CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-164/S-021

Name: Lovenox® (Enoxaparin Sodium) Injection

Sponsor: Rhone-Poulenc Pharmaceuticals, Inc.

Approval Date: April 20, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-021

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 20-164/S-021

Rhone-Poulenc Rorer Pharmaceuticals Inc.
Attention: Mr. Robert W. Babilon
P.O. Box 5096
500 Arcola Road
Collegeville, PA 19426-0800

Dear Mr. Babilon:

Please refer to your supplemental new drug application dated January 12, 1999, received January 13, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox® (enoxaparin sodium) Injection.

This supplemental new drug application provides for additional information in the ADVERSE REACTIONS section, the "Ongoing Safety Surveillance" subsection, of the package insert regarding reports of rare cases of hyperlipidemia.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted labeling dated January 12, 1999 with the revisions listed below. Accordingly, the supplemental application is approved effective on the date of this letter.

> 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.

These revisions are terms of the approval.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-164/S-021." Approval of this submission by FDA is not required before the labeling is used.

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

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

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

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

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

Sincerely,

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

cc:
Archival NDA 20-164/S-021
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/L.Talarico
HFD-180/J.Schmeling
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-103/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-21/ACS (with labeling) - for drug discussed at advisory committee meeting.
HFD-95/DDMS (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: KO/April 19, 1999
final: KO/04/19/99/c:\mydocuments\nda20160-S-021-04-19-99-AP

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-021

LABELING

Labeling: ORIG SE2 021 7A
NDA No: 20-164 Rec'd. 9-99
Reviewed by: [signature]
10/5/99
AP 4-20-00

LOVENOX®
(enoxaparin sodium) Injection

Rx only

OCT - 5 1999

SPINAL / EPIDURAL HEMATOMAS

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

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

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

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

DESCRIPTION

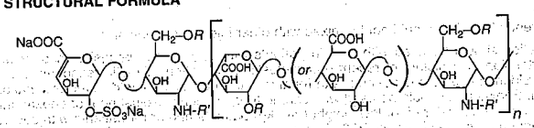
Lovenox Injection is a sterile solution containing enoxaparin sodium, a low molecular weight heparin. It is available in: prefilled syringes (30 and 40 mg), graduated prefilled syringes (60, 80, and 100 mg), and ampules (30 mg). Each dosage unit contains 10 mg enoxaparin sodium per 0.1 mL Water for Injection. The solution is preservative-free and intended for use only as a single-dose injection. (See **DOSAGE AND ADMINISTRATION** and **HOW SUPPLIED** for dosage unit descriptions.)

The pH of the injection is 5.5 to 7.5, with an approximate anti-Factor Xa activity per dosage unit of 1000 IU per every 10 mg of enoxaparin sodium (with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard). Nitrogen is used in the headspace to inhibit oxidation.

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

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

STRUCTURAL FORMULA



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

CLINICAL PHARMACOLOGY

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

Pharmacodynamics: Maximum anti-Factor Xa and anti-thrombin (anti-Factor IIa) activities occur 3 to 5 hours after SC injection of enoxaparin. Mean peak anti-Factor Xa activity was 0.16 IU/mL (1.58 µg/mL) and 0.38 IU/mL (3.83 µg/mL) after the 20 mg and the 40 mg clinically tested SC doses, respectively. Mean (n = 46) peak anti-Factor Xa activity was 1.1 IU/mL at steady state in patients with unstable angina receiving 1.0 mg/kg SC every 12 hours for 14 days. Mean absolute bioavailability of enoxaparin, given SC, based on anti-Factor Xa activity is 92% in healthy volunteers. The volume of distribution of anti-Factor Xa activity is about 6 L. Following intravenous (i.v.) dosing, the total body clearance of enoxaparin is 26 mL/min. After i.v. dosing of enoxaparin labeled with the gamma-emitter, ^{99m}Tc, 40% of radioactivity and 8 to 20% of anti-Factor Xa activity were recovered in urine in 24 hours. Elimination half-life based on anti-Factor Xa activity was 4.5 hours after SC administration. Following a 40 mg SC once a day dose, significant anti-Factor Xa activity persists in plasma for about 12 hours.

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

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

CLINICAL TRIALS

Hip or Knee Replacement Surgery: Lovenox Injection has been shown to prevent 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. After hemostasis was established, treatment was initiated 12 to 24 hours after surgery and was continued for 10 to 14 days after surgery. The data are provided below.

Efficacy of Lovenox Injection in Hip Replacement Surgery

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

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

A double-blind, multicenter study compared three dosing regimens of Lovenox Injection in patients with hip replacement. Treatment was initiated within two days after surgery and was continued for 7 to 11 days after surgery. The data are provided below.

Efficacy of Lovenox Injection in Hip Replacement Surgery

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

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

Lovenox® (enoxaparin sodium) Injection

There was no significant difference between the 30 mg every 12 hours and 40 mg once a day regimens.

Extended Prophylaxis in Hip Replacement Surgery: In a study of extended prophylaxis for patients undergoing hip replacement surgery, patients were treated, while hospitalized, with enoxaparin 40 mg SC, initiated up to 12 hours prior to surgery for the prevention of post-operative deep vein thrombosis. 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 enoxaparin 40 mg (n = 90) once a day SC or to placebo (n = 89) for 3 weeks. In this population of patients, the incidence of deep vein thrombosis during extended prophylaxis was significantly lower for enoxaparin compared to placebo. The data are provided below.

Efficacy of Lovenox Injection with Extended Prophylaxis Following Hip Replacement Surgery

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

[1] p value versus placebo = 0.008
[2] p value versus placebo = 0.537

In a second study, patients undergoing hip replacement surgery were treated, while hospitalized, with enoxaparin 40 mg SC, initiated up to 12 hours prior to surgery. All patients were examined for clinical signs and symptoms of venous thromboembolic disease. In a double-blind design, patients without clinical signs and symptoms of venous thromboembolic disease were randomized to a post-discharge regimen of either enoxaparin 40 mg (n = 131) once a day SC or to placebo (n = 131) for 3 weeks. Similar to the first study the incidence of deep vein thrombosis during extended prophylaxis was significantly lower for enoxaparin compared to placebo, with a statistically significant difference in both total DVT (enoxaparin 21 [16%] versus placebo 45 [34%]; p = 0.001) and proximal DVT (enoxaparin 8 [6%] versus placebo 28 [21%]; p = <0.001).

