard heparin therapy.

<sup>2</sup> VTE = venous thromboembolic event (DVT and/or PE).

<sup>3</sup> The 95% Confidence Intervals for the treatment differences for total VTE were:

Lovenox Injection once a day versus heparin (-3.0 to 3.5)

Lovenox Injection every 12 hours versus heparin (-4.2 to 1.7).

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

of 5 days. Lovenox Injection was equivalent to standard heparin therapy in reducing the risk of recurrent venous thromboembolism. The efficacy data are provided below.

#### Efficacy of Lovenox Injection in Treatment of Deep Vein Thrombosis

Indication	Dosing Regimen <sup>1</sup>	
	<b>Lovenox Inj.</b> 1 mg/kg q12h SC  n (%)	<b>Heparin</b> aPTT Adjusted i.v. Therapy n (%)
All Treated DVT Patients	247 (100)	254 (100)
Patient Outcome		
Total VTE <sup>2</sup> (%)	13 (5.3) <sup>3</sup>	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)

<sup>1</sup> All patients were also treated with warfarin sodium commencing on the evening of the second day of Lovenox Injection or standard heparin therapy.

<sup>2</sup> VTE = venous thromboembolic event (deep vein thrombosis [DVT] and/or pulmonary embolism [PE]).

<sup>3</sup> 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<sup>3</sup> and 50,000/mm<sup>3</sup>) 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<sup>3</sup> 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<sup>3</sup>, Lovenox Injection should be discontinued. Cases of heparin-induced thrombocytopenia with thrombosis have also been observed in clinical practice. Some of these cases were complicated by organ infarction, limb ischemia, or death.

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

**Miscellaneous:** Lovenox multiple-dose vials contain benzyl alcohol as a preservative. The administration of medications containing benzyl alcohol as a preservative to premature neonates has been associated with a fatal "Gaspings 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.

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

**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<sup>2</sup>/day. The maximum human dose in clinical trials was 2.0 mg/kg/day or 78 mg/m<sup>2</sup>/day (for an average body weight of 70 kg, height of 170 cm, and body surface area of 1.8 m<sup>2</sup>).

**Pregnancy: Pregnancy Category B:**

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

*Fetal Risk Summary*

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

*Clinical Considerations*

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

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

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

*Data*

- Human Data-

There are no adequate and well-controlled studies in pregnant women.

A retrospective study reviewed the records of 604 women who used enoxaparin during pregnancy. A total of 624 pregnancies resulted in 693 live births. There were 72 hemorrhagic events (11 serious) in 63 women. There were 14 cases of neonatal hemorrhage. Major congenital anomalies in live births occurred at rates (2.5%) similar to background rates<sup>1</sup>

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

There have been postmarketing reports of fetal death when pregnant women received Lovenox Injection. Causality for these cases has not been determined. Insufficient data, the underlying disease, and the possibility of inadequate anticoagulation complicate the evaluation of these cases.

See **WARNINGS: Pregnant Women with Mechanical Prosthetic Heart Valves** for a clinical study of pregnant women with mechanical prosthetic heart valves.

- **Animal Data - Teratology** studies have been conducted in pregnant rats and rabbits at SC doses of enoxaparin up to 30 mg/kg/day or 211 mg/m<sup>2</sup>/day and 410 mg/m<sup>2</sup>/day, respectively. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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

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

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

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

## ADVERSE REACTIONS

**Hemorrhage:** The incidence of major hemorrhagic complications during Lovenox Injection treatment has been low.

The following rates of major bleeding events have been reported during clinical trials with Lovenox Injection.

### Major Bleeding Episodes Following Abdominal and Colorectal Surgery<sup>1</sup>

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

<sup>1</sup> Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease  $\geq 2$  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<sup>1</sup>

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

<sup>1</sup> Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease  $\geq 2$  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.

<sup>2</sup> Lovenox Injection 30 mg every 12 hours SC initiated 12 to 24 hours after surgery and continued for up to 14 days after surgery.

<sup>3</sup> 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.

<sup>4</sup> 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<sup>1</sup>

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

<sup>1</sup> Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, (2) if the hemorrhage caused a decrease in hemoglobin of  $\geq 2$  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.

<sup>2</sup> The rates represent major bleeding on study medication up to 24 hours after last dose.

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

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

<sup>1</sup> The rates represent major bleeding on study medication up to 12 hours after dose.

<sup>2</sup> Aspirin therapy was administered concurrently (100 to 325 mg per day).

<sup>3</sup> Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease by  $\geq 3$  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<sup>1</sup>

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

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

<sup>2</sup> 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<sup>1</sup> Undergoing Abdominal or Colorectal Surgery**

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

<sup>1</sup> Excluding unrelated adverse events.

**Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Patients<sup>1</sup> Undergoing Hip or Knee Replacement Surgery**

Adverse Event	Dosing Regimen									
	<u>Lovenox Inj.</u> 40 mg q.d. SC				<u>Lovenox Inj.</u> 30 mg q12h SC		<u>Heparin</u> 15,000 U/24h SC		<u>Placebo</u> q12h SC	
	Peri-operative Period n = 288 <sup>2</sup>		Extended Prophylaxis Period n = 131 <sup>3</sup>		n = 1080		n = 766		n = 115	
	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%

<sup>1</sup> Excluding unrelated adverse events.

<sup>2</sup> 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.

<sup>3</sup> 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  $\geq 2\%$  Incidence in Lovenox Injection Treated Medical Patients<sup>1</sup> With Severely Restricted Mobility During Acute Illness**

	Dosing Regimen	
	<u>Lovenox Inj.</u> 40 mg q.d. SC n = 360	<u>Placebo</u> q.d. SC n = 362
<b>Adverse Event</b>	<b>%</b>	<b>%</b>
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

<sup>1</sup> 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  $\leq 1\%$ .

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  $\geq 0.5\%$  Incidence in Lovenox Injection Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction**

	Dosing Regimen	
	<u>Lovenox Inj.</u> 1 mg/kg q12h SC  n = 1578 n (%)	<u>Heparin</u> aPTT Adjusted i.v. Therapy n = 1529 n (%)
<b>Adverse Event</b>		
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  $\geq 2\%$  Incidence in Lovenox Injection Treated Patients<sup>1</sup> Undergoing Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism**

	Dosing Regimen					
	<u>Lovenox Inj.</u> 1.5 mg/kg q.d. SC  n = 298		<u>Lovenox Inj.</u> 1 mg/kg q12h SC  n = 559		<u>Heparin</u> aPTT Adjusted i.v. Therapy n = 544	
	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%

<sup>1</sup> 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 / 3.0mL 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 ( $\pm 3$ ) 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.

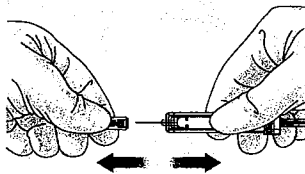
The use of a tuberculin syringe or equivalent is recommended when using Lovenox ampules or multiple-dose vials to assure withdrawal of the appropriate volume of drug.

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.

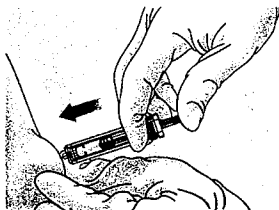
*Subcutaneous Injection Technique:* Patients should be lying down and Lovenox Injection administered by deep SC injection. To avoid the loss of drug when using the 30 and 40 mg prefilled syringes, do not expel the air bubble from the syringe before the injection. Administration should be alternated between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

Lovenox Injection prefilled syringes and graduated prefilled syringes are available with a system that shields the needle after injection.

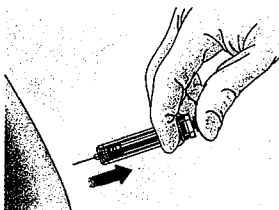
- Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.



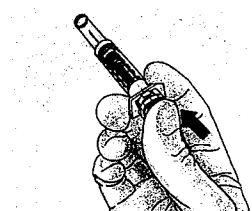
- Inject using standard technique, pushing the plunger to the bottom of the syringe.



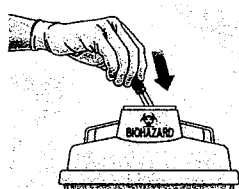
- Remove the syringe from the injection site keeping your finger on the plunger rod.



- Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible “click” will be heard to confirm shield activation.



- Immediately dispose of the syringe in the nearest sharps container.



#### NOTE:

- The safety system can only be activated once the syringe has been emptied.
- Activation of the safety system must be done only after removing the needle from the patient's skin.
- Do not replace the needle shield after injection.
- The safety system should not be sterilized.
- Activation of the safety system may cause minimal splatter of fluid. For optimal safety activate the system while orienting it downwards away from yourself and others.

#### 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 <sup>1</sup>	Anti-Xa Activity <sup>2</sup>	Package Size (per carton)	Label Color	NDC # 0075-
<b>Ampules</b>				
30 mg / 0.3 mL	3000 IU	10 ampules	Medium Blue	0624-03
<b>Prefilled Syringes<sup>3</sup></b>				
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
<b>Graduated Prefilled Syringes<sup>3</sup></b>				
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
<b>Multiple-Dose Vial<sup>4</sup></b>				
300 mg / 3.0 mL	30,000 IU	1 vial	Red	0626-03

<sup>1</sup> 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.

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

<sup>3</sup> Each **Lovenox Injection** syringe is affixed with a 27 gauge x 1/2 inch needle.

<sup>4</sup> Each **Lovenox** multiple-dose vial contains 15 mg / 1.0 mL of benzyl alcohol as a preservative.

### 150 mg/mL Concentration

Dosage Unit / Strength <sup>1</sup>	Anti-Xa Activity <sup>2</sup>	Package Size (per carton)	Syringe Label Color	NDC # 0075-
<b>Graduated Prefilled Syringes<sup>3</sup></b>				
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

<sup>1</sup> 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.

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

<sup>3</sup> 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 by:

Aventis Pharma Specialties

94700 Maisons-Alfort

France

And

Aventis Pharma

Boulevard Industriel



76580 Le Trait

France

Lovenox Injection ampules manufactured by:

Aventis Pharma LTD

Dagenham Essex RM10 7XS

United Kingdom

Lovenox multiple-dose vials manufactured by:

DSM Pharmaceuticals, Inc.

Greenville, NC 27835

Manufactured for:

Aventis Pharmaceuticals Inc.

Bridgewater, NJ 08807

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Rev. XXXX

# **CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**NDA 20-164/S-050**

**LABELING REVIEWS**

**Division of Gastrointestinal and Coagulation Drug Products  
(DGICDP)**

**REGULATORY PROJECT MANAGER LABELING REVIEW**

**Application Number:** NDA 20-164/SLR-050

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

**Sponsor:** Aventis Pharmaceuticals Inc.

**Materials Reviewed:** Package Insert (PI) dated October 25, 2002

**Submission Date:** October 25, 2002

**Receipt Date:** October 29, 2002

**Background and Summary**

**Background:** Lovenox, a low molecular weight heparin (LMWH), was approved March 29, 1993. It is currently approved for the following indications:

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

Aventis Pharmaceuticals, Inc. (Aventis) submitted SLR-040 on August 23, 2000 (received August 24, 2000) as a "Changes Being Effected" (CBE)-0 to add a new subsection to the **WARNINGS** section of the Package Insert (PI) entitled "Prosthetic Heart Valves," to add a new third paragraph to the **PRECAUTIONS** section, **Pregnancy** subsection, to describe two deaths in a study of pregnant women with prosthetic heart valves, and to add and wording to not recommend enoxaparin for use in pregnant women with prosthetic heart valves. DGICDP sent the sponsor an approvable letter on December 21, 2000.

