CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-164/S-005

Name: Lovenox® (Enoxaparin Sodium) Injection

Sponsor: Rhone-Poulenc Rorer Pharmaceuticals

Approval Date: January 30, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-005

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-005

APPROVAL LETTER

JAN 30 1996

NDA 20-164/S-005

Rhone-Poulenc Rorer Pharmaceuticals
Attention: Ronald F. Panner
500 Arcola Road
Collegeville, PA 19426-0107

Dear Mr. Panner:

Please refer to your December 19, 1995 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lovenox (enoxaparin sodium) Injection.

The supplemental application, submitted as "Special Supplement - Changes Being Effected" under 21 CFR 314.70(c), provides for revisions to the WARNINGS and ADVERSE REACTIONS sections of the package insert regarding the potential for adverse events when epidural anesthesia and/or epidural catheters are used.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on December 19, 1995. Accordingly, the supplemental application is approved effective on the date of this letter.

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-240
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
Consumer Safety Officer
(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-005
HFD-180/Div. files
HFD-180/CSO/K.Oliver
HFD-180/S.Fredd
HFD-180/L.Talarico
HFD-103/P.Botstein (with labeling)
HFD-101/L.Carter
DISTRICT OFFICE
HF-2 (with labeling)
HFD-80 (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613 (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/January 26, 1996

final: KO/01/26/96/c:\wpwin\karenfil\nda\20164601.2ko K. Oliver 01/26/96

APPROVAL 1/29/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-005

LABELING

(1)

Lovenox®

APPROVED

(enoxaparin sodium) Injection

IN-1107H

JAN 30 1996

Rev. 11/95

Lovenox® (enoxaparin sodium) Injection

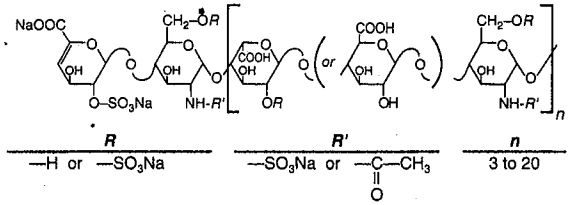
DESCRIPTION

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	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	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.

(2)

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

Drug/Laboratory Test Interactions:
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 2 of 10 normal subjects and in up to 4% of patients during treatment with Lovenox Injection. Similar significant increases in aminotransferase levels have also been observed in patients and normal 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 should be interpreted with caution.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
No long-term studies in animals have been performed to evaluate 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 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.

Pregnancy: Teratogenic Effects
Pregnancy 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 maximum received human dose in clinical trials was 1.5 mg/kg/day or 48.4 mg/m^2/day. 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 while using enoxaparin; none of the cases have been definitively associated with the use of the drug. 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 children 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 Injection and heparin and placebo in patients undergoing hip or knee replacement surgery.

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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 hemoglobin 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/mm³ and 50,000/mm³, 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/mm³ 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.

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 administered by intramuscular injection.

Subcutaneous injection technique: Patients should be lying down and Lovenox Injection administered by deep subcutaneous injection. To avoid the loss of drug, 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.

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.

HOW SUPPLIED

Lovenox Injection is available in packs of 10 prefilled syringes, NDC 0075-0624-30. Each Lovenox (enoxaparin sodium) prefilled syringe is affixed with a 26 gauge x ½ inch needle.

Lovenox contains 30 mg enoxaparin sodium in 0.3 mL of Water for Injection. Lovenox has an anti-Factor Xa activity of approximately 3000 IU (with reference to the W.H.O. First International Low Molecular 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

Printed on recycled paper

RHÔNE-POULENC RORER PHARMACEUTICALS INC.
COLLEGEVILLE, PA 19426

IN-1107H

Rev. 11/95

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-005

LABELING REVIEW

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: 20-164/S-005

JAN 29 1996

Name of Drug: Lovenox (enoxaparin sodium) Injection

Sponsor: Rhone-Poulenc Rorer Pharmaceuticals

Material Reviewed

Submission Date(s): December 19, 1995

Receipt Date(s): December 21, 1995

Background and Summary Description: This supplement, submitted as "Special Supplement - Changes Being Effected" under 21 CFR 314.70(c), provides for revisions to the WARNINGS and ADVERSE REACTIONS sections of the package insert regarding the potential for adverse events when epidural anesthesia and/or epidural catheters are used. The sponsor has submitted final printed labeling (FPL) for the package insert.

Review

The submitted FPL, identified as "IN-1107H Rev. 11/95", was compared to the FPL approved in Supplement 002 on March 9, 1995, identified as "IN-1107F Rev. 4/95". The inserts are identical except for the following:

1. The configuration of the insert was changed from a double fold to a triple fold.

   This editorial changed is ACCEPTABLE.

