CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-164/S-009

Name: Lovenox® (Enoxaparin Sodium) Injection

Sponsor: Rhone-Poulenc Rorer Pharmaceuticals

Approval Date: June 26, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-009

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-009

APPROVAL LETTER

37.1

NDA 20-164/S-009

Rhone-Poulenc Rorer Pharmaceuticals Inc.
Attention: Thomas E. Donnelly, Jr., Ph.D.
500 Arcola Road
Collegeville, PA 19426

JUN 26 1996

Dear Dr. Donnelly:

Please refer to your December 17, 1995 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox (enoxaparin sodium) Injection.

We acknowledge receipt of your amendments dated June 5, 11, 12, and 14, 1996.

The supplemental application provides for a change in the approved pre-filled syringe, replacing the 26 gauge needle with a 27 gauge needle. During the review process, it was determined that the supplemental application also included a request for a new needle shield manufacturer, ———, and that new needle cover supplier was included in the supplemental request. This additional information was reviewed as provided in the supplement.

We have completed the review of this supplemental application, including the submitted draft labeling, 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 draft labeling in the submission dated December 27, 1995. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft package insert labeling submitted on December 27, 1995, with the following revisions:

1. In the WARNINGS section, insert the closing parentheses in the phrase (platelet counts between 100,000/mm^3).

2. In the DOSAGE AND ADMINISTRATION section, the "Adult Dosage:" subsection, insert the following words at the beginning of the first sentence: "In patients undergoing hip or knee replacement surgery, the recommended dose of Lovenox".

Please submit sixteen 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 "FINAL PRINTED LABELING" for approved supplemental NDA 20-164/S-009. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material 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 material and the package insert directly to:

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

Karen Oliver
Regulatory Health Project Manager
(301) 443-0487

Sincerely yours,

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-164/S-009
HFD-180/Div. files
HFD-180/CSO/K.Oliver
HFD-180/S.Fredd
HFD-180/E.Duffy
HFD-180/J.Sieczkowski
HFD-180/L.Talarico
HFD-103/P.Botstein
HFD-820/Yuan Yuan Chiu
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-80/DDIR (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613 (with labeling)
HFD-638/generics (with labeling)
HFD-735/(with labeling) - for all NDAs and supplements for adverse reaction changes.
HFD-560/D.Bowen (with labeling - for OTC Drug Products Only)

drafted: KO/June 20, 1996
r/d Initials: J.Sieczkowski 06/24/96
r/d Initials: E.Duffy 06/24/96
r/d Initials: S.Fredd 06/25/96 06/25/96
final: KO/06/25/96/c:\wpwin\karenfil\nda\20164606.3ko

APPROVAL SF 6/25/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-009

LABELING

Lovenox®

JAN 2 9 1997

(enoxaparin sodium) Injection

IN-1107L

APPROVED Rev. 8/96

Lovenox® (enoxaparin sodium) Injection

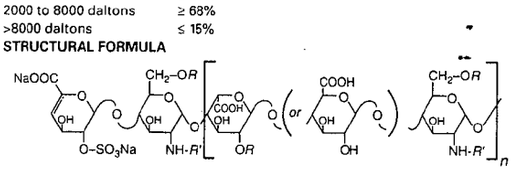
DESCRIPTION

Enoxaparin sodium is a sterile, low molecular weight heparin for injection. Each syringe contains 30 mg enoxaparin sodium in 0.3 mL Water for Injection. The approximate anti-Factor Xa activity per syringe is 3000 IU (with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard). Nitrogen is used in the headspace to inhibit oxidation. The pH of the injection is 5.5-7.5. The solution is preservative-free and intended for use only as a single-dose injection.

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. 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 man enoxaparin is characterized by a higher ratio of anti-Factor Xa to anti-Factor IIa activity (3.35 ± 0.89) than unfractionated heparin (1.22 ± 0.13). Following the administration of a single subcutaneous dose of up to 90 mg of enoxaparin to healthy subjects, no appreciable change was observed in fibrinogen level and other parameters of fibrinolysis. At the recommended doses, single injections of enoxaparin do not significantly influence platelet aggregation or affect global clotting tests (*i.e.*, prothrombin time [PT] or activated partial thromboplastin time [APTT]).

Pharmacodynamics

Maximum anti-Factor Xa and antithrombin (anti-Factor IIa) activities occur 3 to 5 hours after subcutaneous 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 doses, respectively. Mean absolute bioavailability of enoxaparin 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 i.v. dosing, the total body clearance of enoxaparin is 25 mL/min. Elimination half-life based on anti-Factor Xa activity was about 4.5 hours after subcutaneous administration. Following a 40 mg dose significant anti-Factor Xa activity persists in plasma for about 12 hours. There appears to be no appreciable increase in anti-Factor Xa activity after dosing for 3 days in young healthy subjects. Clearance and C_{max} derived from anti-Factor Xa values following single and multiple s.c. dosing in elderly subjects and subjects with renal failure were close to those observed in normal subjects. An increase of 25% in the area under anti-Factor Xa activity versus time curve was observed following once daily dosing in healthy elderly subjects for 10 days. The kinetics of anti-Factor Xa activity in anuric patients undergoing dialysis are similar to those in historical control normal subjects following i.v. dosing.