On August 14, 2001, Aventis resubmitted S-040 (received August 15, 2001) with final printed labeling (FPL) and a draft Dear Health Care Professional (DHCP) letter. The supplement

(SLR-040) was approved January 9, 2002. On February 28, 2002, Aventis distributed the DHCP letter. Aventis submitted the DHCP letter to SLR-040, SLR-045 and SLR-046 and to the FDA Medical Watch on March 18, 2002 (received March 19, 2002).

On April 5, 2002, representatives from DGICDP and Aventis held a teleconference to discuss the Lovenox Pregnancy Labeling revisions and the February 28, 2002 DHCP letter. The sponsor agreed to submit another supplement providing for revised language in the **WARNINGS** and **PRECAUTIONS** sections of the PI.

On April 15, 2002, DGICDP consulted the Office of Drug Safety (ODS) for an updated overview of the safety data in the Adverse Events Reporting System (AERS) from June 2000 to present (see May 3, 2002, ODS Postmarketing Safety Review). The summary of the updated overview of safety noted that no new or significant adverse events were identified that are not currently listed in the enoxaparin product labeling with regard to both congenital anomalies and the other adverse events reported in pregnant women and their fetuses.

On April 5, 2002, DGICDP consulted the Pregnancy Labeling Team (PLT) regarding revisions to the Lovenox PI to add a new subsection to the **WARNINGS** section entitled "**Prosthetic Heart Valves**" and to revise the **PRECAUTIONS** section, **Pregnancy** subsection of the PI (see May 15, 2002 PLT review). The PLT review noted that women with a history of thromboembolic disease or artificial heart valves often require long term anticoagulant therapy and may experience a difficult pregnancy no matter what class of anticoagulant is used. Numerous reports in the literature tout the success and relative safety of low molecular weight heparins (LMWHs) for thromboprophylaxis, treatment of venous thromboembolic disease and various thrombophilias during pregnancy. The optimal dosage is not known, empiric dosage adjustments have not been widely employed nor established, and the frequency of monitoring remains controversial. They further noted that the Academy of Clinical Obstetricians and Gynecologists (ACOG) issued a committee opinion on the use of LMWH during pregnancy that states that LMWHs do not cross the placenta and have no teratogenic effects, patients can receive these drugs with little or no laboratory monitoring, and that there is inadequate information to recommend the use of LMWH for anticoagulation in the case of a pregnant woman with a mechanical heart valve. Lastly, the PLT recommended that more clinically meaningful information from literature to aid clinicians and patients in making decisions regarding drug use during pregnancy be available. Information in the label could include placental transport data, description of inherent risks of not treating disease in pregnant women, dosing recommendations or adjustments necessary during pregnancy, unique maternal and fetal adverse reactions and discussion of therapeutic alternatives.

DGICDP consulted the Division of Reproductive and Urologic Drug Products (DRUDP) on May 15, 2002 (see Memoranda from DRUDP dated June 7, 2002). In the June 7, 2002, memoranda, DRUPD recommended deletion of the newly inserted paragraph in the **PRECAUTIONS** section **Pregnancy** subsection of the Lovenox label. That paragraph read "**Teratogenic effects.** 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 have not been established nor has the incidence been shown to be higher than in the general population.” The recommendation is based upon the lack of creditable supportable data and the absence of animal/or human data that supports this paragraph. Long term use (greater than 15 years of postmarketing surveillance) does not support a plausible teratogenic effect.

On October 25, 2002, (received October 29, 2002) Aventis submitted a new labeling supplement (SLR-050) in response to the agreement made in the April 5, 2002, teleconference between representatives of DGICDP and Aventis to modify the current Lovenox United States Prescribing Information with respect to the **WARNINGS** and **PRECAUTIONS** sections dealing with “mechanical prosthetic heart valves.”

On November 20, 2002, DGICDP consulted the PLT regarding the revised proposed labeling for Lovenox in SLR-050 in patients with prosthetic valves and pregnant women (see January 9, 2003 PLT review).

DGICDP also consulted DRUDP regarding the revised proposed labeling for Lovenox in SLR-050 in patients with prosthetic valves and pregnant women (see DRUDP review dated February 10, 2003). In the DRUDP review, DRUDP agreed with the recommendations presented by Dr. Uhl of the PLT in the January 9, 2003, PLT review.

A meeting was held between DGICDP, the PLT and DRUDP on February 7, 2003. The information presented by the sponsor and current medical practices were discussed regarding the use of LMWH in pregnant women with mechanical prosthetic heart valves. In the cases referenced in the **WARNINGS** section of the Lovenox labeling, a case was made that the women who died in the clinical study may not have been adequately anticoagulated and that pregnant women may need more frequent monitoring. DGICDP agreed to propose further labeling revisions to be circulated to the PLT for comment. (See February 7, 2003, meeting minutes).

## **Review**

### **PACKAGE INSERT**

The PI submitted on October 25, 2002, received October 29, 2002, (no identifier) was compared to the PI from Supplement SCM-043 (submitted September 20, 2002, received September 23, 2002), approved on draft January 23, 2003 (no identifier). The PIs were identical except for the following:

#### **I. DESCRIPTION section**

The sponsor has not included the following revisions to the **DESCRIPTION** section of the PI that were made in S-043, submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003:

- A. The sponsor has not added the term “aqueous” following the term, “sterile” in the first paragraph, first sentence that reads “Lovenox Injection is a sterile, aqueous solution containing enoxaparin sodium, a low molecular weight heparin.” as revised in the approved labeling to S-043.
- B. In the second paragraph, first sentence that reads, “Lovenox Injection is available in two concentrations: **1. 100mg per mL of Water for Injection,**” the sponsor has not deleted the phrase, “of Water for Injection” so that the sentence reads “Lovenox Injection is available in two concentrations: **1. 100 mg per mL**” as revised in the PI labeling to S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003.
- C. In the second paragraph, the sixth line, the sponsor has not added “*Multiple-Dose Vials* 300 mg/3.0 mL” to the list of available syringes and ampules as revised in the PI labeling to S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003.
- D. In the fourth paragraph, first line that reads, “**2. 150 mg per mL of Water for Injection,**” the sponsor has not deleted the phrase “**of Water for Injection.**” as revised in the PI labeling for S-043.
- E. In the fifth paragraph, first sentence that begins, “The Lovenox prefilled syringes . . .” the sponsor has not deleted the term “solutions” and has not added 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.” as revised in the PI labeling in S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2002.
- F. The sponsor has not added the second sentence in the sixth paragraph that reads, “The multiple-dose vial contains 15 mg/1.0 mL benzyl alcohol as a preservative.” that was added in the PI to S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003.
- G. In the sixth paragraph, the sponsor has not deleted the fifth sentence that reads, “Nitrogen is used in the headspace to inhibit oxidation.” that was deleted in the PI to S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003.
- H. In the sixth paragraph, the sixth sentence that begins, “Enoxaparin is obtained by . . .,” the sponsor has not 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.” as was added in the PI to S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003.

- I. In the sixth paragraph, the seventh sentence that begins, "The drug is the sodium . . ." The term "drug" has not been added before the term "substance" so that the sentence reads, "The drug substance is the sodium salt." as in the PI to S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003.

**The above revisions (A-I) were made to the PI in SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003. The revisions should be included in the PI of SLR-050 which is the subject of this review.**

II. **CONTRAINDICATIONS** section

In the second paragraph, first sentence that begins, "Patients with known hypersensitivity . . ." the sponsor has not added 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." as revised in the PI to S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003.

**The addition of the phrase "or any of its constituents" in the second paragraph, first sentence was made in SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003. The addition should be included in the PI of SLR-050.**

III. **WARNINGS** section:

- A. The ninth paragraph in this section of the approved PI to S-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003 was entitled "**Prosthetic Heart Valves.**" The paragraph read as follows:

"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**)."

The sponsor has deleted the above paragraph and proposes to insert a new paragraph entitled "**Pregnant Women with Mechanical Prosthetic Heart Valves.**" The sponsor's proposed paragraph reads as follows:

"The use of Lovenox Injection for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied. In a clinical

study of pregnant women with mechanical prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and fetal death.

[

]

The PLT proposes the following revisions to the proposed paragraph in the January 9, 2003 consult review:

**“Pregnant Women with Mechanical Prosthetic Heart Valves:** The use of Lovenox Injection for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied. In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. There have also been isolated postmarketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. ~~Pregnant w~~Women with mechanical prosthetic heart valves may be at higher risk for thromboembolism during pregnancy, and when pregnant have a higher rate of fetal loss from still birth, spontaneous abortion and premature delivery. (see **PRECAUTIONS: Mechanical Prosthetic Heart Valves**).”

**The Medical Officer should comment on this section.**

- B. The sponsor has not added the **Miscellaneous** subsection following the **Prosthetic Heart Valves** subsection in the **WARNINGS** section that was added to the PI in SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003. 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**).”

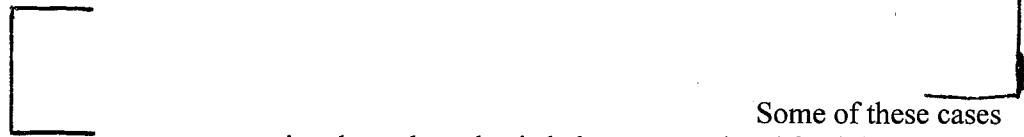
**The addition of the Miscellaneous subsection following the Prosthetic Heart Valves subsection of the WARNINGS section of the PI was made in SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003. The addition should be included in the PI of SLR-050.**



#### IV. PRECAUTIONS section

- A. The sponsor has proposed a new subsection entitled “**Mechanical Prosthetic Heart Valves**” following the **General** subsection. The sponsor proposes to include the following paragraph for the **Mechanical Prosthetic Heart Valves** subsection:

“The use of Lovenox Injection has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves. Isolated



Some of these cases were pregnant women in whom thrombosis led to maternal and fetal deaths. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism (see **WARNINGS, Pregnant Women with Mechanical Prosthetic Heart Valves**).”

The PLT proposes the following revisions to the proposed paragraph in the January 9, 2003 consult review:

“**Mechanical Prosthetic Heart Valves:** The use of Lovenox Injection has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves. Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received enoxaparin for thromboprophylaxis. \_\_\_\_\_ underlying disease and insufficient clinical data, ——— the evaluation of these cases. Some of these cases were pregnant women in whom thrombosis led to maternal and fetal deaths. ~~Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism~~ (see **WARNINGS, Pregnant Women with Mechanical Prosthetic Heart Valves**).”

**The Medical Officer should comment on this section.**

- B. In the **Pregnancy** subsection, *Non-teratogenic Effects* subsection:

1. The sponsor has deleted the second paragraph that reads as follows:

“In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 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**)."

The proposed paragraph in the ninth paragraph of the **WARNINGS** section (see item III. A. above) was a revision of this paragraph. The sponsor proposed to relocate the information in this paragraph to the **WARNINGS** section. The Medical Officer should comment on the deletion of the paragraph from the pregnancy, *Non-teratogenic Effects* subsection.