In a double-blind study, Lovenox Injection 30 mg every 12 hours SC was compared to placebo in 99 patients undergoing knee replacement surgery. 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 deep vein thrombosis after surgery was significantly lower for enoxaparin compared to placebo. The data are provided below.

Efficacy of Lovenox Injection in Knee Replacement Surgery

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

[1] p value versus placebo = 0.0001
CI = Confidence Interval
[2] p value versus placebo = 0.013
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. Treatment was initiated after surgery and continued up to 14 days. The incidence of deep vein thrombosis was significantly lower for enoxaparin compared to heparin.

Abdominal Surgery: In a double-blind, parallel group study of 1115 patients undergoing elective cancer surgery of the gastrointestinal, urological, or gynecological tract, 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 preventing deep vein thrombosis (DVT). The data are provided below.

Efficacy of Lovenox Injection in Abdominal Surgery Patients with Cancer

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

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

In a second double-blind, parallel group study, Lovenox Injection 40 mg SC once a day was compared to heparin 5000 U every 8 hours SC in 1347 patients undergoing colorectal surgery (one-third with cancer). Treatment was initiated approximately 2 hours prior to surgery and continued for approximately 7 to 10 days after surgery. The data are provided below.

Efficacy of Lovenox Injection in Colorectal Surgery

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

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

Treatment of Deep Vein Thrombosis and Pulmonary Embolism: In a multicenter, parallel group study, 900 patients with acute lower extremity deep vein thrombosis (DVT) with or without pulmonary embolism (PE) were randomized to an inpatient (hospital) treatment of either (i) Lovenox Injection 1.5 mg/kg once a day SC, (ii) Lovenox Injection 1.0 mg/kg every 12 hours SC, or (iii) heparin i.v. bolus (5000 IU) followed by a continuous infusion (administered to achieve an aPTT of 55 to 85 seconds). 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 the prevention of recurrent venous thromboembolism (DVT and/or PE).

Efficacy of Lovenox Injection in Treatment of Deep Vein Thrombosis and Pulmonary Embolism

Indication	Dosing Regimen[1] Lovenox 1.5 mg/kg q.d. SC n (%)	Lovenox 1.0 mg/kg q12h SC n (%)	Heparin aPTT Adjusted i.v. Therapy n (%)
All Treated DVT Patients with and without PE	298 (100)	312 (100)	290 (100)
Patient Outcome Total VTE[2] (%)	13 (4.4)[3]	9 (2.9)[3]	12 (4.1)
DVT Only (%)	11 (3.7)	7 (2.2)	8 (2.8)
Proximal DVT (%)	9 (3.0)	6 (1.9)	7 (2.4)
PE (%)	2 (0.7)	2 (0.6)	4 (1.4)

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

Similarly, in a multicenter, open-label, parallel group study, 501 patients with acute proximal deep vein thrombosis were randomized to enoxaparin or heparin. Patients who could not receive outpatient therapy were excluded from entering the study. Eligible patients could be treated in the hospital, but ONLY enoxaparin patients were permitted to go home on therapy (72%). 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 the prevention of recurrent venous thromboembolism.

Efficacy of Lovenox Injection in Treatment of Deep Vein Thrombosis

Indication	Dosing Regimen[1] Lovenox 1.0 mg/kg q12h SC n (%)	Heparin aPTT Adjusted i.v. Therapy n (%)
All Treated DVT Patients	247 (100)	254 (100)
Patient Outcome Total VTE[2] (%)	13 (5.3)[3]	17 (6.7)
DVT Only (%)	11 (4.5)	14 (5.5)
Proximal DVT (%)	10 (4.0)	12 (4.7)
PE (%)	2 (0.8)	3 (1.2)

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

Unstable Angina and Non-Q-Wave Myocardial Infarction: In a multicenter, double-blind, parallel group study, 3171 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). **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.

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 ($p = 0.047$).

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

Indication	Dosing Regimen[1] Lovenox 1 mg/kg q12h SC n (%)	Heparin aPTT Adjusted i.v. Therapy n (%)	Reduction (%)	p Value
All Randomized Unstable Angina and Non-Q-Wave MI Patients	1607 (100)	1564 (100)		
Timepoint[2] 48 Hours	99 (6.2)	115 (7.4)	1.2	0.178
14 Days	266 (16.6)	309 (19.8)	3.2	0.019
30 Days	318 (19.8)	364 (23.3)	3.5	0.016

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

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

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

Indication	Dosing Regimen[1] Lovenox 1 mg/kg q12h SC n (%)	Heparin aPTT Adjusted i.v. Therapy n (%)	Reduction (%)	p Value
All Randomized Unstable Angina and Non-Q-Wave MI Patients	1607 (100)	1564 (100)		
Timepoint[2] 48 Hours	18 (1.1)	21 (1.3)	0.2	0.119
14 Days	79 (4.9)	96 (6.1)	1.2	0.132
30 Days	99 (6.2)	121 (7.7)	1.5	0.081

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

INDICATIONS AND USAGE

- Lovenox Injection is indicated for the prevention of deep vein thrombosis, which may lead to pulmonary embolism:
  - in patients undergoing hip replacement surgery, during and following hospitalization;
  - in patients undergoing knee replacement surgery;
  - in patients undergoing abdominal surgery who are at risk for thromboembolic complications. Patients at risk include patients 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.
- Lovenox Injection is indicated for:
  - the **inpatient treatment** of acute deep vein thrombosis **with and 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.
- Lovenox Injection is indicated for the prevention of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin.

Lovenox® (enoxaparin sodium) Injection

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

CONTRAINDICATIONS

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

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

WARNINGS

Lovenox Injection is not intended for intramuscular administration.

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

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

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

Cases of epidural or spinal hematomas have been reported with the associated use of enoxaparin 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).

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

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

Moderate thrombocytopenia (platelet counts between 100,000/mm^3 and 50,000/mm^3) occurred at a rate of 1.3% in patients given Lovenox Injection, 1.2% in patients given heparin, and 0.6% in patients given placebo in clinical trials.