2. The code number was changed.

   This change is ACCEPTABLE.

3. In the WARNINGS section:

   a. In the "Hemorrhage" subsection, the underlined words were deleted in the following sentence: "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, in patients with indwelling intrathecal or epidural catheters, or in patients treated concomitantly with platelet inhibitors."

As per the January 19, 1996 MEDICAL OFFICER'S review, this deletion is ACCEPTABLE.

b. A new subsection, titled "Neuraxial Anesthesia and Post-operative Indwelling Epidural Catheter Use" was added:

"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."

As per the January 19, 1996 MEDICAL OFFICER'S review, this addition is ACCEPTABLE.

2. In the ADVERSE REACTIONS section, a new subsection, titled "Ongoing Safety Surveillance" was added:

"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."

As per the January 19, 1996 MEDICAL OFFICER'S review, this addition is ACCEPTABLE.

Conclusions

The submitted final printed labeling should be acknowledged and retained.

Karen Oliver, CSO 01/26/96
Karen Oliver
Consumer Safety Officer

cc:
Original NDA 20-164/S-005
HFD-180/Div. Files
HFD-180/
HFD-180/S.Fredd
HFD-180/L.Talarico

1/29/96
Concur
JF

draft: KO/January 25, 1996
r/d Initials: M.Walsh 01/26/96
final: KO/01/26/96/c:\wpwin\karenfil\rev\20164601.1ko

CSO REVIEW

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-005

MEDICAL REVIEW

8J 34.1

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

JAN 19 1996

NDA No.: 20-164

Sponsor: Rhone-Poulanc Rorer

Drug: Lovenox Injection (Enoxaparin sodium)

Indications: Thromboprophylaxis following hip or knee replacement surgery.

Submission: Special Supplement: Labeling Changes (Warning of neuroaxial hematomas).

Date of Submission: 12-19-1995

Date Received (CDER): 12-21-1995

Medical Reviewer: Lilia Talarico, M.D.

Date of Review: 1-18-1996

On March 9, 1995, the package insert for Lovenox (enoxaparin sodium) injection was revised to include the following information in the **WARNING** section: "Lovenox Injection, like other anticoagulants, should be used with extreme caution in condition with increased risk of hemorrhage such as ...,in patients with indwelling intrathecal or epidural catheters,...".

On 7-27-1995, the sponsor was asked to provide any additional information on the potential risks associated with epidural anesthesia and/or epidural catheters in patients receiving Lovenox thromboprophylaxis, including: 1) information on all reported cases of epidural hematomas in patients treated with enoxaparin, 2) background information on the overall risk of adverse events with the use of epidural/spinal anesthesia with or without thromboprophylaxis, 3) information on the overall use of enoxaparin and on the estimated use of enoxaparin with epidural anaesthesia in US and worldwide.

Eleven cases of epidural hematoma were identified from the worldwide postmarketing database as of 8-1-1995: nine were US and two were foreign cases. Four patients had spinal anesthesia, seven patients had epidural anesthesia. One spinal tap was traumatic; four of the epidural anesthesia had indwelling epidural catheter placed for continued analgesia. Nine of the eleven patients had undergone orthopedic surgery.
All cases of epidural hematoma resulted in prolonged hospitalization with permanent and disabling neurological

sequelae for most patients. Delay in diagnosing the epidural hematoma contributed to the poor outcome of most patients. Of the nine cases of epidural hematomas in patients undergoing elective orthopedic surgery, 6 involved patients who had received enoxaparin not in adherence with the prescribing recommendations of the current labeling, namely, thromboprophylaxis with enoxaparin was either started preoperatively or less than 12 hours postoperatively, or NSAID were given concomitantly.

There had been no cases of epidural hematoma reported in any of the clinical trials with more than 9000 patients treated with enoxaparin or other LMWH. Although epidural or spinal anesthesia were frequently used, it is not known whether indwelling epidural catheters were used in any of the clinical trials.

The incidence rates of epidural or spinal hematomas as complications of regional or neuroaxial anesthesia from published reports are between 1:120,000 and 1:250,000, with most cases (60-80%) occurring in patients on anticoagulants or with impaired hemostasis. Additional risk factors include traumatic punctures, multiple attempts, anatomical characteristics and age. Epidural anesthesia, particularly when associated with insertion of epidural catheter, is more frequently associated with hemorrhagic complications than spinal anesthesia. However, the true incidence of epidural hematoma in anticoagulated patients receiving neuroaxial anesthesia is not known.