2. The sponsor has added a new second paragraph that reads as follows:

"(See also **WARNINGS, Pregnant Women with Mechanical Prosthetic heart Valves** and **PRECAUTIONS, Mechanical Prosthetic Heart Valves**)."

The Medical Officer should review the proposed sentence.

3. The sponsor has not included the third paragraph that was added to the PI in SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003. The Paragraph reads as follows:

"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**)."

The addition of this paragraph was made in SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003. The paragraph should be included in the PI of SLR-050.

4. The PLT proposes the following revisions to the Pregnancy subsection of the PI in the January 9, 2003 consult review:

**"Pregnancy: *Teratogenic effects*:** Pregnancy Category B:  
All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes Lovenox's potential to increase the risk of developmental abnormalities above background risk.

*Fetal Risk Summary*

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

*Clinical Considerations*

Pregnancy alone confers an increased risk for thromboembolism, that is even higher for women with \_\_\_\_\_ thromboembolic disease, certain high risk pregnancy

conditions. . While not  
adequately studied, pregnant women with mechanical prosthetic heart valves (see

**WARNINGS: Pregnant Women with Mechanical Prosthetic Heart Valves and  
PRECAUTIONS: Mechanical Prosthetic Heart Valves).**

Pregnant women with thromboembolic disease including prosthetic heart valves, and  
patients with inherited or acquired thrombophilias also have an increased risk of other  
maternal complications and fetal loss regardless of the type of anticoagulant used.

All patients receiving anti-coagulants such as enoxaparin, including pregnant women,  
are at risk for bleeding. Pregnant women receiving enoxaparin should be carefully  
monitored for evidence of bleeding or excessive anticoagulation.

Hemorrhage can occur at any site  
and may lead to death of mother and/or fetus. Pregnant women should be apprised of  
the potential hazard to the fetus and the mother if enoxaparin is administered during  
pregnancy.

Data

• Human Data-

There are no adequate and well-controlled studies in pregnant women.

A retrospective study 604 women who used enoxaparin during  
pregnancy. 624 pregnancies resulted in 693 live births. There were 72  
hemorrhagic events in 63 women, 11 of which were serious. There were 14 cases  
of neonatal hemorrhage. Major congenital anomalies in live births occurred at  
rates (2.5%) similar to background rates.

There have been postmarketing reports of fetal death when pregnant women  
received Lovenox Injection. Causality for these cases has not been determined.

- Animal Data – Teratology studies have been conducted in pregnant rats and rabbits at SC doses of enoxaparin up to 30 mg/kg/day or 211 mg/m<sup>2</sup>/day and 410 mg/m<sup>2</sup>/day, respectively. There was not evidence of teratogenic effects or fetotoxicity due to enoxaparin. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

~~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<sup>2</sup>/day and 410 mg/m<sup>2</sup>/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.~~

[ ]  
The Medical Officer should comment on the proposed revisions.

#### V. DOSAGE AND ADMINISTRATION section

- A. In the third paragraph, first sentence that begins, “**1. 100 mg/mL Concentration:** 30 mg/0.3 mL ampules, . . .” the sponsor has not added the “300 mg/3.0 mL multiple-dose vials” at the end of the first item. Item 1. should read as follows:

“**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.”

The addition of the phrase “300 mg/3.0 mL multiple-dose vials” in the DOSAGE AND ADMINISTRATION section were made in SCM-043 submitted

**September 20, 2002 (received September 23, 2002) and approved January 23, 2003. The additions should be included in the PI of SLR-050.**

- B. In the **Adult Dosage, Administration** subsection, in the paragraph that begins, "Lovenox Injection is a clear, colorless . . ." the sponsor has not revised 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."

To:

"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 revision of the second sentence in the DOSAGE AND ADMINISTRATION section, Adult Dosage, Administration subsection was made in SCM-043 submitted September 20, 2002 (received September 13, 2002) and approved January 23, 2003. The revision should be included in the PI of SLR-050.**

#### VI. **HOW SUPPLIED** section

- A. The sponsor has not included the following revisions that were made in SCM-043, submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003:

1. In the first line, the sponsor has not included the revision made to the established name to revise "**Lovenox<sup>®</sup> (enoxaparin sodium) Injection**" to "**Lovenox<sup>®</sup> (enoxaparin sodium injection)**".
2. In the table entitled, "100 mg/mL Concentration":
  - a. In the fourth column, first row, the sponsor has not deleted the term "syringe."
  - b. In the first column, fifth row, the sponsor has not added the title, "**Multiple-Dose Vial. 300 mg/3.0 mL.**"
  - c. In the second column, fifth row, the sponsor has not added "30,000 IU."
  - d. In the third column, fifth row, the sponsor has not added "1 vial."
  - e. In the fourth column, fifth row, the sponsor has not added the term "Red."
  - f. In the fifth column, fifth row, the sponsor has not added "0626-03."

3. In the second sentence of the first footnote, the sponsor has not added the word "and" after "80" so that the sentence reads, "**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.**"
4. In the footnotes to the table entitled, "100 mg/mL Concentration" the sponsor has not added the footnote that reads, "<sup>4</sup> Each Lovenox multiple-dose vial contains 15 mg/1.0 mL of benzyl alcohol as a preservative."
5. In the first paragraph after the table entitled, "150 mg/mL Concentration," the sponsor has not revised 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]."
6. In the first paragraph after the table entitled, "150 mg/mL Concentration," the sponsor did not add the fifth sentence that reads, "Lovenox multiple-dose vial manufactured for Aventis Pharmaceuticals Products Inc. by DSM Pharmaceuticals, Inc. Greenville, NC 27835."
7. The sponsor has not added the line that reads, "©2002 Aventis Pharmaceuticals, Inc."

**The above revisions (VI A1.-7.) were made in SCM-043 submitted September 20, 2002 (received September 23, 2002) and approved January 23, 2003. The revisions should be included in the PI of SLR-050.**

- B. In the table entitled, "100 mg/mL Concentration," the sponsor has added additional lines between the rows to separate the 30 mg/0.3 mL Prefilled Syringes from the 40 mg/0.4 mL Prefilled Syringes and the 60 mg/0.6 mL, 80 mg/0.8 mL and 100 mg/1 mL Graduated Prefilled Syringes

**This reformatting makes the table clearer. The revisions are editorial and acceptable.**

### **Conclusions**

1. The following item is editorial and is acceptable: VI. B.
2. Items III. A., IV. A., IV. B. 1.- 2. and IV.B.4. should be reviewed by the Medical Officer.

3. Items I., II., III. B., IV. B. 3., V., VI. A. 1.-7., that were approved in SCM-043, submitted September 20, 2002, received September 23, 2002 and approved January 23, 2003 should be incorporated into the PI.
4. Labeling Supplement 050 is approvable pending review of the labeling by the Medical Officer and revisions requested in #3 above.

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Diane Moore, B.S.  
Regulatory Health Project Manager

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Julieann DuBeau, MSN, RN  
Chief, Project Management Staff

Cc:

Archival NDA 20-164/S-050  
HFD-180/Div. Files  
HFD-180/D.Moore  
HFD-180/R.He/K.Robie-Suh/S.Doddapaneni  
HFD-180/RJustice/J.Korvick  
Drafted by: dm/3/12/03  
Initialed by: J.Dubeau 3.25.03  
Final: March 25, 2003  
Filename:N20164S43LblrevCycle3Final.doc  
**RPM LABELING REVIEW**

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/s/

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Diane V. Moore  
3/25/03 11:42:24 AM  
CSO

Julieann DuBeau  
3/25/03 11:48:15 AM  
CSO



**Division of Gastrointestinal and Coagulation Drug Products  
(DGICDP)**

**REGULATORY PROJECT MANAGER LABELING REVIEW**

**Application Number:** NDA 20-164/SLR-050

**Name of Drug:** Lovenox<sup>®</sup> (enoxaparin sodium) Injection

**Sponsor:** Aventis Pharmaceuticals Inc.

**Materials Reviewed:** Package Insert (PI) dated May 9, 2003

**Submission Date:** May 9, 2003

**Receipt Date:** May 12, 2003

**Background and Summary**

**Background:** Lovenox, a low molecular weight heparin (LMWH), was approved March 29, 1993. It is currently approved for the following indications:

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

Aventis Pharmaceuticals, Inc. (Aventis) submitted SLR-040 on August 23, 2000 (received August 24, 2000) as a "Changes Being Effected" (CBE)-0 to add a new subsection to the **WARNINGS** section of the Package Insert (PI) entitled "Prosthetic Heart Valves," to add a new third paragraph to the **PRECAUTIONS** section, **Pregnancy** subsection, to describe two deaths in a study of pregnant women with prosthetic heart valves, and to add wording to not recommend enoxaparin for use in pregnant women with prosthetic heart valves. DGICDP sent the sponsor an approvable letter on December 21, 2000.

On August 14, 2001, Aventis resubmitted S-040 (received August 15, 2001) with final printed labeling (FPL) and a draft Dear Health Care Professional (DHCP) letter. The supplement

(SLR-040) was approved January 9, 2002. On February 28, 2002, Aventis distributed the DHCP letter. Aventis submitted the DHCP letter to SLR-040, SLR-045 and SLR-046 and to the FDA Medical Watch on March 18, 2002 (received March 19, 2002).

On April 5, 2002, representatives from DGICDP and Aventis held a teleconference to discuss the Lovenox Pregnancy Labeling revisions and the February 28, 2002 DHCP letter. The sponsor agreed to submit another supplement providing for revised language in the **WARNINGS** and **PRECAUTIONS** sections of the PI.

On April 15, 2002, DGICDP consulted the Office of Drug Safety (ODS) for an updated overview of the safety data in the Adverse Events Reporting System (AERS) from June 2000 to April 2002 (see May 3, 2002, ODS Postmarketing Safety Review). The summary of the updated overview of safety noted that no new or significant adverse events were identified that are not currently listed in the enoxaparin product labeling with regard to both congenital anomalies and the other adverse events reported in pregnant women and their fetuses.

On April 5, 2002, DGICDP consulted the Pregnancy Labeling Team (PLT) regarding revisions to the Lovenox PI to add a new subsection to the **WARNINGS** section entitled "**Prosthetic Heart Valves**" and to revise the **PRECAUTIONS** section, **Pregnancy** subsection of the PI (see May 15, 2002 PLT review). The PLT review noted that women with a history of thromboembolic disease or artificial heart valves often require long term anticoagulant therapy and may experience a difficult pregnancy no matter what class of anticoagulant is used. Numerous reports in the literature tout the success and relative safety of low molecular weight heparins (LMWHs) for thromboprophylaxis, treatment of venous thromboembolic disease and various thrombophilias during pregnancy. The optimal dosage is not known, empiric dosage adjustments have not been widely employed nor established, and the frequency of monitoring remains controversial. They further noted that the Academy of Clinical Obstetricians and Gynecologists (ACOG) issued a committee opinion on the use of LMWH during pregnancy that states that LMWHs do not cross the placenta and have no teratogenic effects, patients can receive these drugs with little or no laboratory monitoring, and that there is inadequate information to recommend the use of LMWH for anticoagulation in the case of a pregnant woman with a mechanical heart valve. Lastly, the PLT recommended that more clinically meaningful information from literature to aid clinicians and patients in making decisions regarding drug use during pregnancy be available. Information in the label could include placental transport data, description of inherent risks of not treating disease in pregnant women, dosing recommendations or adjustments necessary during pregnancy, unique maternal and fetal adverse reactions and discussion of therapeutic alternatives.