Platelet counts less than 50,000/mm^3 occurred at a rate of 0.1% in patients given Lovenox Injection, in 0.2% of patients given heparin, and 0% of patients given placebo in the same trials.

Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm^3, enoxaparin should be discontinued. Rare cases of thrombocytopenia with thrombosis have also been observed in clinical practice. The rate of incidence of this complication in usual medical practice is unknown.

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. Enoxaparin 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 <30mL/min).

If thromboembolic events occur despite enoxaparin prophylaxis, appropriate therapy should be initiated.

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

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

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

Pregnancy: *Teratogenic Effects:* Pregnancy Category B: Teratology studies have been conducted in pregnant rats and rabbits at SC doses of enoxaparin up to 30 mg/kg/day or 211 mg/m^2/day and 410 mg/m^2/day, respectively. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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

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

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

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.

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

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

[1] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥2g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major. In the knee replacement surgery trials, intraocular hemorrhages were also considered major hemorrhages.
[2] Lovenox 30 mg every 12 hours SC initiated 12 to 24 hours after surgery and continued for up to 14 days after surgery.
[3] Lovenox 40 mg SC once a day initiated up to 12 hours prior to surgery and continued for up to 7 days after surgery.
[4] Lovenox 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 enoxaparin patients versus 1.8% of the placebo patients.

Major Bleeding Episodes in Abdominal and Colorectal Surgery[1]

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

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

Major Bleeding Episodes in Deep Vein Thrombosis and Pulmonary Embolism Treatment[1]

Indication	Dosing Regimen[2]: Lovenox 1.5 mg/kg q.d. SC	Lovenox 1.0 mg/kg q12h SC	Heparin aPTT Adjusted i.v. Therapy
Deep Vein Thrombosis and Pulmonary Embolism Treatment	n = 298 5 (2%)	n = 559 9 (2%)	n = 554 9 (2%)

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

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

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

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

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 enoxaparin group, are provided below.

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

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

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

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

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

[1] Excluding unrelated adverse events.

Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Patients[1] Undergoing Treatment for Deep Vein Thrombosis and Pulmonary Embolism

	Dosing Regimen: Lovenox 1.5 mg/kg q.d. SC n = 298		Lovenox 1.0 mg/kg q12h SC n = 559		Heparin aPTT Adjusted i.v. Therapy n = 544	
Adverse Event	**Severe**	**Total**	**Severe**	**Total**	**Severe**	**Total**
Injection Site Hemorrhage	0%	5%	0%	3%	<1%	<1%
Injection Site Pain	0%	2%	0%	2%	0%	0%
Hematuria	0%	2%	0%	<1%	<1%	2%

[1] Excluding unrelated adverse events.

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 enoxaparin therapy occurred at an incidence of ≤1%.

Non-major hemorrhagic episodes, primarily injection site ecchymoses and hematomas, were more frequently reported in patients treated with SC enoxaparin 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 enoxaparin group, are provided below (irrespective of relationship to drug therapy).

Lovenox® (enoxaparin sodium) Injection

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

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

Ongoing Safety Surveillance: Since 1993, there have been more than 60 reports of epidural or spinal hematoma formation with concurrent use of enoxaparin 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 reports include: 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, and thrombocytosis. 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**).

Adult Dosage: *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. Up to 14 days administration (average duration 7 to 10 days) of Lovenox Injection 30 mg every 12 hours has been well tolerated in controlled clinical trials. For hip replacement surgery, a dose of **40 mg once a day** SC, given initially 12 (±3) hours prior to surgery, may be considered. Following the initial phase of thromboprophylaxis in hip replacement surgery patients (Lovenox Injection 30 mg every 12 hours or 40 mg once a day), continued prophylaxis with Lovenox Injection 40 mg once a day administered by SC injection for 3 weeks is recommended.

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.

Treatment of Deep Vein Thrombosis and 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 **1.0 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 **1.0 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 Lovenox Injection administration has been well tolerated in controlled clinical trials.

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. The usual duration of treatment is 2 to 8 days. 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.

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

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

Lovenox Injection is administered by SC injection. It must not be administered by intramuscular injection.

Subcutaneous Injection Technique: Patients should be lying down and Lovenox Injection administered by deep SC injection. To avoid the loss of drug when using the 30 and 40 mg prefilled syringes, do not expel the air bubble from the syringe before the injection. Administration should be alternated between the left and right anterolateral and left and right posterolateral abdominal wall. The whole length of the needle should be introduced into a skin fold held between the thumb and forefinger; the skin fold should be held throughout the injection. To minimize bruising, do not rub the injection site after completion of the injection. An automatic injector, Lovenox EasyInjector™, is available for patients to administer Lovenox Injection packaged in 30 mg and 40 mg prefilled syringes. Please see directions accompanying the Lovenox EasyInjector™ automatic injection device.

HOW SUPPLIED

Lovenox® (enoxaparin sodium) Injection is available in:

Dosage Unit	Strength[1]	Package Size (per carton)	Anti-Xa Activity[2]	NDC # 0075-
Ampules	30 mg / 0.3 mL	10 ampules	3000 IU	0624-03
Prefilled Syringes[3]	30 mg / 0.3 mL	10 syringes	3000 IU	0624-30
	40 mg / 0.4 mL	10 syringes	4000 IU	0620-40
Graduated Prefilled Syringes[3]	60 mg / 0.6 mL	10 syringes	6000 IU	0621-60
	80 mg / 0.8 mL	10 syringes	8000 IU	0622-80
	100 mg / 1.0 mL	10 syringes	10 000 IU	0623-00

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

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

Keep out of the reach of children.

Lovenox Injection prefilled and graduated prefilled syringes manufactured in France.
Lovenox Injection ampules manufactured in England.