The decline of anti-Factor Xa activity with time was parallel to the decay curve of plasma total radioactivity (^{99m}Tc) in healthy volunteers. Following intravenous dosing of enoxaparin labeled with the gamma-emitter, ^{99m}Tc, 40% of radioactivity and 8-20% of anti-Factor Xa activity were recovered in urine in 24 hours.

CLINICAL TRIALS

Lovenox has been shown to prevent postoperative deep vein thrombosis (DVT) following hip or knee replacement surgery.

In a double-blind study, Lovenox 30 mg q12h sc was compared to placebo in hip replacement patients. Treatment was initiated within 12-24 hours post-surgery and was continued for 10-14 days post-operatively.

	Treatment Group	
Treatment Group	Lovenox	Placebo
Dosing Regimen	30 mg q12h	q12h
	n (%)	n (%)
All Treated Patients	50 (100%)	50 (100%)
Treatment Failures		
Total DVT (%)	5 (10%)*	23 (46%)
Proximal DVT (%)	1 (2%)**	11 (22%)

*p value versus placebo = 0.0002
**p value versus placebo = 0.0134

A double-blind, multicenter study compared three dosing regimens of Lovenox in hip replacement patients. Treatment was initiated within two days post-surgery and was continued for 7-11 days post-operatively.

	Treatment Group Lovenox		
Dose	10 mg QD	30 mg q12h	40 mg QD
	n (%)	n (%)	n (%)
All Treated Patients	161 (100%)	208 (100%)	199 (100%)
Treatment Failures			
Total DVT (%)	40 (25%)	22 (11%)*	27 (14%)**
Proximal DVT (%)	17 (11%)	8 (4%)	9 (5%)

*p value versus Lovenox 10 mg QD = 0.0008
**p value versus Lovenox 10 mg QD = 0.0168

There was no significant difference between the 30 mg BID and 40 mg QD regimens.

In a double-blind study with 99 patients undergoing knee replacement surgery, Lovenox 30 mg q12h sc was compared to placebo. Treatment was initiated within 12-24 hours post-operatively and was continued up to 15 days post-operatively. The incidence of post-operative proximal and total deep vein thrombosis was significantly lower for enoxaparin compared to placebo.

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

*p value versus placebo = 0.0001
CI = Confidence Interval
**p value versus placebo = 0.013
CL = Confidence Limit

Additionally, in an open-label, parallel group, randomized clinical study in patients undergoing elective knee replacement surgery, Lovenox 30 mg q12h sc was compared to unfractionated heparin 5000 U q8h sc. Treatment was initiated post-operatively and continued up to 14 days. The incidence of deep vein thrombosis was significantly lower for enoxaparin compared to heparin.

Lovenox®

(enoxaparin sodium) Injection

JAN 2 9 1997

APPROVED Rev. 8/96

IN-1107L

Lovenox® (enoxaparin sodium) Injection

DESCRIPTION

Enoxaparin sodium is a sterile, low molecular weight heparin for injection. Each syringe contains 30 mg enoxaparin sodium in 0.3 mL Water for Injection. The approximate anti-Factor Xa activity per syringe is 3000 IU (with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard). Nitrogen is used in the headspace to inhibit oxidation. The pH of the injection is 5.5-7.5. The solution is preservative-free and intended for use only as a single-dose injection.

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. The molecular weight distribution is:

<2000 daltons	≤ 20%
2000 to 8000 daltons	≥ 68%
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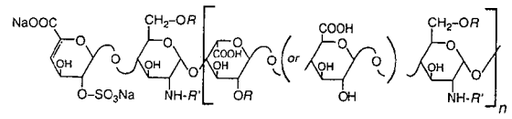
STRUCTURAL FORMULA



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 man enoxaparin is characterized by a higher ratio of anti-Factor Xa to anti-Factor IIa activity (3.35 ± 0.89) than unfractionated heparin (1.22 ± 0.13). Following the administration of a single subcutaneous dose of up to 90 mg of enoxaparin to healthy subjects, no appreciable change was observed in fibrinogen level and other parameters of fibrinolysis. At the recommended doses, single injections of enoxaparin do not significantly influence platelet aggregation or affect global clotting tests (*i.e.*, prothrombin time [PT] or activated partial thromboplastin time [APTT]).

Pharmacodynamics

Maximum anti-Factor Xa and antithrombin (anti-Factor IIa) activities occur 3 to 5 hours after subcutaneous 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 doses, respectively. Mean absolute bioavailability of enoxaparin 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 i.v. dosing, the total body clearance of enoxaparin is 25 mL/min. Elimination half-life based on anti-Factor Xa activity was about 4.5 hours after subcutaneous administration. Following a 40 mg dose significant anti-Factor Xa activity persists in plasma for about 12 hours. There appears to be no appreciable increase in anti-Factor Xa activity after dosing for 3 days in young healthy subjects. Clearance and C_{max} derived from anti-Factor Xa values following single and multiple s.c. dosing in elderly subjects and subjects with renal failure were close to those observed in normal subjects. An increase of 25% in the area under anti-Factor Xa activity versus time curve was observed following once daily dosing in healthy elderly subjects for 10 days. The kinetics of anti-Factor Xa activity in anuric patients undergoing dialysis are similar to those in historical control normal subjects following i.v. dosing.