DGICDP consulted the Division of Reproductive and Urologic Drug Products (DRUDP) on May 15, 2002 (see Memoranda from DRUDP dated June 7, 2002). In the June 7, 2002, memoranda, DRUPD recommended deletion of the newly inserted paragraph in the **PRECAUTIONS** section **Pregnancy** subsection of the Lovenox label. That paragraph read "**Teratogenic effects.** 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 have not been established nor has the incidence been shown to be higher than in the general population.” The recommendation is based upon the lack of creditable supportable data and the absence of animal or human data that supports this paragraph. Long term use (greater than 15 years of postmarketing surveillance) does not support a plausible teratogenic effect.

On October 25, 2002, (received October 29, 2002) Aventis submitted a new labeling supplement (SLR-050) in response to the agreement made in the April 5, 2002, teleconference between representatives of DGICDP and Aventis to modify the current Lovenox United States Prescribing Information with respect to the **WARNINGS** and **PRECAUTIONS** sections dealing with “mechanical prosthetic heart valves.”

On November 20, 2002, DGICDP consulted the PLT regarding the revised proposed labeling for Lovenox in SLR-050 in patients with prosthetic valves and pregnant women (see January 9, 2003 PLT review).

DGICDP also consulted DRUDP regarding the revised proposed labeling for Lovenox in SLR-050 in patients with prosthetic valves and pregnant women (see DRUDP review dated February 10, 2003). In the DRUDP review, DRUDP agreed with the recommendations presented by Dr. Uhl of the PLT in the January 9, 2003, PLT review.

A meeting was held between DGICDP, the PLT and DRUDP on February 7, 2003. The information presented by the sponsor and current medical practices were discussed regarding the use of LMWH in pregnant women with mechanical prosthetic heart valves. In the cases referenced in the **WARNINGS** section of the Lovenox labeling, a case was made that the women who died in the clinical study may not have been adequately anticoagulated and that pregnant women may need more frequent monitoring. DGICDP agreed to propose further labeling revisions to be circulated to the PLT for comment. (See February 7, 2003, meeting minutes).

An approvable action was taken on April 23, 2003. The sponsor was requested to revise the **WARNINGS** section of the PI, including the **Pregnant Women with Mechanical Prosthetic Heart Valves** subsection, the **Miscellaneous** subsection, the **PRECAUTIONS** section, including the **Mechanical Prosthetic Heart Valves** subsection, and the **Pregnancy** subsection of the PI. The sponsor submitted revised labeling in an amendment on May 9, 2003 (received May 12, 2003) which was a complete response to the approvable action and began review cycle two.

## Review

### PACKAGE INSERT

The PI submitted on May 9, 2003, received May 12, 2003, (no identifier) was compared to the PI from Supplement SCM-043 (submitted September 20, 2002, received

September 23, 2002), approved on draft January 23, 2003 (no identifier). The PIs were identical except for the following:

I. **WARNINGS** section:

- A. The ninth paragraph in this section of the approved PI to S-043 (submitted September 20, 2002; received September 23, 2002; approved January 23, 2003) was entitled "**Prosthetic Heart Valves.**" The paragraph read as follows:

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

In the October 25, 2002, submission to S-050 (received October 29, 2002) the sponsor proposed to delete the above paragraph and insert a new paragraph entitled "**Pregnant Women with Mechanical Prosthetic Heart Valves.**" The sponsor's proposed paragraph read as follows:

"The use of Lovenox Injection for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied. In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and fetal death.

[

]

The Agency proposed the following revisions to the proposed paragraph in the April 23, 2003, approvable letter to the sponsor for S-050. (Note: Agency additions are denoted with underlined text and deletions are denoted with ~~striketrough~~ text).

**"Pregnant Women with Mechanical Prosthetic Heart Valves:** The use of Lovenox Injection ~~is not recommended~~ for thromboprophylaxis in ~~patients~~ pregnant women with mechanical prosthetic heart valves ~~has not been adequately studied.~~ In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. These deaths may have been due to therapeutic failure or

inadequate anticoagulation. No patients in the heparin/warfarin group died. There also have been isolated postmarketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. 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 Women with mechanical prosthetic heart valves may be at higher risk for thromboembolism during pregnancy, and, when pregnant, have a higher rate of fetal loss from still birth, spontaneous abortion and premature delivery. Therefore, frequent monitoring of peak and trough anti-Factor Xa levels, and adjusting of dosage may be needed. (see PRECAUTIONS: Pregnancy).

On May 9, 2003, the sponsor proposed the following paragraph in response to the April 23, 2003, Agency letter:

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

The sponsor has incorporated the proposed revisions from the April 23, 2003, Agency letter into the WARNINGS section of the Lovenox PI and added the phrase “Although a causal relationship has not been established, these . . .” and added the number of patients in the heparin/warfarin group in the cited clinical study. The disclaimer sentence and the addition of the number of women in the clinical trial in the heparin/warfarin group is acceptable per the Medical Officer, Dr. Ruyi He in verbal comment to Ms. Diane Moore, RPM on May 22, 2003.

In the sixth sentence that begins, “Women with mechanical prosthetic . . .” the words “still birth” should be presented as one word “stillbirth.” This should be corrected at the next printing.


B. **Miscellaneous** subsection:

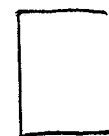
In the third sentence that begins "Because benzyl alcohol may cross . . ." the sponsor has added the word "and" before the word "only" so that the sentence reads "Because benzyl alcohol may cross the placenta, Lovenox multiple-dose vials, preserved with benzyl alcohol, should be used with caution in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

The addition of the word "and" was requested in the Agency Approvable letter dated April 23, 2003 for S-050. The addition is editorial and acceptable.

II. **PRECAUTIONS** section


- A. In the October 25, 2002, submission to S-050 (received October 29, 2002; no identifier) the sponsor proposed to add the following new subsection entitled "**Mechanical Prosthetic Heart Valves**" following the **General** subsection:


"The use of Lovenox Injection has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves. 



Some of these cases were pregnant women in whom thrombosis led to maternal and fetal deaths. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism (see **WARNINGS, Pregnant Women with Mechanical Prosthetic Heart Valves**)."

The Agency proposed the following paragraph for the **Mechanical Prosthetic Heart Valves** subsection in the April 23, 2003, Approvable letter to S-050 (additions are denoted with underlined text and deletions are denoted with ~~striketrough~~ text):

**"Mechanical Prosthetic Heart Valves:** The use of Lovenox Injection has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves and has not been adequately studied for long-term use. Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received enoxaparin for thromboprophylaxis. 

 Some of these cases were pregnant women in whom thrombosis led to maternal and fetal deaths. The evaluation of these cases is complicated by insufficient data, the underlying disease and the possibility of inadequate anticoagulation. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism

(see **WARNINGS, Pregnant Women with Mechanical Prosthetic Heart Valves**)."

The sponsor proposed the following revised wording for the **Mechanical Prosthetic Heart Valves** paragraph in the May 9, 2003 submission (received May 12, 2003; no identifier); (additions are denoted with underlined text and deletions are denoted with ~~strikethrough~~ text):

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

The proposed labeling revisions are in accordance with the labeling requested in the Agency April 23, 2003, Approvable letter to S-050. The sponsor's proposed revisions to the wording in the April 23, 2003, Agency letter are editorial and acceptable.

B. In the **Pregnancy** subsection, *Non-teratogenic Effects* subsection:

1. In the October 25, 2002, submission (received October 26, 2002) the sponsor proposed to delete the second paragraph that read as follows:

"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**)."

The deletion of this paragraph was included in the proposed **PRECAUTIONS** section of the PI in the Agency April 23, 2003, Approvable letter to S-050. The deletion is acceptable.

2. Following the above paragraph, in the October 25, 2002, submission to S-050 (received October 26, 2002; no identifier), the sponsor had added a new sentence that reads as follows:

**“(See also WARNINGS, Pregnant Women with Mechanical Prosthetic heart Valves and PRECAUTIONS, Mechanical Prosthetic Heart Valves.)”**

The sentence **“(See WARNINGS, Pregnant Women with Mechanical Prosthetic heart Valves and PRECAUTIONS, Mechanical Prosthetic Heart Valves.)”** was moved to a new subsection titled **“Clinical Considerations”** in the May 9, 2003 submission (received May 12, 2003; no identifier). (Note: the word **“also”** was deleted from the sentence). The sentence is acceptable (see comment II.B.3. below).

3. The Agency requested the sponsor to make the following revisions to the Pregnancy section of the PI in the April 23, 2003, Approvable letter to S-050 (additions are noted with underlined text and deletions are noted with ~~strikethrough~~ text):

**“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<sup>2</sup>/day and 410 mg/m<sup>2</sup>/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.~~

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



~~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**).~~

See **WARNINGS: Pregnant Women with Mechanical Prosthetic Heart Valves** for a clinical study of pregnant women with mechanical prosthetic heart valves.

- Animal Data – Teratology studies have been conducted in pregnant rats and rabbits at SC doses of enoxaparin up to 30 mg/kg/day or 211 mg/m<sup>2</sup>/day and 410 mg/m<sup>2</sup>/day, respectively. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.”

In the May 9, 2003, submission (received on May 12, 2003), the sponsor proposed the following revisions to the above Agency proposed labeling for the **Pregnancy** subsection of the PI. Additions are noted with underlined text and deletions are noted with ~~strikethrough~~ text:

a. **Pregnancy:** Pregnancy Category B:

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

*Fetal Risk Summary*

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

*Clinical Considerations* subsection

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

Pregnancy alone confers an increased risk for thromboembolism, that is even higher for women with thromboembolic disease and certain high risk pregnancy conditions. While not adequately studied, pregnant women with mechanical

prosthetic heart valves may be at even higher risk for thrombosis. ~~It is not known if dose adjustment or monitoring of Anti-Xa activity of enoxaparin are necessary during pregnancy~~ (see **WARNINGS: Pregnant Women with Mechanical Prosthetic Heart Valves** and **PRECAUTIONS: Mechanical Prosthetic Heart Valves**).

Pregnant women with thromboembolic disease, including those with mechanical prosthetic heart valves, and those with inherited or acquired thrombophilias, also have an increased risk of other maternal complications and fetal loss regardless of the type of anticoagulant used.

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

~~Consideration for use of a shorter acting agent should be specifically addressed as delivery approaches.~~

#### *Data*

- Human Data-

There are no adequate and well-controlled studies in pregnant women.

A retrospective study ~~reviewed the records of~~ 604 women who used enoxaparin during pregnancy. A total of 624 pregnancies resulted in 693 live births. There were 72 hemorrhagic events (11 serious) in 63 women. There were 14 cases of neonatal hemorrhage. Major congenital anomalies in live births occurred at rates (2.5%) similar to background rates<sup>1</sup>.

There have been postmarketing reports of fetal death when pregnant women received Lovenox Injection. Causality for these cases has not been determined. ~~The evaluation of these cases is complicated by insufficient~~ Insufficient data, the underlying disease, and the possibility of inadequate anticoagulation complicate the evaluation of these cases.

~~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).~~

See WARNINGS: Pregnant Women with Mechanical Prosthetic Heart Valves for a clinical study of pregnant women with mechanical prosthetic heart valves.

- Animal Data – Teratology studies have been conducted in pregnant rats and rabbits at SC doses of enoxaparin up to 30 mg/kg/day or 211 mg/m<sup>2</sup>/day and 410 mg/m<sup>2</sup>/day, respectively. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.”