RHÔNE-POULENC RORER PHARMACEUTICALS INC.
COLLEGEVILLE, PA 19426

IN-1107T
Rev. 6/99

NDA 20-164/S-021
Lovenox® (enoxaparin sodium) Injection
FINAL PRINTED LABELING
IN-2828E Rev 6/99 : Dagenham

Labeling: ORIG SLR 021 9A
NDA No: 20-164 Rec'd. 9-99
Reviewed by: [signature] 10/5/99

NDA 20-164

LOVENOX® (enoxaparin sodium) Injection

OCT - 5 1999

IN-2828E
Rev. 6/99

Rx only

SPINAL / EPIDURAL HEMATOMAS

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

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

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

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

DESCRIPTION

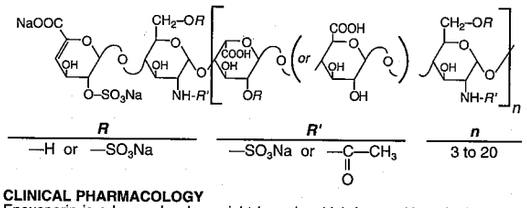
Lovenox Injection is a sterile solution containing enoxaparin sodium, a low molecular weight heparin. It is available in: prefilled syringes (30 and 40 mg), graduated prefilled syringes (60, 80, and 100 mg), and ampules (30 mg). Each dosage unit contains 10 mg enoxaparin sodium per 0.1 mL Water for Injection. The solution is preservative-free and intended for use only as a single-dose injection. (See **DOSAGE AND ADMINISTRATION** and **HOW SUPPLIED** for dosage unit descriptions.)

The pH of the injection is 5.5 to 7.5, with an approximate anti-Factor Xa activity per dosage unit of 1000 IU per every 10 mg of enoxaparin sodium (with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard). Nitrogen is used in the headspace to inhibit oxidation.

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

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

STRUCTURAL FORMULA



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

CLINICAL PHARMACOLOGY

Enoxaparin is a low molecular weight heparin which has antithrombotic properties. In humans, enoxaparin given at a dose of 1.5 mg/kg subcutaneously (SC) is characterized by a higher ratio of anti-Factor Xa to anti-Factor IIa activity (mean±SD, 14.0±3.1) (based on areas under anti-Factor activity versus time curves) compared to the ratios observed for heparin (mean±SD, 1.22±0.13). Increases of up to 1.8 times the control values were seen in the thrombin time (TT) and the activated partial thromboplastin time (aPTT). Enoxaparin at a 1 mg/kg dose, 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).

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LOVENOX® (enoxaparin sodium) Injection

S9902A

Pharmacodynamics: Maximum anti-Factor Xa and anti-thrombin (anti-Factor IIa) activities occur 3 to 5 hours after SC injection of enoxaparin. Mean peak anti-Factor Xa activity was 0.16 IU/mL (1.58 µg/mL) and 0.38 IU/mL (3.83 µg/mL) after the 20 mg and the 40 mg clinically tested SC doses, respectively. Mean (n = 46) peak anti-Factor Xa activity was 1.1 IU/mL at steady state in patients with unstable angina receiving 1.0 mg/kg SC every 12 hours for 14 days. Mean absolute bioavailability of enoxaparin, given SC, based on anti-Factor Xa activity is 92% in healthy volunteers. The volume of distribution of anti-Factor Xa activity is about 6 L. Following intravenous (i.v.) dosing, the total body clearance of enoxaparin is 26 mL/min. After i.v. dosing of enoxaparin labeled with the gamma-emitter, ^{99m}Tc, 40% of radioactivity and 8 to 20% of anti-Factor Xa activity were recovered in urine in 24 hours. Elimination half-life based on anti-Factor Xa activity was 4.5 hours after SC administration. Following a 40 mg SC once a day dose, significant anti-Factor Xa activity persists in plasma for about 12 hours.

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

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

CLINICAL TRIALS

Hip or Knee Replacement Surgery: *Lovenox Injection has been shown to prevent 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. After hemostasis was established, treatment was initiated 12 to 24 hours after surgery and was continued for 10 to 14 days after surgery. The data are provided below.

Efficacy of Lovenox Injection in Hip Replacement Surgery

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

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

A double-blind, multicenter study compared three dosing regimens of Lovenox Injection in patients with hip replacement. Treatment was initiated within two days after surgery and was continued for 7 to 11 days after surgery. The data are provided below.

Efficacy of Lovenox Injection in Hip Replacement Surgery

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

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

There was no significant difference between the 30 mg every 12 hours and 40 mg once a day regimens.

Extended Prophylaxis in Hip Replacement Surgery: In a study of extended prophylaxis for patients undergoing hip replacement surgery, patients were treated, while hospitalized, with enoxaparin 40 mg SC, initiated up to 12 hours prior to surgery for the prevention of post-operative deep vein thrombosis. 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 enoxaparin 40 mg (n = 90) once a day SC or to placebo (n = 89) for 3 weeks. In this population of patients, the incidence of deep vein thrombosis during extended prophylaxis was significantly lower for enoxaparin compared to placebo. The data are provided below.

Efficacy of Lovenox Injection with Extended Prophylaxis Following Hip Replacement Surgery

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

[1] p value versus placebo = 0.008
[2] p value versus placebo = 0.537

In a second study, patients undergoing hip replacement surgery were treated, while hospitalized, with enoxaparin 40 mg SC, initiated up to 12 hours prior to surgery. All patients were examined for clinical signs and symptoms of venous thromboembolic disease. In a double-blind design, patients without clinical signs and symptoms of venous thromboembolic disease were randomized to a post-discharge regimen of either enoxaparin 40 mg (n = 131) once a day SC or to placebo (n = 131) for 3 weeks. Similar to the first study the incidence of deep vein thrombosis during extended prophylaxis was significantly lower for enoxaparin compared to placebo, with a statistically significant difference in both total DVT (enoxaparin 21 [16%] versus placebo 45 [34%]; p = 0.001) and proximal DVT (enoxaparin 8 [6%] versus placebo 28 [21%]; p = <0.001).

In a double-blind study, Lovenox Injection 30 mg every 12 hours SC was compared to placebo in 99 patients undergoing knee replacement surgery. 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 deep vein thrombosis after surgery was significantly lower for enoxaparin compared to placebo. The data are provided below.

Efficacy of Lovenox Injection in Knee Replacement Surgery

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

[1] p value versus placebo = 0.0001
CI = Confidence Interval
[2] p value versus placebo = 0.013
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. Treatment was initiated after surgery and continued up to 14 days. The incidence of deep vein thrombosis was significantly lower for enoxaparin compared to heparin.

Abdominal Surgery: In a double-blind, parallel group study of 1115 patients undergoing elective cancer surgery of the gastrointestinal, urological, or gynecological tract, 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 preventing deep vein thrombosis (DVT). The data are provided below.