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Treatment Group	Treatment Group	
Dosing Regimen	Lovenox 30 mg q12h n (%)	Placeb q12h n (%)
All Treated Patients	50 (100%)	50 (100
Treatment Failures		
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Treatment Group	Treatment (Lovenox
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Lovenox®
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APPROVED Rev. 8/96

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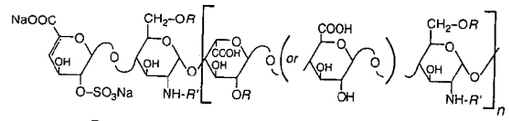
<2000 daltons	≤ 20%
2000 to 8000 daltons	≥ 68%
>8000 daltons	≤ 15%

STRUCTURAL FORMULA



R	R'	n
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CLINICAL PHARMACOLOGY

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Treatment Group	Treatment Group: Lovenox 30 mg q12h n (%)	Placeb q12h n (%)
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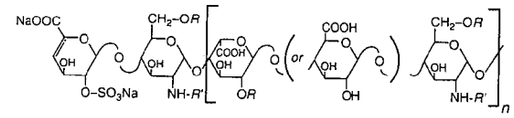

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Lovenox® (enoxaparin sodium) Injection

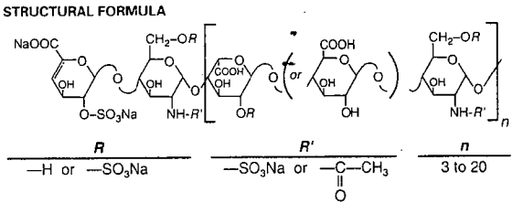
DESCRIPTION

Enoxaparin sodium is a sterile, low molecular weight heparin for injection. Each syringe contains 30 mg enoxaparin sodium in 0.3 mL Water for Injection. The approximate anti-Factor Xa activity per syringe is 3000 IU (with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard). Nitrogen is used in the headspace to inhibit oxidation. The pH of the injection is 5.5-7.5. The solution is preservative-free and intended for use only as a single-dose injection.

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. 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 man enoxaparin is characterized by a higher ratio of anti-Factor Xa to anti-Factor IIa activity (3.35 ± 0.89) than unfractionated heparin (1.22 ± 0.13). Following the administration of a single subcutaneous dose of up to 90 mg of enoxaparin to healthy subjects, no appreciable change was observed in fibrinogen level and other parameters of fibrinolysis. At the recommended doses, single injections of enoxaparin do not significantly influence platelet aggregation or affect global clotting tests (*i.e.*, prothrombin time [PT] or activated partial thromboplastin time [APTT]).

Pharmacodynamics

Maximum anti-Factor Xa and antithrombin (anti-Factor IIa) activities occur 3 to 5 hours after subcutaneous 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 doses, respectively. Mean absolute bioavailability of enoxaparin 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 i.v. dosing, the total body clearance of enoxaparin is 25 mL/min. Elimination half-life based on anti-Factor Xa activity was about 4.5 hours after subcutaneous administration. Following a 40 mg dose significant anti-Factor Xa activity persists in plasma for about 12 hours. There appears to be no appreciable increase in anti-Factor Xa activity after dosing for 3 days in young healthy subjects. Clearance and C_{max} derived from anti-Factor Xa values following single and multiple s.c. dosing in elderly subjects and subjects with renal failure were close to those observed in normal subjects. An increase of 25% in the area under anti-Factor Xa activity versus time curve was observed following once daily dosing in healthy elderly subjects for 10 days. The kinetics of anti-Factor Xa activity in anuric patients undergoing dialysis are similar to those in historical control normal subjects following i.v. dosing.

The decline of anti-Factor Xa activity with time was parallel to the decay curve of plasm tivity (^{99m}Tc) in healthy volunteers. Following intravenous dosing of enoxaparin l gamma-emitter, ^{99m}Tc, 40% of radioactivity and 8-20% of anti-Factor Xa activity we urine in 24 hours.

CLINICAL TRIALS

Lovenox has been shown to prevent postoperative deep vein thrombosis (DVT) follov replacement surgery.

In a double-blind study, Lovenox 30 mg q12h sc was compared to placebo in hip replac Treatment was initiated within 12-24 hours post-surgery and was continued for 10-14 c tively.

	Treatment Group	
Treatment Group	Lovenox	Placebo
Dosing Regimen	30 mg q12h	q12h
	n (%)	n (%)
All Treated Patients	50 (100%)	50 (100%)
Treatment Failures		
Total DVT (%)	5 (10%)*	23 (46%)
Proximal DVT (%)	1 (2%)**	11 (22%)

*p value versus placebo = 0.0002
**p value versus placebo = 0.0134

A double-blind, multicenter study compared three dosing regimens of Lovenox in h patients. Treatment was initiated within two days post-surgery and was continued for operatively.