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

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**The above revisions are editorial and acceptable.**

### III. DOSAGE AND ADMINISTRATION section

- A. In the third paragraph, first sentence that reads “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.” the sponsor has added a redundant period at the end of the sentence.

**The second period should be deleted at the next printing.**

- B. *Subcutaneous Injection Technique* sub-subsection, of the **Administration** subsection

1. In the first paragraph, the sponsor has deleted the sixth and seventh sentences that read as follows:

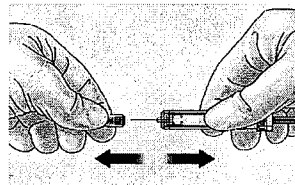
“ An automatic injector, Lovenox EasyInjector™, is available for patients to administer Lovenox Injection packaged in 30 mg and 40 mg prefilled syringes. Please see directions accompanying the Lovenox EasyInjector™ automatic injection device.”

**Since the sponsor is discontinuing the EasyInjector™ product, the deletion of these two sentences is acceptable.**

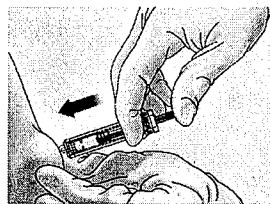
2. In the first paragraph, following the fifth sentence that begins “To minimize bruising, . . .” the sponsor has added the following section to describe the use of the needle safety system to shield needle after injection (based on manufacturer’s device labeling):

“Lovenox Injection prefilled syringes and graduated prefilled syringes are available with a system that shields the needle after injection.

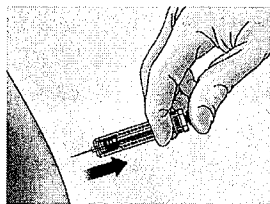
- Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.



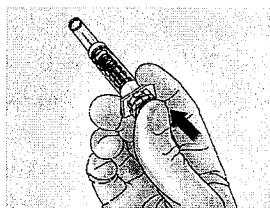
- Inject using standard technique, pushing the plunger to the bottom of the syringe.



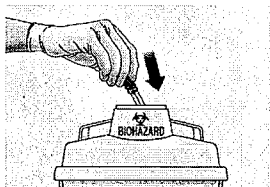
- Remove the syringe from the injection site keeping your finger on the plunger rod.



- Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible “click” will be heard to confirm shield activation.



- Immediately dispose of the syringe in the nearest sharps container.



**NOTE:**

- The safety system can only be activated once the syringe has been emptied.
- Activation of the safety system must be done only after removing the needle from the patient's skin.
- Do not replace the needle shield after injection.
- The safety system should not be sterilized.
- Activation of the safety system may cause minimal splatter of fluid. For optimal safety activate the system while orienting it downwards away from yourself and others."

**This addition was proposed in a "Changes Being Effected" (CBE) Supplement (S-051) submitted December 19, 2002 (received December 20, 2002). The addition is acceptable per Dr. Ruyi He, Medical Officer, in a verbal comment to Diane Moore, RPM on April 18, 2003 (see RPM review to S-051 dated June 19, 2003).**

**IV. HOW SUPPLIED section**

- A. In the table entitled, "100 mg/mL Concentration," the sponsor has added additional lines between the rows to separate the 30 mg/0.3 mL Prefilled Syringes row from the 40 mg/0.4 mL Prefilled Syringe row; and to separate the 60 mg/0.6 mL, 80 mg/0.8 mL and 100 mg/1 mL Graduated Prefilled Syringes rows.

**This reformatting makes the table clearer. The revisions are editorial and acceptable.**

- B. The sponsor revised the section following the table entitled "100 mg/mL Concentration" from:

"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

© 2002 Aventis Pharmaceuticals Inc.  
Prescribing information as of XXXX”

to

“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 by:  
Aventis Pharma Specialties  
94700 Maisons-Alfort  
France.

And

Aventis Pharma  
Boulevard Industriel  
76580 Le Trait  
France

Lovenox Injection ampules manufactured in England by:

Aventis Pharma LTD  
Dagenham Essex RM107XS  
United Kingdom

Lovenox multiple-dose vials manufactured for Aventis Pharmaceuticals Products Inc.  
by DSM Pharmaceuticals, Inc.  
Greenville, NC 27835.

**Aventis Pharmaceuticals Products Inc.**  
BRIDGEWATER, NJ 08807

Manufactured for:

Aventis Pharmaceuticals Inc.  
Bridgewater, NJ 08807

© 2002 Aventis Pharmaceuticals Inc.  
Prescribing information as of XXXX”  
Rev. January 2003 XXXX”

**The revisions update the manufacturing information for the Lovenox products.**  
**The revisions are editorial and acceptable.**

### **Conclusions**

1. The following items are acceptable: II.B.1., II.B.2. and III.B.1.
2. The following items are editorial and acceptable Items: I.B., II.A., II.B.3., IV.A. and IV.B.
3. The following items are acceptable per the Medical Officer: I.A. and III.B.2. The minor editorial revision noted in I.A. should be corrected at the next printing.
4. Item III. A. should be corrected at the next printing.
5. An Approval letter should be drafted for Supplement 050.

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Diane Moore, B.S.  
Regulatory Health Project Manager

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Ruyi He, M.D.  
Medical Officer

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

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Julieann DuBeau, MSN, RN  
Chief, Project Management Staff

cc:

Archival NDA 20-164/S-050  
HFD-180/Div. Files  
HFD-180/D.Moore  
HFD-180/R.He/K.Robie-Suh/S.Doddapaneni  
HFD-180/RJustice/J.Korvick

NDA 20-164/S-050; Cycle 2  
RPM LABELING REVIEW  
May 9, 2003 submission

Page 17

Drafted by: dm/5/22/03  
Initialed by: R.He 6.19.03/K.Robie-Suh 6.23.03/J.DuBeau 6.26.03  
Final: June 26, 2003  
Filename:N20164S50LbrevCycle2Rev1.doc  
**RPM LABELING REVIEW**



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/s/

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Diane V. Moore  
6/26/03 02:44:38 PM  
CSO

Ruyi He  
6/26/03 04:28:01 PM  
MEDICAL OFFICER

Kathy Robie-Suh  
6/26/03 04:46:46 PM  
MEDICAL OFFICER

Julieann DuBeau  
6/27/03 11:01:03 AM  
CSO

# **CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**NDA 20-164/S-050**

**MEDICAL REVIEWS**

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

NDA: NDA 20-164/SLR-050

Sponsor: AVENTIS PHARMACEUTICAL PRODUCTS, INC  
300 Somerset Corporate Boulevard  
Bridgewater, NJ 08807-2854 USA

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

Subject: Labeling supplement: Mechanical Prosthetic Heart Valves

Date submitted: October 29, 2002

Date received: October 29, 2002

Review completed: March 13, 2002

Reviewer: Ruyi He, M.D.

**1 EXECUTIVE SUMMARY**

This is a labeling supplement submission to provide information and direction to practitioners regarding use of Lovenox in patients with mechanical prosthetic heart valves. Revisions to the Warnings and Precautions of the labeling are proposed. In this review, I provide my comments and recommendations on the enoxaparin labeling changes in patients (pregnant, or non-pregnant) with mechanical prosthetic heart valves and on the pregnancy section of labeling.

**2 BACKGROUND:**

Supplement 040 submitted as a Supplement-Changes Being Effected" supplement was approved on January 9, 2002. This supplement provided for the following changes: (1) in the WARNINGS section, the addition of a new subsection, titled "Prosthetic Heart Valves"; and (2) in the PRECAUTIONS section, the Pregnancy subsection, the addition of a third paragraph describing a clinical study of pregnant women with prosthetic heart valves given enoxaparin to prevent thromboembolism. On February 28, 2002, the sponsor distributed a Dear Health Care Practitioner letter per FDA request to inform above changes in the labeling.

In the **WARNINGS** section the following subsection was added:

**Prosthetic Heart Valves:** The use of Lovenox Injection is not recommended for

thromboprophylaxis in patients with prosthetic heart valves. Cases of prosthetic heart valve thrombosis have been reported in patients with prosthetic valves who have received enoxaparin for thromboprophylaxis. Some of these cases were pregnant women in whom thrombosis led to maternal deaths and fetal deaths. Pregnant women with prosthetic heart valves may be at higher risk for thromboembolism (see **PRECAUTIONS: Pregnancy**).

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

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

The *Non-teratogenic Effects* subsection was revised:

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

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

Following the above changes, the sponsor has received more than 2,000 phone calls mainly regarding management of prosthetic heart valve and pregnancy. While intended by the company to be a warning, the labeling change might have been interpreted by practitioners as a contraindication for use of Lovenox in patients with prosthetic heart valves or for its use during pregnancy. Only 1 call was related to congenital anomalies. In a teleconference with the sponsor on April 5, 2002, it was concluded that the Warning and Precautions sections might need further revision with regard the prosthetic valves and pregnancy. The sponsor agreed to submit a labeling supplement.

In this submission, the sponsor provides a proposal to modify the current Lovenox labeling with respect to the "Warnings" section dealing with "mechanical prosthetic heart valves". In

the following section, I will provide my comments for those changes. FDA Pregnancy Labeling Team provided recommendations regarding pregnancy labeling (see Review dated January 9, 2003).

### **3 SAFETY UPDATE IN PATIENTS WITH OF MECHANICAL PROSTHETIC HEART VALVE**

The Aventis Pharmacovigilance Safety database currently contains 16 cases of mechanical prosthetic heart valve thrombosis for patients receiving enoxaparin. Eight case reports involve pregnant women with mechanical prosthetic heart valves (including the two aforementioned cases in the South African clinical trial). Of the other 6 cases involving pregnant women, five are spontaneous reports and one is a literature report. The other eight case reports consist of non-pregnant patients with mechanical prosthetic heart valves; seven are spontaneous reports and one is a literature report.

### **4 USE OF LOVENOX IN PREGNANT WOMEN WITH MECHANICAL PROSTHETIC HEART VALVES.**

#### **Current labeling in the WARNINGS section:**

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

#### **Current labeling in the PRECAUTIONS section, **Pregnancy** subsection second paragraph**

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**).

#### **The sponsor's rationales and proposals:**

Aventis recommends language addressing the use of Lovenox in pregnant women with mechanical prosthetic heart valves remain in the Lovenox USPI "Warnings" section.

There were two cases of fatal mechanical prosthetic heart valve thrombosis in pregnant women who received enoxaparin for thromboprophylaxis during the course of an open-label, randomized, controlled clinical trial in South Africa. There have also been isolated postmarketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves. Based on this information and the fact that pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism, Aventis recommends language addressing the use of Lovenox in pregnant women with mechanical prosthetic heart valves remain in the Lovenox USPI "Warnings" section as following:

**"WARNINGS"**

**Pregnant Women with Mechanical Prosthetic Heart Valves:** The use of Lovenox Injection for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied. In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. There have been isolated postmarketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis." Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism.

**Reviewer's comments and recommendations:**

The rationales and proposed changes above are generally acceptable. However, I recommend the paragraph be modified as following (deletion shown as ~~strikeout~~ and addition shown as underline):

**"WARNINGS"**

**Pregnant Women with Mechanical Prosthetic Heart Valves:** The use of Lovenox Injection for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied. In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. No patients in the heparin/warfarin group died. There have been isolated postmarketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis." Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism. Therefore, frequent monitoring of peak and trough levels, and adjusting of dosage may be needed.