Based on the 1992 hospital discharge data and from independent survey of surgeons and anesthesiologists, it has been estimated that in US 370,000 of the 418,000 patients undergoing hip or knee replacement surgery received thromboprophylaxis. Approximately 225,000 patients had neuroaxial anesthesia, approximately 210,000 of them had thromboprophylaxis, and approximately 97,000 anticoagulated patients operated on with epidural anesthesia had epidural catheter placed for analgesia.
Measures to prevent the occurrence of this rare but serious complication include: strict adherence to prescription recommendations, atraumatic technique of epidural or spinal puncture, optimal timing of initiation of anesthesia and placement or removal of epidural catheters relative to the anticoagulant effect, awareness of the possibility of such complication with close monitoring of patients and prompt intervention as needed.

The total number of patients receiving thromboprophylaxis with enoxaparin was estimated at approximately 91,000 per year. Of these, approximately 26,000 and 23,000 per year had spinal anesthesia and epidural anesthesia respectively. Approximately 8,700 of the patients with epidural anesthesia had indwelling epidural catheter placed. Based on two year marketing of

enoxaparin, the overall frequency of epidural hematoma reported with the use of enoxaparin and neuroaxial anesthesia can be calculated at about 1:25,000 enoxaparin exposures per year with spinal anesthesia, about 1:6250 enoxaparin exposures per year with epidural anesthesia, and 1:3480 enoxaparin exposures per year with epidural indwelling catheters. The relative risk of epidural hematoma with enoxaparin compared to other methods of thromboprophylaxis or to other LMWHs is unknown.
The labeling of Lovenox was revised to include the information concerning the risk of hemorrhage in patients with indwelling intrathecal or epidural catheters on 3-9-1995.

The sponsor has continued the post-marketing monitoring of complications of neuroaxial anesthesia and has undertaken focus group meeting with orthopedic surgeons and anesthesiologists regarding the current information in the package insert **WARNING** section. No new neuroaxial hemorrhages or other serious adverse events have been reported. However, the sponsor has submitted a new revision of the package insert in order to increase the visibility and add clarity to this safety information.
The changes requested include:

1) Deletion of ",,,in patients with indwelling intrathecal or epidural catheter,..." from the **Hemorrhage** paragraph in the **WARNING** section, and addition of the following separate paragraph in the **WARNING** section:

> **Neuroaxial Anesthesia and Post-operative Indwelling Epidural Catheter Use:** Spinal/Epidural anesthesia: As with other anticoagulants, there have been rare cases of neuroaxial 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.

2) Addition of the following paragraph at the end of the **ADVERSE REACTIONS** section:

> Ongoing Safety Surveillance: There have been rare reports of neuroaxial 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.

Recommendations: The revised package insert for Lovenox Injection can be approved.

Although rare, neuroaxial hemorrhage is a serious adverse event with disastrous consequences, therefore, the potential risk of such event should be adequately emphasized in the package insert.

Lilia Talarico MD

Lilia Talarico, M.D.

cc:
NDA 20-164
HFD-180
HFD-180/SFredd
HFD-180/LTalarico
HFD-181/CSO
HFD-180/JChoudary
HFD-180/JGibbs
f/t 1/19/96 jgw
MED\N\20164601.0LT

1/19/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-164/S-005

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

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DEC 27 1995

NDA 20-164/S-005

Rhone-Poulenc Rorer Pharmaceuticals
Attention: Mr. Ronald F. Panner
500 Arcola Road
Collegeville, PA 19426-0107

Dear Mr. Panner:

We acknowledge receipt of your supplemental application for the following:

Name of Drug Product: Lovenox (enoxaparin sodium) Injection

NDA Number: NDA 20-164

Supplement Number: S-005

Therapeutic Classification: Standard

Date of Supplement: December 19, 1995

Date of Receipt: December 21, 1995

This supplement, submitted as "Special Supplement - Changes Being Effected" under 21 CFR 314.70(c), provides for revisions to the WARNINGS and ADVERSE REACTIONS sections of the package insert regarding the potential for adverse events when epidural anesthesia and/or epidural catheters are used.

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 February 19, 1996 in accordance with 21 CFR 314.101(a).

All communications concerning this supplemental application should be addressed as follows:

Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation
Drug Products, HFD-180
Attention: DOCUMENT CONTROL ROOM, 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions, please contact me at (301) 443-0487.

Sincerely yours,

Karen Oliver
Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-164/S-005
HFD-180/Div. Files
HF-2 (with labeling)
HFD-80
HFD-180/CSO/K.Oliver
DISTRICT OFFICE
HFD-735/D.Barash

drafted: KO/December 26, 1995 KOliver 12/26/95
Final: KO/12/26/95/c:\wpwin\karenfil\nda\20164512.0ko

SUPPLEMENT ACKNOWLEDGEMENT