	Treatment Group Lovenox		
Dose	10 mg QD	30 mg q12h	40
	n (%)	n (%)	r
All Treated Patients	161 (100%)	208 (100%)	199
Treatment Failures			
Total DVT (%)	40 (25%)	22 (11%)*	27 (
Proximal DVT (%)	17 (11%)	8 (4%)	9

*p value versus Lovenox 10 mg QD = 0.0008
**p value versus Lovenox 10 mg QD = 0.0168
There was no significant difference between the 30 mg BID and 40 mg QD regimens.

In a double-blind study with 99 patients undergoing knee replacement surgery, l q12h sc was compared to placebo. Treatment was initiated within 12-24 hours post- was continued up to 15 days post-operatively. The incidence of post-operative proxima vein thrombosis was significantly lower for enoxaparin compared to placebo.

	Treatment Group	
Treatment Group	Lovenox	Placebo
Dosing Regimen	30 mg q12h	q12h
	n (%)	n (%)
All Knee Replacement Patients	47 (100%)	52 (100%)
Treatment Failures		
Total DVT (%)	5 (11%)* (95% CI: 1 - 21%)	32 (62%) (95% CI: 4
Proximal DVT (%)	0 (0%)** (95% Upper CL: 5%)	7 (13%) (95% CI: 3

*p value versus placebo = 0.0001
CI = Confidence Interval
**p value versus placebo = 0.013
CL = Confidence Limit

Additionally, in an open-label, parallel group, randomized clinical study in patients und knee replacement surgery, Lovenox 30 mg q12h sc was compared to unfractionated q8h sc. Treatment was initiated post-operatively and continued up to 14 days. The in vein thrombosis was significantly lower for enoxaparin compared to heparin.

)X®

sodium) Injection

JAN 29 1997

APPROVED Rev. 8/96

) Injection

le, low molecular weight heparin for injection. Each syringe contains 0.3 mL Water for Injection. The approximate anti-Factor Xa activity per rence to the W.H.O. First International Low Molecular Weight Heparin ı is used in the headspace to inhibit oxidation. The pH of the injection is /ative-free and intended for use only as a single-dose injection.

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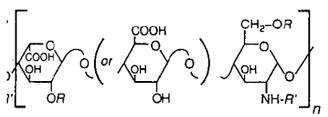
0%
8%
5%



R'	n
$-SO_3Na$ or $-C(=O)-CH_3$	3 to 20

weight heparin which has antithrombotic properties. In man enoxaparin atio of anti-Factor Xa to anti-Factor IIa activity (3.35 ± 0.89) than unfrac- Following the administration of a single subcutaneous dose of up to y subjects, no appreciable change was observed in fibrinogen level and is. At the recommended doses, single injections of enoxaparin do not aggregation or affect global clotting tests (*i.e.*, prothrombin time [PT] or in time [APTT]).

antithrombin (anti-Factor IIa) activities occur 3 to 5 hours after subcuta- ı. Mean peak anti-Factor Xa activity was 0.16 IU/mL (1.58 µg/mL) and the 20 mg and the 40 mg clinically tested doses, respectively. Mean oxaparin based on anti-Factor Xa activity is 92% in healthy volunteers. anti-Factor Xa activity is about 6 L. Following i.v. dosing, the total body mL/min. Elimination half-life based on anti-Factor Xa activity was about ıdministration. Following a 40 mg dose significant anti-Factor Xa activity 2 hours. There appears to be no appreciable increase in anti-Factor Xa in young healthy subjects. Clearance and C_{max} derived from anti-Factor d multiple s.c. dosing in elderly subjects and subjects with renal failure in normal subjects. An increase of 25% in the area under anti-Factor Xa s observed following once daily dosing in healthy elderly subjects for actor Xa activity in anuric patients undergoing dialysis are similar to those in historical control normal subjects following i.v. dosing.

The decline of anti-Factor Xa activity with time was parallel to the decay curve of plasma total radioactivity (^{99m}Tc) in healthy volunteers. Following intravenous dosing of enoxaparin labeled with the gamma-emitter, ^{99m}Tc, 40% of radioactivity and 8-20% of anti-Factor Xa activity were recovered in urine in 24 hours.

CLINICAL TRIALS

Lovenox has been shown to prevent postoperative deep vein thrombosis (DVT) following hip or knee replacement surgery.

In a double-blind study, Lovenox 30 mg q12h sc was compared to placebo in hip replacement patients. Treatment was initiated within 12-24 hours post-surgery and was continued for 10-14 days post-operatively.