In addition, I agree with the modifications proposed by the Agency Pregnancy Labeling Team for this paragraph (shown in double underline).

**"WARNINGS"**

**Pregnant Women with Mechanical Prosthetic Heart Valves:** The use of Lovenox Injection for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied. In a clinical study of pregnant women with mechanical prosthetic

heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. No patients in the heparin/warfarin group died. There have also been isolated postmarketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis.” ~~Pregnant w~~ Women with mechanical prosthetic heart valves may be at higher risk for thromboembolism during pregnancy, and when pregnant have a higher rate of fetal loss from still birth, spontaneous abortion and premature delivery. Therefore, frequent monitoring of peak and trough levels, and adjusting of dosage may be needed.

## **5 USE OF LOVENOX IN (NON-PREGNANT) PATIENTS WITH MECHANICAL PROSTHETIC HEART VALVES.**

For the current labeling, please see the current labeling in section 3 above.

### **The sponsor’s rationales and proposals:**

Aventis proposes to move Use of Lovenox in (non-pregnant) patients with mechanical prosthetic heart valves from “WARNINGS” section to the “PRECAUTIONS” section.

Enoxaparin is not specifically indicated for use in patients with mechanical prosthetic heart valves. However, low molecular weight heparins (LMWH) are used in current clinical practice as a standard of care in some settings, such as bridging therapy, pregnancy, and anticoagulant management of non-pregnant patients with prosthetic mechanical heart valves. The use of LMWH in this patient population has not been adequately studied in controlled clinical settings. However, The sponsor considers that based upon the clinical experience and an evidence-based approach within this patient population, language regarding the use of Lovenox in non-pregnant patients with mechanical heart valves is more appropriately placed in the “Precautions” section of the USPI, as opposed to the “Warnings” section. Therefore, Aventis proposes to provide wording in the “Precautions” section of the Lovenox USPI as following:

### **“PRECAUTIONS”**

**Mechanical Prosthetic Heart Valves:** The use of Lovenox Injection has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves. Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received enoxaparin for thromboprophylaxis. \_\_\_\_\_

\_\_\_\_\_ Some of these cases were pregnant women in whom thrombosis led to maternal and fetal deaths. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism (see **WARNINGS, Pregnant Women with Mechanical Prosthetic Heart Valves**).

### **Reviewer’s comments and recommendations:**

Two recent reports (Thromb Haemost 2001; Abstract P2323 and Circulation 2000;101:1083) evaluated a total of 417 patients with mechanical prosthetic heart valves who require interruption of oral anticoagulation for bridging therapy. One-third of patients was treated with enoxaparin and no thromboembolic events were reported. An expert panel (American Health Consults; October 2002) suggested enoxaparin 1 mg/kg sc q 12 h is safe and effective bridging therapy. However, no adequate study has been conducted to evaluate the safety and effectiveness of long-term use of enoxaparin. Of 2146 calls to the sponsor during 2/26/02 to 4/30/02 regarding Lovenox labeling, 1148 were specific regarding prosthetic heart valve.

The proposal moving Use of Lovenox in (non-pregnant) patients with mechanical prosthetic heart valves from “WARNINGS” section to the “PRECAUTIONS” section is acceptable. I recommend the paragraph be modified as following (deletion shown as ~~strikeout~~ and addition shown as underline):

#### “PRECAUTIONS”

**Mechanical Prosthetic Heart Valves:** The use of Lovenox Injection has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves and has not been adequately studied for long-term use. Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received enoxaparin for thromboprophylaxis. \_\_\_\_\_

Some of these cases were pregnant women in whom thrombosis led to maternal and fetal deaths. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism (see **WARNINGS, Pregnant Women with Mechanical Prosthetic Heart Valves**).

## 6 PREGNANCY LABELING CHANGES

The sponsor did not propose any pregnancy labeling changes except in pregnant patients with mechanical prosthetic heart valves as discussed above. The sponsor has received 520 phone calls regarding use of enoxaparin during pregnancy and 1 call regarding congenital anomalies between 2/26/02 and 4/30/02.

The Pregnancy Labeling team has reviewed the proposed label from the sponsor (WARNINGS and PRECAUTIONS sections) and proposes changes to the Lovenox (enoxaparin sodium) labeling (see The Pregnancy Labeling team review signed January 9, 2003). All recommendations are acceptable except following minor modifications:

- In the first paragraph of the sub-sub-section of *Clinical Considerations*, subsection of **Pregnancy**, section of **PRECAUTIONS**: the second sentence which reads “While not adequately studied, pregnant women with mechanical prosthetic heart valves treated for thromboprophylaxis with enoxaparin may be at even higher risk” should be revised. I recommend this sentence be modified as following: “While not adequately studied, pregnant women with mechanical prosthetic heart valves \_\_\_\_\_”



\_\_\_\_\_ may be at even higher risk for thrombosis. \_\_\_\_\_

- In the sub-sub-section of *Human data*, subsection of **Pregnancy**, section of **PRECAUTIONS**:

Because there are no adequate and well-controlled studies in pregnant women and literature reports are not reviewed by the Agency, it may not be necessary to list all literature reports in the labeling. In addition, the clinical study of pregnant women with mechanical prosthetic valves is repeated from WARNING section. I recommend that Human data subsection be modified as following:

*Human data*

There are no adequate and well-controlled studies in pregnant women.

A retrospective study — 604 women who used enoxaparin during pregnancy. A total of 624 pregnancies resulted in 693 live births. There were 72 hemorrhagic events (11 serious) in 63 women, 11 of which were serious. There were 14 cases of neonatal hemorrhage. Major congenital anomalies in live births occurred at rates (2.5%) similar to background rates.

There have been postmarketing reports of fetal death when pregnant women received Lovenox Injection. Causality for these cases has not been determined.

See **WARNINGS: Pregnant Women with Mechanical Prosthetic Heart** for a clinical study of pregnant women with mechanical prosthetic heart valves.

The Pregnancy Labeling team is an expert team for pregnancy labeling in the Agency and has more experience in pregnancy labeling. I concur with the recommendations from the Pregnancy labeling Team review with changes as shown (deletion shown as ~~strikeout~~ and addition shown as underline):

**Pregnancy:** Pregnancy Category B:

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

*Fetal Risk Summary*

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

*Clinical Considerations*

Pregnancy alone confers an increased risk for thromboembolism, that is even higher for women with preexisting thromboembolic disease, certain high risk pregnancy

conditions. \_\_\_\_\_ While not adequately studied, pregnant women with mechanical prosthetic heart valves \_\_\_\_\_ may be at even higher risk for thrombosis (see **WARNINGS: Pregnant Women with Mechanical Prosthetic Heart Valves and PRECAUTIONS: Mechanical Prosthetic Heart Valves**).

Pregnant women with thromboembolic disease including prosthetic heart valves, and patients with inherited or acquired thrombophilias also have an increased risk of other maternal complications and fetal loss regardless of the type of anticoagulant used.

All patients receiving anti-coagulants such as enoxaparin, including pregnant women, are at risk for bleeding. Pregnant women receiving enoxaparin should be carefully monitored for evidence of bleeding or excessive anticoagulation. \_\_\_\_\_ Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.

\_\_\_\_\_ Consideration for use of a shorter acting agent should be specifically addressed as delivery approaches.

#### *Data*

##### • Human Data –

There are no adequate and well-controlled studies in pregnant women.

A retrospective study \_\_\_\_\_ 604 women who used enoxaparin during pregnancy. A total of 624 pregnancies resulted in 693 live births. There were 72 hemorrhagic events (11 serious) in 63 women, ~~11 of which were serious.~~ There were 14 cases of neonatal hemorrhage. Major congenital anomalies in live births occurred at rates (2.5%) similar to background rates.

There have been postmarketing reports of fetal death when pregnant women received Lovenox Injection. Causality for these cases has not been determined.

~~In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. There have been isolated postmarketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis.~~

See **WARNINGS: Pregnant Women with Mechanical Prosthetic Heart Valves** for a clinical study in pregnant women with mechanical heart valves.

• Animal Data - Teratology studies have been conducted in pregnant rats and rabbits at SC doses of enoxaparin up to 30 mg/kg/day or 211 mg/m<sup>2</sup>/day and 410 mg/m<sup>2</sup>/day, respectively. There was no evidence of teratogenic effects or fetotoxicity due to

enoxaparin. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

## 7 CONCLUSIONS

Excepting the points discussed above, the proposed changes by the sponsor for the enoxaparin labeling in patients with mechanical prosthetic heart valves, and the proposed changes by the pregnancy labeling team in pregnant women are acceptable.

The sponsor should be informed of the above modifications and asked to revise the enoxaparin package insert accordingly.

---

Ruyi He, MD

IND: NDA 20-164/SLR-050  
HFD-180/Div. Files  
HFD-180/R. Justice  
HFD-180/J. Korvick  
HFD-180/K.Robie-Suh  
HFD-180/R.He  
HFD-180/S. Doddapaneni  
HFD-180/L.Zhou  
HFD-180/J. Choudary  
HFD-180/T. Permutt  
HFD-181/D. Moore  
f/t 3/13/03 rh  
N/20164/SLR050.RH

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this page is the manifestation of the electronic signature.**  
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/s/

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Ruyi He  
3/14/03 03:36:55 PM  
MEDICAL OFFICER

Kathy Robie-Suh  
3/14/03 04:16:52 PM  
MEDICAL OFFICER  
Concur.

# **CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**NDA 20-164/S-050**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 20-164/S-050

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 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, 30, 40, 60, 80 and 100 mg.
NDA Number:	20-164
Supplement number:	S-050
Date of supplement:	October 25, 2002
Date of receipt:	October 30, 2002

This supplemental application proposes the following change(s): revisions to the **WARNINGS** section of the Lovenox package insert (PI) regarding mechanical prosthetic heart valves.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 29, 2002, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 30, 2003.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:

Center for Drug Evaluation and Research  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180  
Attention: Document Room 8B-45  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and research  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180  
Attention: Document Room 8B-45  
5600 Fishers Lane  
Rockville, Maryland 20857

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

Sincerely,

*{See appended electronic signature page}*

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

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this page is the manifestation of the electronic signature.**  
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/s/

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Diane V. Moore  
12/17/02 12:17:32 PM



DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			<h2 style="margin: 0;">REQUEST FOR CONSULTATION</h2>	
TO (Division/Office): <b>Division of Reproductive and Urologic Drug Products (HFD-580): Attention: Dr. Daniel Shames and Dr. Phill Price. Parklawn Building Room 17B-45.</b>			FROM: HFD-180 (Division of Gastrointestinal and Coagulation Drug Products) Diane Moore, PKLN 6B-45	
DATE November 20, 2002	IND NO.	NDA NO. 20-164	TYPE OF DOCUMENT SLR-050	DATE OF DOCUMENT (October 25, 2002)
NAME OF DRUG  Lovenox		PRIORITY CONSIDERATION  Standard	CLASSIFICATION OF DRUG  Low Molecular Weight Heparin	DESIRED COMPLETION DATE  January 10, 2003
NAME OF FIRM: <b>Aventis Pharmaceuticals</b>				
REASON FOR REQUEST				
I. GENERAL				
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 33%;"> <input type="checkbox"/> NEW PROTOCOL  <input type="checkbox"/> PROGRESS REPORT  <input type="checkbox"/> NEW CORRESPONDENCE  <input type="checkbox"/> DRUG ADVERTISING  <input type="checkbox"/> ADVERSE REACTION REPORT  <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION  <input type="checkbox"/> MEETING PLANNED BY         </div> <div style="width: 33%;"> <input type="checkbox"/> PRE-NDA MEETING  <input type="checkbox"/> END OF PHASE II MEETING  <input type="checkbox"/> RESUBMISSION  <input type="checkbox"/> SAFETY/EFFICACY  <input type="checkbox"/> PAPER NDA  <input type="checkbox"/> CONTROL SUPPLEMENT         </div> <div style="width: 33%;"> <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER  <input type="checkbox"/> FINAL PRINTED LABELING  <input checked="" type="checkbox"/> LABELING REVISION  <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE  <input type="checkbox"/> FORMULATIVE REVIEW  <input type="checkbox"/> OTHER (SPECIFY BELOW):         </div> </div>				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):	
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input checked="" type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input checked="" type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
<p><b>COMMENTS/SPECIAL INSTRUCTIONS</b> Lovenox (enoxaparin sodium) labeling was revised in January 2002 to include additional post-marketing information regarding use of Lovenox in patients with prosthetic valves and pregnant women. The labeling revisions in the 1/9/02 approval included: a) S-040 which incorporated new information in the WARNINGS section regarding prosthetic valves, in the PRECAUTIONS section, Pregnancy subsection regarding pregnant women with prosthetic valves; b) supplement S-045 which updated the number of spinal epidural hematomas; and c) Supplement S-046 which provided for revisions to the PRECAUTIONS: Pregnancy subsection. The approval resulted in changing the WARNINGS sections and PRECAUTIONS: Pregnancy subsection. A "Dear Health Care Professional" letter was sent out regarding the changes. The labeling changes, though accurate, provoked some controversy in the practice community. Internal consultation with HFD-580, the Pregnancy Labeling Task Force and ODS resulted in recommendations that the sections of the labeling relating to pregnancy be restructured according to the proposed Pregnancy Labeling Rule and that some of the content and wording be modified. (See Memos dated 6/7/02 P Price, 6/7/02 D Hixon and 5/15/02 K Uhl and ODS Postmarketing Safety Review dated 5/3/02 M Truffa).</p> <p><b>The sponsor has submitted a supplement (letter date 10/25/02) providing additional information about use of Lovenox</b></p>				

in patients with prosthetic valves and proposing changes to the WARNINGS and PRECAUTIONS sections of the labeling regarding use of Lovenox in patients with prosthetic valves. Some of these changes relate to pregnant women with prosthetic valves and some information has been relocated to the WARNINGS section from the PRECAUTIONS: Pregnancy section of the labeling. The sponsor has provided a quantification of calls received regarding labeling revisions in these sections approved 1/9/02 (Supplements 040, 045 and 046) and an AAPRC report on use of enoxaparin in patients with prosthetic valves and/or pregnancy.

- Please review the additional information and proposed labeling in regard to the appropriate labeling for Lovenox use in pregnancy and see if you have any additional comments or recommendations for the labeling.
- Please be as specific as possible with regard to recommended wording for the labeling.
- Also, we would appreciate it if you could participate in an internal meeting to discuss the labeling in early February.

[Note: This is an electronic submission and is available in the edr].

Thank you for your continued input toward arriving at appropriate labeling for this product. If you need additional information, please contact Diane Moore (7-7476) or Dr. Ruyi He (7-7456).

SIGNATURE OF REQUESTER Diane Moore	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

**APPEARS THIS WAY  
ON ORIGINAL**

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this page is the manifestation of the electronic signature.**  
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/s/

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Diane V. Moore  
11/21/02 04:05:37 PM

MEMORANDUM

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

DATE: January 2, 2003

TO: Robert Justice, MD  
Director, HFD-180

THROUGH: Sandra Kweder, MD  
Deputy Director, OND, HFD-020  
Chair, Pregnancy Labeling Task Force

FROM: Kathleen Uhl, MD  
Dianne L. Kennedy, RPh, MPH  
Pregnancy Labeling Team  
Office of New Drugs, HFD-020

NDA: 20-164 SLR-050  
Sponsor: Aventis Pharmaceutical Products, Inc.  
Drug name: Lovenox (enoxaparin sodium)  
Consult sent: November 20, 2002  
Consult received: November 21, 2002  
Due date: January 10, 2003  
SUBJECT: Updating pregnancy section of labeling

**I. EXECUTIVE SUMMARY**

The Pregnancy Labeling team was asked to provide comment on the pregnancy section of labeling for Lovenox (enoxaparin sodium).

**II. BACKGROUND**

Lovenox (enoxaparin) labeling was revised in January 2002. Specifically, the product labeling was changed to inform health professionals that the use of Lovenox is not recommended for thromboprophylaxis in patients with prosthetic heart valves and added postmarketing information about congenital anomalies and non-teratogenic effects on pregnant women and the fetus. A "Dear Health Care Professional" letter was sent out regarding the changes as well. Since that time, the Agency and the sponsor have received comments from the medical community expressing concern regarding the labeling changes. Aventis Pharmaceutical Products, Inc. submitted a labeling supplement in October 2002 providing additional information about the use of Lovenox in pregnant patients. The Pregnancy Labeling Team (dated 5/15/02 K Uhl), Division of Reproductive and Urologic Drug Products (dated 6/7/02 P Price, 6/7/02 D Hixon), and the Office of

Drug Safety (dated 5/3/02 M Truffa) have provided memos to HFD-180 regarding enoxaparin use in pregnancy.

#### **IV. PROPOSED PREGNANCY LABELING**

The Pregnancy Labeling team has reviewed the proposed label from the sponsor (WARNINGS and PRECAUTIONS sections) and propose the following changes to the Lovenox (enoxaparin sodium) labeling:

##### **WARNINGS**

**Pregnant Women with Mechanical Prosthetic Heart Valves:** The use of Lovenox Injection for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied. In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. There have also been isolated postmarketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. ~~Pregnant w~~Women with mechanical prosthetic heart valves may be at higher risk for thromboembolism during pregnancy, and when pregnant have a higher rate of fetal loss from still birth, spontaneous abortion and premature delivery.

##### **PRECAUTIONS**

**Mechanical Prosthetic Heart Valves:** The use of Lovenox Injection has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves. Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received enoxaparin for thromboprophylaxis. \_\_\_\_\_ underlying disease and insufficient clinical data, — the evaluation of these cases. Some of these cases were pregnant women in whom thrombosis led to maternal and fetal deaths. ~~Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism—(see~~ **WARNINGS, Pregnant Women with Mechanical Prosthetic Heart Valves).**

**Pregnancy: *Teratogenic Effects:*** Pregnancy Category B:

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

##### **Fetal Risk Summary**

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

##### **Clinical Considerations**

Pregnancy alone confers an increased risk for thromboembolism, that is even higher for women with preexisting thromboembolic disease, certain high risk pregnancy conditions,  
\_\_\_\_\_. While not adequately

studied, pregnant women with mechanical prosthetic heart valves \_\_\_\_\_ may be at even higher risk (see WARNINGS: Pregnant Women with Mechanical Prosthetic Heart Valves and PRECAUTIONS: Mechanical Prosthetic Heart Valves).

Pregnant women with thromboembolic disease including prosthetic heart valves, and \_\_\_\_\_ with inherited or acquired thrombophilias also have an increased risk of other maternal complications and fetal loss regardless of the type of anticoagulant used.

All patients receiving anti-coagulants such as enoxaparin, including pregnant women, are at risk for bleeding. Pregnant women receiving enoxaparin should be carefully monitored for evidence of bleeding or excessive anticoagulation. \_\_\_\_\_

\_\_\_\_\_ Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.

\_\_\_\_\_ Consideration for use of a shorter acting, \_\_\_\_\_ should be specifically addressed as delivery approaches.

#### Data

- Human Data –

There are no adequate and well-controlled studies in pregnant women.

A retrospective study \_\_\_\_\_ 604 women who used enoxaparin during pregnancy. 624 pregnancies resulted in 693 live births. There were 72 hemorrhagic events in 63 women, 11 of which were serious. There were 14 cases of neonatal hemorrhage. Major congenital anomalies in live births occurred at rates (2.5%) similar to background rates. \_\_\_\_\_

[ \_\_\_\_\_ ]  
There have been postmarketing reports of fetal death when pregnant women received Lovenox Injection. Causality for these cases has not been determined.

In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. There have been isolated postmarketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis.

- Animal Data - Teratology studies have been conducted in pregnant rats and rabbits at SC doses of enoxaparin up to 30 mg/kg/day or 211 mg/m<sup>2</sup>/day and 410 mg/m<sup>2</sup>/day, respectively. There was no evidence of teratogenic effects or fetotoxicity due to

enoxaparin. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

~~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<sup>2</sup>/day and 410 mg/m<sup>2</sup>/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.~~

~~(See also **WARNINGS, Pregnant Women with Mechanical Prosthetic Heart Valves and PRECAUTIONS, Mechanical Prosthetic Heart Valves.**)~~

## **V. CONCLUSIONS**

The Pregnancy Labeling Team has reviewed the pregnancy section of labeling for Lovenox (enoxaparin sodium) and proposes recommendations.

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Kathleen Uhl, MD

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Dianne L. Kennedy, RPh, MPH

Pregnancy Labeling Team

### **Copies:**

NDA	20-164 ALR-050
HFD-020	Kweder, Kennedy, Uhl
HFD-180	Justice, Korvick, Robie-Suh, R He , D Moore
HFD-580	Shames, P Price

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/s/

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Kathleen Uhl  
1/9/03 10:14:51 AM  
MEDICAL OFFICER

final consult on pregnancy labeling for lovenox

Sandra L. Kweder  
1/9/03 10:50:08 AM  
MEDICAL OFFICER



## **MEMORANDUM OF MEETING**

**MEETING DATE:** February 7, 2003  
**TIME:** 1:30 - 2:30 PM  
**LOCATION:** Conference Room "K" (Parklawn)  
**APPLICATION:** NDA 20-164/S-050; Lovenox<sup>®</sup> (enoxaparin sodium) Injection  
**TYPE OF MEETING:** Labeling  
**MEETING CHAIR:** Dr. Kathy Robie-Suh  
**MEETING RECORDER:** Ms. Diane Moore

### **FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:**

#### **Division of Gastrointestinal and Coagulation Drug Products (DGICDP; HFD-180)**

Robert L. Justice, M.D., M.S., Director  
Joyce Korvick, M.D., M.P.H., Deputy Director  
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Coagulation Drug Product  
Ruyi He, M.D. - Medical Officer, DGICDP (HFD-180)  
Min Lu, M.D. - Medical Officer, DGICDP (HFD-180)  
Diane Moore - Regulatory Health Project Manager, DGICDP (HFD-180)

#### **Office on New Drugs (HFD-020)**

Sandra Kweder, M.D., Office Director (via telephone)  
Uhl, Kathleen, M.D., Medical Officer (via telephone)

#### **Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)**

Donna Griebel, M.D., Deputy Director  
Scott Monroe, M.D., Medical Team Leader  
Ronald Orleans, M.D. Medical Officer

### **BACKGROUND:**

On October 25, 2002, (received October 29, 2002) Aventis, Inc. (Aventis) submitted a labeling supplement (SLR-050) in response to the agreement made in the April 5, 2002, teleconference between representatives of DGICDP and Aventis to modify the current Lovenox United States Prescribing Information with respect to the **WARNINGS** and **PRECAUTIONS** sections dealing with "mechanical prosthetic heart valves."