Efficacy of Lovenox Injection in Abdominal Surgery Patients with Cancer

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

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

In a second double-blind, parallel group study, Lovenox Injection 40 mg SC once a day was compared to heparin 5000 U every 8 hours SC in 1347 patients undergoing colorectal surgery (one-third with cancer). Treatment was initiated approximately 2 hours prior to surgery and continued for approximately 7 to 10 days after surgery. The data are provided below.

Efficacy of Lovenox Injection in Colorectal Surgery

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

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

Treatment of Deep Vein Thrombosis and Pulmonary Embolism: In a multicenter, parallel group study, 900 patients with acute lower extremity deep vein thrombosis (DVT) with or without pulmonary embolism (PE) were randomized to an inpatient (hospital) treatment of either (i) Lovenox Injection 1.5 mg/kg once a day SC, (ii) Lovenox Injection 1.0 mg/kg every 12 hours SC, or (iii) heparin i.v. bolus (5000 IU) followed by a continuous infusion (administered to achieve an aPTT of 55 to 85 seconds). 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 the prevention of recurrent venous thromboembolism (DVT and/or PE).

Efficacy of Lovenox Injection in Treatment of Deep Vein Thrombosis and Pulmonary Embolism

	Dosing Regimen[1]		
	Lovenox	Lovenox	Heparin
	1.5 mg/kg q.d. SC	1.0 mg/kg q12h SC	aPTT Adjusted i.v. Therapy
Indication	n (%)	n (%)	n (%)
All Treated DVT Patients with and without PE	298 (100)	312 (100)	290 (100)
Patient Outcome Total VTE[2] (%)	13 (4.4)[3]	9 (2.9)[3]	12 (4.1)
DVT Only (%)	11 (3.7)	7 (2.2)	8 (2.8)
Proximal DVT (%)	9 (3.0)	6 (1.9)	7 (2.4)
PE (%)	2 (0.7)	2 (0.6)	4 (1.4)

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

Similarly, in a multicenter, open-label, parallel group study, 501 patients with acute proximal deep vein thrombosis were randomized to enoxaparin or heparin. Patients who could r
outpatient therapy were excluded from entering the study. Eligible patients could be tre
hospital, but ONLY enoxaparin patients were permitted to go home on therapy (72%
were randomized to either Lovenox Injection 1 mg/kg every 12 hours SC or heparin
(5000 IU) followed by a continuous infusion administered to achieve an aPTT of 60 to 8
(in-patient treatment). All patients also received warfarin sodium as described in the
study. Lovenox Injection or standard heparin therapy was administered for a minimum
Lovenox Injection was equivalent to standard heparin therapy in the prevention of
venous thromboembolism.

Efficacy of Lovenox Injection in Treatment of Deep Vein Thrombosis

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

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

Unstable Angina and Non-Q-Wave Myocardial Infarction: In a multicenter, double-l
allel group study, 3171 patients who recently experienced unstable angina or no
myocardial infarction were randomized to either Lovenox Injection 1 mg/kg every 12 hc
heparin i.v. bolus (5000 U) followed by a continuous infusion (adjusted to achieve an a
to 85 seconds). **All** patients were also treated with aspirin 100 to 325 mg per day. Treat
initiated within 24 hours of the event and continued until clinical stabilization, revasc
procedures, or hospital discharge, with a maximal duration of 8 days of therapy. The
incidence of the triple endpoint of death, myocardial infarction, or recurrent angina was
Lovenox Injection compared with heparin therapy at 14 days after initiation of treatr
lower incidence of the triple endpoint was sustained up to 30 days after initiation of t
These results were observed in an analysis of both all-randomized and all-treated patie

Urgent revascularization procedures were performed less frequently in the Lovenox
group as compared to the heparin group, 6.3% compared to 8.2% at 30 days (p = 0.04

**Efficacy of Lovenox Injection in Unstable Angina and Non-Q-Wave Myocardial In
(Combined Endpoint of Death, Myocardial Infarction, or Recurrent Angina**

	Dosing Regimen[1]			
	Lovenox	Heparin	Reduction	p
	1 mg/kg q12h SC	aPTT Adjusted i.v. Therapy	(%)	
Indication	n (%)	n (%)		
All Randomized Unstable Angina and Non-Q-Wave MI Patients	1607 (100)	1564 (100)		
Timepoint[2] 48 Hours	99 (6.2)	115 (7.4)	1.2	
14 Days	266 (16.6)	309 (19.8)	3.2	
30 Days	318 (19.8)	364 (23.3)	3.5	

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

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

**Efficacy of Lovenox Injection in Unstable Angina and Non-Q-Wave Myocardial In
(Combined Endpoint of Death or Myocardial Infarction)**

	Dosing Regimen[1]			
	Lovenox	Heparin	Reduction	p
	1 mg/kg q12h SC	aPTT Adjusted i.v. Therapy	(%)	
Indication	n (%)	n (%)		
All Randomized Unstable Angina and Non-Q-Wave MI Patients	1607 (100)	1564 (100)		
Timepoint[2] 48 Hours	18 (1.1)	21 (1.3)	0.2	
14 Days	79 (4.9)	96 (6.1)	1.2	
30 Days	99 (6.2)	121 (7.7)	1.5	

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

INDICATIONS AND USAGE

- Lovenox Injection is indicated for the prevention of deep vein thrombosis, which may le
monary embolism:
  - in patients undergoing hip replacement surgery, during and following hospitalization;
  - in patients undergoing knee replacement surgery;
  - in patients undergoing abdominal surgery who are at risk for thromboembolic comp
  Patients at risk include patients who are over 40 years of age, obese, undergoin
  under general anesthesia lasting longer than 30 minutes or who have additional ri
  such as malignancy or a history of deep vein thrombosis or pulmonary embolism.
- Lovenox Injection is indicated for:
  - the **inpatient treatment** of acute deep vein thrombosis **with and without pu
  embolism,** when administered in conjunction with warfarin sodium;
  - the **outpatient treatment** of acute deep vein thrombosis **without pulmonary emboli**
  administered in conjunction with warfarin sodium.
- Lovenox Injection is indicated for the prevention of ischemic complications of unstab
and non-Q-wave myocardial infarction, when concurrently administered with aspirin.