	Treatment Group	
Treatment Group	**Lovenox**	**Placebo**
Dosing Regimen	30 mg q12h	q12h
	n (%)	n (%)
All Treated Patients	50 (100%)	50 (100%)
Treatment Failures		
Total DVT (%)	5 (10%)*	23 (46%)
Proximal DVT (%)	1 (2%)**	11 (22%)

*p value versus placebo = 0.0002
**p value versus placebo = 0.0134

A double-blind, multicenter study compared three dosing regimens of Lovenox in hip replacement patients. Treatment was initiated within two days post-surgery and was continued for 7-11 days post-operatively.

	Treatment Group Lovenox		
Dose	**10 mg QD**	**30 mg q12h**	**40 mg QD**
	n (%)	n (%)	n (%)
All Treated Patients	161 (100%)	208 (100%)	199 (100%)
Treatment Failures			
Total DVT (%)	40 (25%)	22 (11%)*	27 (14%)**
Proximal DVT (%)	17 (11%)	8 (4%)	9 (5%)

*p value versus Lovenox 10 mg QD = 0.0008
**p value versus Lovenox 10 mg QD = 0.0168

There was no significant difference between the 30 mg BID and 40 mg QD regimens.

In a double-blind study with 99 patients undergoing knee replacement surgery, Lovenox 30 mg q12h sc was compared to placebo. Treatment was initiated within 12-24 hours post-operatively and was continued up to 15 days post-operatively. The incidence of post-operative proximal and total deep vein thrombosis was significantly lower for enoxaparin compared to placebo.

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

*p value versus placebo = 0.0001
CI = Confidence Interval
**p value versus placebo = 0.013
CL = Confidence Limit

Additionally, in an open-label, parallel group, randomized clinical study in patients undergoing elective knee replacement surgery, Lovenox 30 mg q12h sc was compared to unfractionated heparin 5000 U q8h sc. Treatment was initiated post-operatively and continued up to 14 days. The incidence of deep vein thrombosis was significantly lower for enoxaparin compared to heparin.

INDICATIONS AND USAGE

Lovenox Injection is indicated for prevention of deep vein thrombosis, which may lead to pulmonary embolism, following hip or knee replacement surgery.

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 cannot be used interchangeably (unit for unit) with unfractionated heparin or other low molecular weight heparins as they differ in their manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units and dosage. Special attention and compliance with the instructions for use specific to each proprietary medicinal product is therefore required.

Lovenox 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.

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.

Neuraxial Anesthesia and Post-operative Indwelling Epidural Catheter Use:

Spinal/Epidural Anesthesia: As with other anticoagulants, there have been rare cases of neuraxial hematomas reported with the concurrent use of enoxaparin and spinal/epidural anesthesia resulting in long-term or permanent paralysis. The risk of these rare events may be higher with the use of post-operative indwelling epidural catheters.

Thrombocytopenia:

Thrombocytopenia can occur with the administration of Lovenox. Moderate thrombocytopenia (platelet counts between 100,000/mm^3 and 50,000/mm^3) occurred at a rate of 1.9% in patients given Lovenox, 2.0% in patients given heparin, and 1.7% in patients given placebo following hip or knee replacement surgery in clinical trials.

Platelet counts less than 50,000/mm^3 occurred at a rate of 0.1% in patients given Lovenox, 0.5% in patients given heparin, and 0% in 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 at present.

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 and hemorrhage. Elderly patients and patients with renal insufficiency may show delayed elimination of enoxaparin. Enoxaparin should be used with care in these patients.

If thromboembolic events occur despite enoxaparin prophylaxis, Lovenox should be discontinued and appropriate therapy 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.

Drug Interactions:

It is recommended that agents which affect hemostasis be discontinued prior to Lovenox therapy as they may enhance the risk of hemorrhage. These agents include medications such as: oral anticoagulants, and/or platelet inhibitors including acetylsalicylic acid, salicylates, NSAIDs (including ketorolac

romethamine), dipyridamole, or sulfinpyrazone. If co-administration cannot be avoided and their use s essential, conduct close clinical and laboratory monitoring (see Laboratory Tests, PRECAUTIONS).

)rug/Laboratory Test Interactions:

:levations of Serum Aminotransferases

\symptomatic increases in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels ıreater than three times the upper limit of normal of the laboratory reference range have been eported in 2 of 10 normal subjects and in up to 4% of patients during treatment with Lovenox® ıjection. Similar significant increases in aminotransferase levels have also been observed in patients ınd normal volunteers treated with heparin and other low molecular weight heparins. Such eleva- ions are fully reversible and are rarely associated with increases in bilirubin. Since aminotransferase leterminations are important in the differential diagnosis of myocardial infarction, liver disease and ıulmonary emboli, elevations that might be caused by drugs like Lovenox should be interpreted with :aution.

:arcinogenesis, Mutagenesis, Impairment of Fertility:

Vo long-term studies in animals have been performed to evaluate carcinogenic potential of enoxa- ıarin. Enoxaparin was not mutagenic in *in vitro* tests, including the Ames test, mouse lymphoma cell orward mutation test, and human lymphocyte chromosomal aberration test and the *in vivo* rat bone narrow chromosomal aberration test. Enoxaparin was found to have no effect on fertility or repro- luctive performance of male and female rats at subcutaneous doses up to 20 mg/kg/day or 141 mg/m^2/day. The maximum received human dose in clinical trials was 1.5 mg/kg/day or 48.4 mg/m^2/day.