The sponsor included a report in the submission to SLR-050 from the Anticoagulation in Prosthetic Valves and Pregnancy Consensus Report group published in the *Clinical Cardiology Consensus Reports*, October 1, 2002 entitled "Anticoagulation and Enoxaparin Use in Patients with Prosthetic heart Valves and/or Pregnancy."

DGICDP consulted the Pregnancy Labeling Team (PLT) and DRUDP regarding congenital anomalies and maternal and fetal deaths, the 'Dear Doctor' letter regarding the modification of the labeling from S-040. (See attached timeline.)

#### MEETING OBJECTIVE:

To discuss the labeling proposed for Lovenox regarding the use of enoxaparin in pregnant women with mechanical prosthetic heart valves and the pregnancy section of the package insert.

#### DISCUSSION POINTS:

1. The PLT originally reviewed the label after the labeling in SLR-040 was published and the public uproar occurred. The May 15, 2002, consult noted congenital anomalies that were based on literature rather than study data.
2. The PLT consult dated January 9, 2003, made comments on the labeling in regard to the Proposed Pediatric Rule. In preparation for this meeting, the October 1, 2002, Clinical Cardiology Consensus Report was received and reviewed. After consideration of that report, the PLT recommends that the Mechanical prosthetics subsection of the **WARNINGS** section entitled "**Mechanical Prosthetic Heart Valves**" be deleted. The PLT believes that the Lovenox product should not be "singled out" for the adverse events seen in the study comparing enoxaparin and heparin and Coumadin because the adverse events described in the subsection are also seen with Coumadin and Warfarin.

Doses were not adjusted for patient weight in the studies and patients who developed clots may have been under-dosed. The preferred dose is 1 mg/kg/bid. In the study, no patient deaths occurred in the uncontrolled group (heparin and Coumadin) and two patients died in the enoxaparin group. In patients receiving enoxaparin, doses were not weight-adjusted. The two women who died had many clotting events and the two deaths may have occurred because the women received inadequate clinical care and not necessarily because of an adverse event with the drug.

Page 2 of the Anticoagulation in Prosthetic Valves and Pregnancy Consensus Report group published in the October 1, 2002, *Clinical Cardiology Consensus Reports*, the American College of Cardiology/American Heart Association (ACC/AHA) advised against the use of enoxaparin in pregnant women with prosthetic heart valves. The proposed labeling is a large warning based on two patients who appeared to have

inadequate medical care, not the failure of the drug. It was noted in the Fetal Risk summary on page 2 of the article, that LMWH do not cross the placenta.

3. DRUDP takes a somewhat more cautious approach regarding the use of enoxaparin in pregnant women with prosthetic valves than the recommendation made by the PLT. DRUPD believes the labeling proposed in the PLT consult dated January 9, 2003 is appropriate.
4. Coumadin is contra-indicated in pregnant women (it has been shown to have teratogenic effects). Heparin is adequate when used in pregnant women, however, it is not as efficacious as Coumadin as there are more thrombosis and deaths with heparin compared to Coumadin. Coumadin is used more frequently outside the U.S.

#### CONCLUSIONS:

1. In the cases referenced in the **WARNINGS** section, the women may not have been adequately anticoagulated. Pregnant women may need more frequent monitoring.
2. A good study is needed with adequate dosing to support the labeling. In the **WARNINGS** section of the labeling — cases are referenced in which patients received Lovenox and — pregnant women died. The warning regarding adverse events in pregnant women with prosthetic heart valves should be in the **PRECAUTIONS** section rather than in the **WARNING** section.
3. Enoxaparin is currently one of the standards of care for pregnant women. We should encourage Aventis to compare enoxaparin to heparin in pregnant women with regard to dosing, pharmacokinetics (PK) with and without prosthetic heart valves.

#### ACTION ITEMS:

- DGICDP will send revised labeling to the PLT and DRUDP for comment.

*{See appended electronic signature page}*

*{See appended electronic signature page}*

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Signature, recorder

\_\_\_\_\_  
Signature, Chair

drafted: dm/2/28/03

revised: K.Robie-Suh 3.3.03

initialed: R.He, M.Lu, K.Robie-Suh 3.4.03/K. Uhl 3.5.03/J.Korvick, S. Monroe 3.6.03  
D.Griebel 3.12.03/K.Robie-Suh 4.2.03

Finalized: April 3, 2003

Filename: N20164S50IN2703.doc

**Lovenox (enoxaparin sodium, injection)**  
**NDA 20-164**

**Mechanical Prosthetic Heart Valves**

**Timeline**

**Letter Date:**

- August 23, 2000 (received August 24, 2000) "Changes Being Effected" (CBE)-0 Lovenox<sup>®</sup> Labeling Supplement -040 (SLR-040) submitted to add a new Prosthetic Heart Valves subsection to the **WARNINGS** section and an new third paragraph to the **PRECAUTIONS** section **Pregnancy** subsection to describe two deaths and not recommend enoxaparin for use in pregnant women with prosthetic heart valves.
- December 21, 2000 – Approvable letter to S-040 sent to sponsor.
- August 14, 2001 – (received August 15, 2001) Aventis resubmitted S-040 with final printed labeling (FPL) and a draft Dear Health Care Professional (DHCP) letter.
- November 12, 2001- (received November 13, 2001) Aventis submitted updated DHCP letter.
- November 28, 2001 – (received November 29, 2001) Aventis submitted an amended DHCP letter.
- January 9, 2002 – Approval letter for S-040, S-045 and S-046 sent to sponsor.
- February 28, 2002 – Aventis distributed DHCP letter.
- March 18, 2002 – (received March 19, 2002) Aventis submitted DHCP letter to SLR-040, SLR-045 and SLR-046 and to MedWatch.
- April 5, 2002 – Teleconference held between representatives of Aventis and the Division of Gastrointestinal and Coagulation Drug Products (DGICDP) to discuss the Lovenox Pregnancy labeling revisions and the February 28, 2002 DHCP letter. The sponsor agreed to submit another supplement providing for revised language in the **WARNINGS** and **PRECAUTIONS** section of the package insert.

- April 5, 2002 – Consult sent to Pregnancy Working Group for SLR-040 requesting the Groups' perspective on the new labeling and anticoagulation in pregnancy in general.
- April 5, 2002 – Consult sent to DRUDP for SLR-040 requesting the Divisions' perspective on the new labeling and anticoagulation in pregnancy in general.
- April 15, 2002- Consult sent to the Office of Drug Safety (ODS) Postmarketing Safety Review for updated overview of the safety data in the Adverse Events Reporting System (AERS) from June 2000 to present.
- May 3, 2002- Final signoff of consult from ODS Postmarketing Safety Review for updated overview of the safety data in the Adverse Events Reporting System (AERS) from June 2000 to present.
- May 15, 2002 – Final signoff of consult from Pregnancy Working Group for SLR-040 requesting the Groups' perspective on the new labeling and anticoagulation in pregnancy in general.
- May 15, 2002 – Final signoff of consult to S-040 from the Division of Reproductive and Urologic Drug Products (DRUDP) Medical Officer, Dr. Price, regarding the new subsection to the **WARNINGS** section entitled "Prosthetic Heart Valves" and the revisions to the Pregnancy subsection of the **PRECAUTIONS** section.
- June 7, 2002 – Memorandum from DRUDP Medical Team Leader to SLR-040 in agreement with Dr. Price that the available data do not support a plausible fetal toxic effect of Lovenox.
- October 25, 2002 – (received October 29, 2002) Aventis submits SLR-050 as a prior approval supplement to modify the current Lovenox United States Prescribing Information (USPI) with respect to the **WARNINGS** section dealing with "Mechanical prosthetic heart valves."
- November 20, 2002 – DGICDP consulted the Pregnancy Labeling Group regarding the revised proposed labeling for Lovenox in SLR-050 in patients with prosthetic valves and pregnant women.

November 20, 2002 – DGICDP consulted the DRUDP regarding the revised proposed labeling for Lovenox in SLR-050 in patients with prosthetic valves and pregnant women.

January 9, 2003 - Final signoff of consult from Pregnancy Working Group for SLR-050 regarding the revised proposed labeling for Lovenox in SLR-050 in patients with prosthetic valves and pregnant women.

February 12, 2003- Final sign-off of consult from DRUDP for SLR-050. DRUDP agrees with the recommendations of Dr. Uhl and the PLT and recommends no additional changes to the draft label beyond those proposed by Dr. Uhl, and is in agreement with the new labeling format for Lovenox proposed in the consult dated January 9, 2003.

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Diane V. Moore  
4/2/03 06:07:18 PM

Kathy Robie-Suh  
4/3/03 08:35:40 AM

February 10, 2003

From: Phill H. Price, M.D.

Through: Scott Monroe, M.D. Medical Team Leader HFD-580  
Donna Griebel, M.D. Deputy Division Director HFD-580

To: Diane Moore, CSO, HFD-180  
Kathy M. Robie-Suh, HFD-180 Medical Team Leader

Subject: Supplement SLR-050 for Lovenox, NDA 20-164, to make changes to WARNING and PRECAUTIONS sections of the labeling regarding (1) the use of Lovenox in patients with prosthetic valves and (2) the risk of congenital defects secondary to the use of Lovenox in pregnant women. Previous labeling changes in S-040, S045 and S046 resulted in changes to these sections and a "Dear Health Care Professional" letter was sent out regarding these changes.

Proposed Draft Labeling in Supplement SLR-050 has been reviewed, specifically the Warnings and Precautions section of the Lovenox label. Reference is made to an excellent memorandum and recommendations from Dr. Kathleen Uhl, M.D. and the Pregnancy Labeling team to Sandra Kweder, M.D., Deputy Director for OND, HFD-020 dated January 2, 2003.

In this memorandum, Dr. Uhl has used a *proposed draft pregnancy-labeling* format that would be consistent with draft labels for a number of indications for which a significant number of pregnant women will be treated. This format is more concise and is improved over the previous label and the changes recommended by the sponsor. For example, under Warnings, the paragraph relating to pregnant women with mechanical prosthetic heart valves is retained, but the last sentence clarifies the whole paragraph.

Under PRECAUTIONS, major formatting changes have been made. They include a second paragraph relating to mechanical prosthetic heart valves, the pregnancy category B, a fetal risk summary, clinical considerations, and data (both human and animal). Importantly, a statement is made that there are no adequate and well-controlled studies in pregnant women. Following this is a human data section that includes a large retrospective study with maternal and neonatal outcomes.

Importantly, the sponsor's paragraph under teratogenic effects that had reported congenital anomalies in infants of mothers treated with Lovenox has been deleted.

This reviewer is in agreement with the recommendations of Dr. Uhl and the pregnancy labeling team. At present, we recommend no additional changes to the draft label beyond those proposed by Dr. Uhl, and are in agreement with the new labeling format for Lovenox.

Phill H. Price, M.D.



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Phill H. Price  
2/10/03 06:34:11 PM  
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Scott Monroe  
2/10/03 06:37:16 PM  
MEDICAL OFFICER

Donna Griebel  
2/12/03 08:58:21 AM  
MEDICAL OFFICER