See **DOSAGE AND ADMINISTRATION: Adult Dosage** for appropriate dosage regime

CONTRAINDICATIONS

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

Patients with known hypersensitivity to heparin or pork products should not be tre
Lovenox Injection.

WARNINGS

Lovenox Injection is not intended for intramuscular administration.

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

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

Hemorrhage: Lovenox Injection, like other anticoagulants, should be used with extrem
in conditions with increased risk of hemorrhage, such as bacterial endocarditis, con
acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disea
orrhagic stroke, or shortly after brain, spinal, or ophthalmological surgery, or in patien
concomitantly with platelet inhibitors.

**Cases of epidural or spinal hematomas have been reported with the associate
enoxaparin and spinal/epidural anesthesia or spinal puncture resulting in long-ter
manent paralysis. The risk of these events is higher with the use of post-o
indwelling epidural catheters or by the concomitant use of additional drugs
hemostasis such as NSAIDs (see boxed WARNING; ADVERSE REACTIONS,
Safety Surveillance; and PRECAUTIONS, Drug Interactions).**

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

Thrombocytopenia: Thrombocytopenia can occur with the administration of Lovenox I

Moderate thrombocytopenia (platelet counts between 100,000/mm^3 and 50,000/mm^3) oc
a rate of 1.3% in patients given Lovenox Injection, 1.2% in patients given heparin, an
patients given placebo in clinical trials.

Lovenox® (enoxaparin sodium) Injection

Platelet counts less than 50,000/mm³ occurred at a rate of 0.1% in patients given Lovenox Injection, in 0.2% of patients given heparin, and 0% of patients given placebo in the same trials.

Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm³, enoxaparin should be discontinued. Rare cases of thrombocytopenia with thrombosis have also been observed in clinical practice. The rate of incidence of this complication in usual medical practice is unknown.

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. Enoxaparin 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 <30mL/min).

If thromboembolic events occur despite enoxaparin prophylaxis, appropriate therapy should be initiated.

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of enoxaparin. Enoxaparin was not mutagenic in *in vitro* tests, including the Ames test, mouse lymphoma cell forward mutation test, and human lymphocyte chromosomal aberration test, and the *in vivo* rat bone marrow chromosomal aberration test. Enoxaparin was found to have no effect on fertility or reproductive performance of male and female rats at SC doses up to 20 mg/kg/day or 141 mg/m²/day. The maximum human dose in clinical trials was 2.0 mg/kg/day or 78 mg/m²/day (for an average body weight of 70 kg, height of 170 cm, and body surface area of 1.8 m²).

Pregnancy: *Teratogenic Effects:* Pregnancy Category B: Teratology studies have been conducted in pregnant rats and rabbits at SC doses of enoxaparin up to 30 mg/kg/day or 211 mg/m²/day and 410 mg/m²/day, respectively. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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

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

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

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.

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

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

[1] Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥2g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major. In the knee replacement surgery trials, intraocular hemorrhages were also considered major hemorrhages.
[2] Lovenox 30 mg every 12 hours SC initiated 12 to 24 hours after surgery and continued for up to 14 days after surgery.
[3] Lovenox 40 mg SC once a day initiated up to 12 hours prior to surgery and continued for up to 7 days after surgery.
[4] Lovenox 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 enoxaparin patients versus 1.8% of the placebo patients.

Major Bleeding Episodes in Abdominal and Colorectal Surgery[1]

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

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

Major Bleeding Episodes in Deep Vein Thrombosis and Pulmonary Embolism Treatment[1]

	Dosing Regimen[2]		
Indication	Lovenox 1.5 mg/kg q.d. SC	Lovenox 1.0 mg/kg q12h SC	Heparin aPTT Adjusted i.v. Therapy
Deep Vein Thrombosis and Pulmonary Embolism Treatment	n = 298 5 (2%)	n = 559 9 (2%)	n = 554 9 (2%)

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

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

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

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

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 enoxaparin group, are provided below.

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

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

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

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

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

[1] Excluding unrelated adverse events.

Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Patients[1] Undergoing Treatment for Deep Vein Thrombosis and Pulmonary Embolism

	Dosing Regimen					
	Lovenox 1.5 mg/kg q.d. SC n = 298		Lovenox 1.0 mg/kg q12h SC n = 559		Heparin aPTT Adjusted i.v. Therapy n = 544	
Adverse Event	Severe	Total	Severe	Total	Severe	Total
Injection Site Hemorrhage	0%	5%	0%	3%	<1%	<1%
Injection Site Pain	0%	2%	0%	2%	0%	0%
Hematuria	0%	2%	0%	<1%	<1%	2%

[1] Excluding unrelated adverse events.

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 enoxaparin therapy occurred at an incidence of ≤1%.

Non-major hemorrhagic episodes, primarily injection site ecchymoses and hematomas, were more frequently reported in patients treated with SC enoxaparin 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 enoxaparin group, are provided below (irrespective of relationship to drug therapy).

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

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

Ongoing Safety Surveillance: Since 1993, there have been more than 60 reports of epidural or spinal hematoma formation with concurrent use of enoxaparin 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 reports include: 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, and thrombocytosis. 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**).

Adult Dosage: *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. Up to 14 days administration (average duration 7 to 10 days) of Lovenox Injection 30 mg every 12 hours has been well tolerated in controlled clinical trials. For hip replacement surgery, a dose of **40 mg once a day** SC, given initially 12 (±3) hours prior to surgery, may be considered. Following the initial phase of thromboprophylaxis in hip replacement surgery patients (Lovenox Injection 30 mg every 12 hours or 40 mg once a day), continued prophylaxis with Lovenox Injection 40 mg once a day administered by SC injection for 3 weeks is recommended.

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 adminis-

tration is 7 to 10 days; up to 12 days administration has been well tolerated in clinical trials.

Treatment of Deep Vein Thrombosis and 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 **1.0 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 **1.0 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 Lovenox Injection administration has been well tolerated in controlled clinical trials.

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. The usual duration of treatment is 2 to 8 days. 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.

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

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

Lovenox Injection is administered by SC injection. It must not be administered by intramuscular injection.