'regnancy: Teratogenic Effects

'regnancy category B: Teratology studies have been conducted in rats and rabbits at subcutaneous doses of enoxaparin up to 30 mg/kg/day or 211 mg/m^2/day and 410 mg/m^2/day, respectively. The naximum received human dose in clinical trials was 1.5 mg/kg/day or 48.4 mg/m^2/day. There was no ıvidence of teratogenic effects or fetotoxicity due to enoxaparin. There are, however, no adequate ınd well-controlled studies in pregnant women. Because animal reproduction studies are not always ıredictive 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 while using enoxaparin; ıone of the cases have been definitively associated with the use of the drug. In one case, placental ıemorrhage 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 ıpprised of the potential hazard to the fetus.

Nursing Mothers:

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

'ediatric Use:

Safety and effectiveness of enoxaparin in pediatric patients has not been established.

ADVERSE REACTIONS

Hemorrhage:

The incidence of hemorrhagic complications during Lovenox injection treatment has been low.

The following rates of major bleeding events have been reported during clinical trials with Lovenox njection and heparin and placebo in patients undergoing hip or knee replacement surgery.

Major Bleeding Episodes*

	Enoxaparin 30 mg q12h	Heparin 15000 U/24h	Placebo
Hip Replacement Surgery	n = 786 31 [4%]	n = 541 32 [6%]	n = 50 2 [4%]
Knee Replacement Surgery	n = 294 3 [1%]	n = 225 3 [1%]	n = 65 2 [3%]

*Bleeding complications were considered major if accompanied by a significant clinical event or if ıemoglobin decreased by ≥ 2 g/dL or transfusion of 2 or more units of blood products was required.

Thrombocytopenia:

During clinical trials with Lovenox Injection, moderate thrombocytopenia, defined as a platelet count between 100,000/mm^3 and 50,000/mm^3, occurred at a rate of 1.9% in patients given Lovenox, 2.0% in patients given heparin, and 1.7% in patients given placebo following hip or knee replacement surgery.

Platelet counts less than 50,000/mm^3 occurred at a rate of 0.1% in patients given Lovenox, 0.5% in patients given heparin, and 0% in patients given placebo in the same trials. Rare cases of thrombocytopenia with thrombosis have also been observed in clinical practice (see WARNINGS).

Local Irritation:

Mild local irritation, pain, hematoma and erythema may follow subcutaneous 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, and that occurred at a rate of at least 2% in the enoxaparin group, are shown below.

Adverse Events Occurring at ≥ 2% Incidence in Enoxaparin Treated Patients*

	Enoxaparin 30 mg q12h n = 1080		Heparin 15000 U/24h n = 766		Placebo n = 115	
Adverse Event	**Severe**	**Total**	**Severe**	**Total**	**Severe**	**Total**
Fever	<1%	5%	<1%	4%	0%	3%
Hemorrhage	<1%	4%	1%	4%	0%	3%
Nausea	<1%	3%	<1%	2%	0%	2%
Hypochromic anemia	<1%	2%	2%	5%	<1%	7%
Edema	<1%	2%	<1%	2%	0%	2%
Peripheral edema	<1%	3%	<1%	4%	0%	3%

* (Excluding Unrelated Adverse Events)

Ongoing Safety Surveillance

There have been rare reports of neuraxial hematoma formation with concurrent use of enoxaparin and spinal/epidural anesthesia, and post-operative indwelling catheters. These events resulted in varying degrees of neurologic injuries including long-term or permanent paralysis.

Other reports include: skin necrosis at the injection site, inflammatory nodules at the injection site, purpura, systemic allergic reactions, and thrombocythemia.

OVERDOSAGE:

SYMPTOMS/TREATMENT:

Accidental overdosage following administration of Lovenox Injection may lead to hemorrhagic complications. This may be largely neutralized by the slow intravenous 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 conventional 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 subcutaneous 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

Adult Dosage:

In patients undergoing hip or knee replacement surgery, the recommended dose of Lovenox Injection is 30 mg twice daily administered by subcutaneous injection with the initial dose given within 12-24 hours post-operatively provided hemostasis has been established. Treatment should be continued throughout the period of post-operative care until the risk of deep vein thrombosis has diminished. Up to 14 days administration has been well tolerated in controlled clinical trials. The average duration of administration is 7 to 10 days.

All patients should be screened prior to prophylactic administration of Lovenox to rule out a bleeding disorder. There is usually no need for daily monitoring of the effect of Lovenox in patients with normal presurgical coagulation parameters.

Administration:

Lovenox Injection is administered by subcutaneous injection. It must not be a cular injection.

Subcutaneous injection technique: Patients should be lying down and Loven by deep subcutaneous injection. To avoid the loss of drug, do not expel the ai before the injection. Administration should be alternated between the left and and right posterolateral abdominal wall. The whole length of the needle shoulc fold held between the thumb and forefinger; the skin fold should be held thr minimize bruising, do not rub the injection site after completion of the injectior

Enoxaparin injection is a clear colorless to pale-yellow sterile solution and as v products should be inspected visually for particulate matter and discoloration p

HOW SUPPLIED

Lovenox Injection is available in packs of 10 prefilled syringes, NDC 0075-0624- parin sodium) prefilled syringe is affixed with a 27 gauge x ½ inch needle.

Lovenox contains 30 mg enoxaparin sodium in 0.3 mL of Water for Injection. L- Xa activity of approximately 3000 IU (with reference to the W.H.O. First Inte Weight Heparin Reference Standard).

Lovenox Injection should be stored at or below 25°C. Do not freeze.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.
Made in France

RHÔNE-POULENC RORER PHARMACEUTICALS INC.
COLLEGEVILLE, PA 19426

IN-1107L

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-009

LABELING REVIEWS

37.1

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

JUN - 7 1996

Application Number: 20-164/S-009

Name of Drug: Lovenox® (enoxaparin sodium) Injection

Sponsor: Rhone-Poulenc Rorer Pharmaceuticals Inc.

Material Reviewed

Submission Date(s): December 27, 1995

Receipt Date(s): December 27, 1995

Background and Summary Description: This supplement provides for a change in the approved pre-filled syringe, replacing the 26 G needle with a 27 G needle.

Review

The submitted annotated draft package insert labeling was compared to the final printed labeling (FPL) approved in Supplement 005 on January 30, 1996, identified as "IN-1107H Rev.11/95". The inserts are identical except for the following:

1. In the WARNINGS section, the closing parentheses in the phrase (platelet counts between 100,000/mm^3) has been deleted.

   This is UNACCEPTABLE. Request that the firm re-insert the closing parentheses.

2. In the DOSAGE AND ADMINISTRATION section, the "Adult Dosage:" subsection, the words "In patients undergoing hip or knee replacement surgery, the recommended dose of Lovenox" have been deleted from the first sentence of the subsection.

   This is UNACCEPTABLE. Request that the firm re-insert the deleted words.

3. In the HOW SUPPLIED section, the words "26 gauge" were replaced with the words "27 gauge".

   This change is ACCEPTABLE.

4. The recycled logo and words "Printed on recycled paper" were deleted.

This change is ACCEPTABLE.

5. The identification code and revision date to be updated.

This change is ACCEPTABLE.

Conclusions

The firm should be requested to:

1. In WARNINGS section, insert the closing parentheses.

2. In the first sentence of the DOSAGE AND ADMINISTRATION section, the "Adult Dosage:" subsection, insert the words "In patients undergoing hip or knee replacement surgery, the recommended dose of Lovenox".

Karen Oliver
Consumer Safety Officer

cc:
Original NDA 20-164/S-009
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/S.Fredd
HFD-180/J.Sieczkowski
HFD-180/L.Talarico

6/7/96

r/d Init: J.Sieczkowski 06/06/96
r/d Init: E.Duffy 06/06/96
r/d Init: S.Fredd 06/07/96

draft: KO/June 4, 1996
final: KO/06/07/96/c:\wpwin\karenfil\rev\20164606.0ko

CSO REVIEW

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-164/S-009
NDA 20-164/S-014

JAN 23 1997

Name of Drug: Lovenox (enoxaparin sodium) Injection

Sponsor: Rhone-Poulenc Rorer Pharmaceuticals Inc.

Material Reviewed

Submission Date(s): September 19, 1996 (S-009)
September 20, 1996 (S-014)

Receipt Date(s): September 20, 1996
September 23, 1996

Background and Summary Description: Supplement 009 provides for a change in the approved pre-filled syringe, replacing the 26 G needle with a 27 G needle and for a new needle shield manufacturer, ——— The September 20, 1996 submission provides for final printed labeling (FPL) for supplement 009. Supplement 014, submitted September 20, 1996 as "Special Supplement - Changes Being Effected, provides for changes in the PRECAUTIONS section, the "Pediatric Use" subsection, and the ADVERSE REACTIONS, the "Ongoing Safety Surveillance" subsection. The FPL submitted for supplements 009 and 014 are identical, identified as "IN-1107L Rev. 8/96", incorporating the changes approved June 26, 1996 for S-009 and the "Special Supplement - Changes Being Effected" changes in S-014.

Review

The package insert, identified as "IN-1107L Rev. 8/96" submitted September 19 and September 20, 1996 in Supplements 009 and 014, respectively, was compared to the draft package insert submitted December 27, 1995 and the revisions listed in the June 26, 1996 approval letter. The package inserts were identical except for the following:

1. The identification number has been changed.

   This change is ACCEPTABLE.

2. In the CLINICAL PHARMACOLOGY section, the "i.e" has been italicized to read "*i.e.*"

This change is ACCEPTABLE.

3. In the WARNINGS section, the "Neuraxial Anesthesia and Post-operative Indwelling Epidural Catheter Use" subsection, the underlining from the sub-subheading was deleted to read: "Spinal/Epidural Anesthesia".