Subcutaneous Injection Technique: Patients should be lying down and Lovenox Injection administered by deep SC injection. To avoid the loss of drug when using the 30 and 40 mg prefilled syringes, do not expel the air bubble from the syringe before the injection. Administration should be alternated between the left and right anterolateral and left and right posterolateral abdominal wall. The whole length of the needle should be introduced into a skin fold held between the thumb and forefinger; the skin fold should be held throughout the injection. To minimize bruising, do not rub the injection site after completion of the injection. An automatic injector, Lovenox EasyInjector™, is available for patients to administer Lovenox Injection packaged in 30 mg and 40 mg prefilled syringes. Please see directions accompanying the Lovenox EasyInjector™ automatic injection device.

HOW SUPPLIED

Lovenox® (enoxaparin sodium) Injection is available in:

Dosage Unit	Strength[1]	Package Size (per carton)	Anti-Xa Activity[2]	NDC # 0075-
Ampules	30 mg / 0.3 mL	10 ampules	3000 IU	0624-03
Prefilled Syringes[3]	30 mg / 0.3 mL	10 syringes	3000 IU	0624-30
	40 mg / 0.4 mL	10 syringes	4000 IU	0620-40
Graduated Prefilled Syringes[3]	60 mg / 0.6 mL	10 syringes	6000 IU	0621-60
	80 mg / 0.8 mL	10 syringes	8000 IU	0622-80
	100 mg / 1.0 mL	10 syringes	10 000 IU	0623-00

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

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

[3] Each Lovenox syringe is affixed with a 27 gauge x 1/2 inch needle.

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

Keep out of the reach of children.

Lovenox Injection prefilled and graduated prefilled syringes manufactured in France.
Lovenox Injection ampules manufactured in England.

RHÔNE-POULENC RORER PHARMACEUTICALS INC.
COLLEGEVILLE, PA 19426

IN-2828E

Rev. 6/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-021

LABELING REVIEWS

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-164/S-021
NDA 20-164/S-031

Name of Drug: Lovenox® (enoxaparin sodium) Injection

Sponsor: Rhone-Poulenc Rorer Pharmaceuticals Inc.

Material Reviewed

Submission Date(s): September 8, 1999 (S-021), Final Printed Labeling
September 8, 1999 (S-031), Final Printed Labeling

Receipt Date(s): September 9, 1999 (S-021)
September 9, 1999 (S-031)

Background and Summary Description:

Supplement -021, submitted September 8, 1999, approved April 20, 1999, provides for the addition of the following information in the ADVERSE REACTIONS section, the "Ongoing Safety Surveillance" subsection, of the package insert:

> "Very rare cases of hyperlipidemia have been reported, with one case of hyperlipidemia, reported in a diabetic pregnant woman; causality has not been determined."

The final printed labeling (FPL), submitted September 8, 1999 to Supplement –021, was in response to the April 20, 1999 approval letter.

Supplement –031, submitted September 8, 1999 under 21 CFR 314.70(c), "Special Supplement—Changes Being Effected" provides FPL, with the following revisions:

1. In the DOSAGE AND ADMINISTRATION section:

   a. The first sentence of the first paragraph reads:

      "All patients should be evaluated for a bleeding disorder before administration of Lovenox Injection, unless the medication is needed urgently."

   b. The second sentence of the "Subcutaneous Injection Technique:" subsection reads:

      "To avoid the loss of drug when using the 30 and 40 mg prefilled syringes..."

2. In the ADVERSE REACTIONS section, the "Ongoing Safety Surveillance" subsection, the information approved in Supplement –021 regarding hyperlipidemia was provided.

Review

The final printed labeling (FPL) for the package inserts submitted for Supplement –021 and –031 are identical, incorporating the revisions provided for in both supplements. The package inserts, identified as "IN-2828E Rev. 6/99 508539BC"(Maisons Alfort) and "IN-1107T Rev. 6/99" (Dagenham), were compared to the package inserts approved December 31, 1998 in Supplement –015, identified as "IN-1107S Rev. 12/98 508539B" and "IN-2828D-Rev. 12/98", respectively; the revisions requested in the April 20, 1999 approval letter for Supplement –021; and the changes provided for in CBE Supplement –031. Deletions are shown as ~~strikeouts~~ and additions shown as double underlines.

1. In the ADVERSE REACTIONS section, the "Ongoing Safety Surveillance" subsection, the following sentence has been added:

   "Very rare cases of hyperlipidemia have been reported, with one case of hyperlipidemia, reported in a diabetic pregnant woman; causality has not been determined."

Comment: This revision, requested in the Agency's April 20, 1999 approval letter for S-021, is acceptable.

2. In the DOSAGE AND ADMINISTRATION section:

   a. The first sentence of the first paragraph has been revised as follows:

      "All patients should be evaluated for a bleeding disorder before ~~prophylactic~~ administration of Lovenox Injection, unless the medication is needed urgently."

   b. The second sentence of the "Subcutaneous Injection Technique:" subsection has been revised as follows:

      "To avoid the loss of drug when using the 30 and 40 mg prefilled syringes, do not expel the air bubbles from the syringe before the injection."

Comment: These two changes, provided for in S-031, were found acceptable in the medical officer review dated September 13, 1999.

3. The phrase "Rx only" has been moved from after the "HOW SUPPLIED" section to the right side of the title sections.

4. The copyright statement has been revised as follows: "©19989"

5. For the Maisons Alfort package insert,

   a. The identifier at the top of the package insert has been revised from:

      "IN-1107S Rev. 12/98 508539B"

      to:

      "IN-1107T Rev. 6/99 508539C"

   b. The identifier at the end of the package insert has been revised from:

      "IN-1107S Rev. 12/98"

      to:

      "IN-1107T Rev. 6/99"

6. For the Dagenham package insert, the identifier at the top and at the end of the package insert has been revised from:

   "IN-2828D Rev. 12/98"

   to:

   "IN-2828E Rev. 6/99"

Comment: These are appropriate editorial revisions.

Conclusions

The identical FPL submitted for Supplement –021 and Supplement –031 are acceptable. The FPL should be acknowledged and retained for Supplement –021 and approved for Supplement -031.