This change is ACCEPTABLE.

4. A solid-black, rectangular box was added to the front of the package insert, the bottom right corner.

This addition is ACCEPTABLE.

5. In the PRECAUTIONS section:

   a. In the "Drug/Laboratory Test Interactions: Elevations of Serum Aminotranferases" subsection, the "®" symbol was added after the word "Lovenox" to read "Lovenox®".

   This addition is ACCEPTABLE.

   b. In the "Pediatric Use" subsection, the underlined words in the following sentence have been changed in response to the Federal Register Notice of December 13, 1994 regarding: "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of 'Pediatric Use' Subsection in the Labeling; Final Rule".

   from: "Safety and effectiveness of enoxaparin <u>in children</u> has not been established."

   to: "Safety and effectiveness of enoxaparin <u>in pediatric patients</u> has not been established."

   This change should be reviewed by the MEDICAL OFFICER.

6. In the ADVERSE REACTIONS section:

   a. In the "Thrombocytopenia" subsection, the "®" symbol was deleted after the word "Lovenox®" to read "Lovenox".

      This deletion is ACCEPTABLE.

   b. In the "Ongoing Safety Surveillance" subsection, the following was added: "Other reports include: skin necrosis at the injection site, inflammatory nodules at the injection site, purpura, systemic allergic reactions, and thrombocythemia."

      This addition should be reviewed by the MEDICAL OFFICER.

Conclusions

1. The following changes are ACCEPTABLE: 1., 2., 3., 4., 5.a. and 6.a.

2. The following changes should be reviewed by the MEDICAL OFFICER: 5.b.and 6.b.

Karen Oliver 01/23/97
Karen Oliver
Regulatory Health Project Manager

cc:
Original NDA 20-164/S-009
NDA 20-164/S-014
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/S.Fredd
HFD-180/L.Talarico
HFD-180/N.Markovic
draft: KO/January 3, 1997
final: KO/01/23/97/c:\wpwin\karenfil\rev\20164701.0ko

CSO REVIEW

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-009

MEDICAL REVIEW

52'1

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

Application Number: NDA 20-164/S-009
NDA 20-164/S-014

JAN 15 1997

Subject:	Proposal for Final Printed Labeling for Supplement 009.
Drug:	Lovenox® (enoxaparin sodium) Injection
Sponsor:	Rhone-Poulenc Rorer Pharmaceuticals Inc.
Submission Date:	September 20, 1996
Assignment Date:	01/03/97
Completion Date:	01/10/97
Medical Officer:	Nenad Markovic, M.D.
Review Number:	2016414.R46

Background:

The supplement S-014 provides for final printed labeling (FTP) for supplement S-009, NDA 20-164. This supplement was submitted (September 19, 1996) for a change in the approved pre-filled syringe replacing the 26G needle with a 27G needle and for a needle shield manufacturer, ——— . The Supplement 014 (September 20, 1996) provides for changes in the Labeling, section PRECAUTIONS, subsection *Pediatric Use*, and the section ADVERSE REACTIONS, subsection *Ongoing Safety Surveillance*.

Both supplements have been previously reviewed by the Consumer Safety Officer, except the changes identified in her review as #5b (PRECAUTIONS), and 6b (ADVERSE REACTIONS). This two particulars are the subject of this review.

Requested Change of the Labeling for Lovenox(enoxaparin sodium) Injection, identified as "IN-1107L Rev. 8/96."

#1. Section PRECAUTIONS, subsection *Pediatric Use*.

Suggested change of the phrase ". . .in children. . ." to ". . .in pediatric patients. . ." is in accordance with Federal Register Notice of December 13, 1994.

This change is acceptable

#2. Section ADVERSE REACTIONS, subsection *Ongoing Safety Surveillance.*

A new text was added as a paragraph 2 from above: "*Other reports include: skin necrosis at the injection site, inflammatory nodules at the injection site, purpura, systemic allergic reactions, and thrombocythemia.*"

This change **is not sufficient.**

Comment:

The change is not sufficient due to new information. The FDA Postmarketing and Pharmacovigilance group have analyzed safety record of Lovenox Injection and have made their recommendation.

In a Memorandum signed by Carol Pamer, R.Ph., Postmarketing Safety Evaluator, HFD-735, through Vincent Guinee, M.D., M.P.H, Director, Division of Pharmacovigilance and Epidemiology, HFD-730 to Steven Fredd, M.D., Director DGCDP, from December 31, 1996, the following recommendations were made:

a. "The following localized dermatological adverse events were thought to have sufficient documentation to merit consideration for inclusion in the next labeling for Lovenox injection: skin necrosis at injection site, prolonged bleeding at injection site, hypersensitivity reaction at or near injection site, and possible scarring, masses resulting from injection site reactions."

b. "The following generalized dermatological adverse events were put in the same category: vesiculobullous rash, urticaria. Three cases of epidermal necrolysis were reported but without sufficient documentation to be labeled."

The sponsor's and Pharmacovigilance proposed texts are compared with the COSTART terminology (Table 1).