The currently approved package insert is now considered:

Maisons Alfort: "IN-1107T Rev. 6/99"
Dagenham: "IN-2828E Rev. 6/99"

Regulatory Health Project Manager

Director

cc:
Original NDA 20-164/S-021, S-031
HFD-180/Div. Files
HFD-180/A.Kacuba
HFD-180/K.Oliver

Draft: A.Kacuba/September 30, 1999
R/d Initials: K.Oliver/October 4, 1999
Final: AK/October 24, 1999
Filename: c:\wpfiles\20164-S-021-FA&S-031-CBE-lab-review.doc
CSO REVIEW

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-021

MEDICAL REVIEW

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	20-164/SLR021
Drug name:	Lovenox®
Generic name:	Enoxaparin sodium
Other names:	PK 10169 Enoxaparine Pharmuka 10169
Chemical name:	Alkaline degradation product of porcine intestinal mucosa 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
Sponsor:	Rhône-Poulenc Rorer Pharmaceuticals, Inc.
Pharmacologic Category:	Low Molecular Weight Heparin Anticoagulant Antithrombotic
(Proposed) Indications:	For the prevention of deep veinthrombosis which may lead to pulmonary embolism following hip or knee replacement surgery
Dosage Form(s) and Route(s) of Administration:	40 mg, subcutaneous injection
NDA Drug Classification:	
Important Related Drugs:	Dalteparin (Fragmin®) Ardeparin (Normiflo®) Danaparoid (Orgaran®)
Date of Submission: Date received by HFD-180: Date of Review:	1/12/99 1/13/99 4/1/99
Medical Reviewer:	John William Schmeling, M.D., Ph.D.

1. TABLE OF CONTENTS

2. MATERIAL REVIEWED

A single-volume labeling supplement was reviewed.

3. RELATED REVIEW

Medical officers review of NDA 20-164 dated August 24, 1998.

4. BACKGROUND

The Agency, on April 14, 1998, requested that the sponsor review reports regarding enoxaparin and hyperlipidemia, especially in pregnancy, and to determine whether there should be a label revision for Lovenox® regarding hyperlipidemia in pregnancy.

The sponsor subsequently, on July 16, 1998, submitted a special supplement, and indicated that no labeling revision was needed.

A medical officer's review, dated August 24, 1998, of this supplement, disagreed and recommended that the post-marketing label warnings should include a description of the case reports of hyperlipidemia in association with Lovenox®. Further, it was recommended that the sponsor should state on the label that one of the patients in whom marked hyperlipidemia occurred was pregnant.

5. LABELING REVIEW

1.1 Proposed addition

Proposed addition to ADVERSE REACTIONS, Ongoing Safety Surveillance section:

> Other reports include: local reactions at the injection site (i.e., skin necrosis, nodules, inflammation, oozing), systemic allergic reactions (i.e., pruritus, urticaria), vesiculobullous rash, purpura, and thrombocytosis. Very rare cases of hyperlipidemia have been reported, with one case of hypertriglyceridemia reported in a diabetic pregnant woman; causality has not been determined.

1.2 Comment

The diabetic pregnant woman developed hyperlipidemia, including hypercholesterolemia and hypertriglyceridemia .

The sentence should read:

> Very rare cases of hyperlipidemia have been reported, with one case of ~~hypertriglyceridemia~~ hyperlipidemia, with marked hypertriglyceridemia, reported in a diabetic pregnant woman; causality has not been determined.

John W. Schmeling, M.D.,
Ph.D.

cc:
NDA 20-164/SLR021
HFD-180
HFD-180/LTalarico
HFD-180/JSchmeling
HFD-181/PM
HFD-180/JChoudary
HFD-180/EDuffy
f/t 4/9/99 jgw
N/20164904.JWS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-021

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 20-164/S-021

Rhone-Poulenc Rorer Phamaceuticals Inc.
Attention: Mr. Robert W. Babilon
P.O. Box 5096
500 Arcola Road
Collegeville, PA 19426-0800

Dear Mr. Babilon:

We acknowledge receipt of your labeling supplemental application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

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

NDA Number: 20-164

Supplement Number: S-021

Date of Supplement: January 12, 1999

Date of Receipt: January 13, 1999

This supplement proposes the following change(s): the addition of the following sentence to the ADVERSE REACTIONS section, the "Ongoing Safety Surveillance" subsection: "Very rare cases of hyperlipidemia have been reported, with one case of hypertriglyceridemia reported in a diabetic pregnant woman; causality has not been determined."

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 14, 1999 in accordance with 21 CFR 314.101(a).

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

U.S. Postal/Courier/Overnight Mail:

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

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

Sincerely,

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

cc:
Archival NDA 20-164/S-021
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/L.Talarico
HFD-180/J.Schmeling
DISTRICT OFFICE

Drafted by: KO/January 22, 1999
final: KO/01/22/99
filename: c:\mydocuments\NDA20164-S-021-01-22-99-ack

SUPPLEMENT ACKNOWLEDGEMENT (AC)

NDA 20-164/S-021

Rhone-Poulenc Rorer Pharmaceuticals Inc.
Attention: Edmond Roland, M.D.
P.O. Box 5096
500 Arcola Road
Collegeville, PA 19426-0800

Dear Dr. Roland:

We acknowledge receipt of your September 8, 1999 submission containing final printed labeling in response to April 20, 1999 letter approving your supplemental new drug application for Lovenox® (enoxaparin sodium) Injection.

We also acknowledge Supplement –031, submitted September 8, 1999 under 21 CFR 314.70(c) and approved October 5, 1999, that provided for changes in the DOSAGE AND ADMINISTRATION section of the package insert.

We have reviewed the labeling that you submitted in accordance with our April 20, 1999 approval letter and the changes approved October 5, 1999 in Supplement –031, and we find it acceptable.

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

Sincerely yours,

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

cc:
Archival NDA 20-164/S-021
HFD-180/division file
HFD-180/K.Oliver
HF-2/MedWatch (with labeling)
HFD-094/DDMS (with labeling)
HFD-103/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/OPDRA (with labeling)
DISTRICT OFFICE

Drafted by: A.Kacuba/September 30, 1999
Initialed by: K.Oliver/October 4, 1999
Final: AK/October 4, 1999
Filename: c:wpfiles\20164-S-021-AR.doc

ACKNOWLEDGE AND RETAIN (AR)