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
APPLICATION NUMBER:
NDA 20-164/S-005

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APPLICATION NUMBER:
NDA 20-164/S-005

APPROVAL LETTER
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

APPROVAL

[Signature] 1/29/96
# Lovenox® (enoxaparin sodium) Injection

## DESCRIPTION
Enoxaparin sodium is a sterile, low molecular weight heparin for injection. Each syringe contains 30 mg enoxaparin sodium in 6.2 mL Water for Injection. The approximate anti-Factor Xa activity per syringe is 2000 IU with reference to the KVI/KNL First International Low Molecular Weight Heparin Reference Standard. Enoxaparin is used in the treatment of deep vein thrombosis and for prevention of thromboembolism after total hip and knee replacement surgery.

Enoxaparin is obtained by alkaline degradation of heparin benzyl ester derived from porcine intestinal mucosa. Its structure is characterized by a 3-O-sulfate-4-enoxaparinonic acid group at the non-reducing end and a 2-O-sulfate-4-O-glucosaminyl 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** 5-20%
- **2000 to 4000 daltons** 2-8%
- **>4000 daltons** 5-15%

![Structural Formula](image)

## CLINICAL PHARMACOLOGY
Enoxaparin sodium is a low molecular weight heparin which has antithrombotic properties. In man, enoxaparin is characterized by a higher ratio of anti-Factor Xa activity to anti-Factor IIa activity (53.6 ± 0.88) than unfractionated heparin (1.2 ± 0.13). Following the administration of a single subcutaneous dose of up to 50 mg of enoxaparin to healthy subjects, no structural changes were observed in aortic plaques as assessed by the increase in heparin-binding capacity of aortic wall tissue. Single subcutaneous doses of enoxaparin do not significantly influence platelet aggregation or effect local clotting tests (i.e., prothrombin time [PT] or activated partial thromboplastin time [aPTT]).

### Pharmacodynamics
Maximum anti-Factor Xa and anti-Factor IIa activities occur 3 to 8 hours after subcutaneous injection of enoxaparin. Mean peak anti-Factor Xa activity was 5.1 ± 1.9 ng/mL and 2.9 ± 1.7 ng/mL 0.5 and 1.0 hours after the injection of 30 and 60 mg doses, respectively. Mean peak anti-Factor IIa activity was 0.8 ± 0.2 ng/mL and 0.4 ± 0.1 ng/mL 1.0 hours after the injection of 30 and 60 mg doses, respectively. Following intravenous administration, peak anti-Factor Xa activity was 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 from plasma is 2.0 hours. Following subcutaneous administration, approximately 50% is eliminated in the 24 hours following the injection of 30 mg enoxaparin sodium.

### 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 his replacement patients. Treatment was initiated within 24 hours post-surgery and was continued for 10-14 days post-operatively.

## 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 thromboembolism 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.

### WARNINGS
Lovenox Injection is not intended for intramuscular administration. Lovenox cannot be used interchangeably with other heparin or low molecular weight heparins. Lovenox Injection should be used with extreme caution in patients with a history of heparin-induced thrombocytopenia.
Thrombocytopenia:

Thrombocytopenia can occur with the administration of Lovenox. Moderate thrombocytopenia (platelet counts between 50,000/mm³ and 100,000/mm³) occurred at a rate of 1.5% 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/mm³ occurred at a rate of 0.1% in patients given Lovenox, 0.5% in patients given heparin, and 0.0% in patients given placebo in the same trials.

Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm³, enoxaparin should be discontinued. Rare cases of thrombocytopenia with thromboplastin 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 and heparin. 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:

Regular 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, aspirin, platelet inhibitors including dipyridamole, and salicylates. NSAIDs (including ketorolac tromethamine, ibuprofen, and aspirin) or warfarin should also be avoided and their use is essential, conduct close clinical and laboratory monitoring. (See Laboratory Tests, PRECAUTIONS)

Drugs/Laboratory Test Interactions:

Elevation of Serum Aminotransferases:

Asymptomatic increase in serum aminotransferase levels greater than three times the upper limit of the laboratory reference range or in up to 20% of normal subjects and in up to 45% of patients during treatment with Lovenox injection. Similar increases in serum aminotransferase levels have also been observed in patients and normal volunteers treated with heparin and other low molecular weight heparins. Such elevations are usually reversible and are rarely associated with cases of jaundice or hepatitis. Since these elevations are important in the differential diagnosis of myocardial infarction, liver disease and worsening congestive heart failure, the differential diagnosis of jaundice or hepatitis should be considered in all patients with symptoms of these conditions.

Fetal Development:

No long-term studies in animals have been performed to evaluate teratogenic potential of enoxaparin. Enoxaparin was shown to be non-mutagenic in in vitro and in vivo tests including the Ames test, mouse lymphoma cell forward mutation test, and the micronucleus test in bone marrow cells. Enoxaparin was shown to be non-genotoxic by the mouse lymphoma forward mutation test. Enoxaparin was shown to be non-genotoxic by the mouse lymphoma forward mutation test. Enoxaparin was shown to be non-genotoxic by the mouse lymphoma forward mutation test. Enoxaparin was shown to be non-genotoxic by the mouse lymphoma forward mutation test.
Major Bleeding Episodes*  

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>N</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>795</td>
<td>647</td>
<td>76</td>
</tr>
<tr>
<td>Heparin</td>
<td>647</td>
<td>56</td>
<td>6</td>
</tr>
<tr>
<td>Placebo</td>
<td>76</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

*Breeding complications were considered major if accompanied by a significant clinical event or if hemorrhagic decrease by 3 g or transfusion of 2 or more units of blood products was required.

**Thrombocytopenia**: During clinical trials with Lovence® injection (adenosine, uracan, and uracan), a platelet count between 30,000-50,000/μl, occurred in 0.8% of patients given Lovence, 2.0% in patients given heparin, and 0.5% in patients given heparin, and 1.5% in patients given placebo following hip or knee surgery replacement. Platelet counts less than 50,000/μl occurred in 0.1% of patients given Lovence, 0.0% in patients given heparin, and 0.0% 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, and irritation may occur due to subcutaneous injection. Patients should be advised to avoid prolonged standing or sitting in one position after injection.

Other: Other adverse events that were thought to be possibly related to treatment with Lovence 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 placebo group, are shown below.

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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Enoxaparin</th>
<th>Heparin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Hematuria</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Hypotensive spells</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Edema</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

* (Excluding Unrelated Adverse Events)

Ongoing Safety Surveillance: There have been rare reports of neuropsychiatric abnormalities with concurrent use of enoxaparin and antineoplastic agents, and post-operative inducing analgesics. These events resulted in varying degrees of neuropsychiatric abnormalities, including delirium and confusion.

**OVERDOSAGE**: Symptoms/Treatment: Overdose following administration of Lovence 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 Lovence injection received. 1 mg of protamine sulfate should be administered in every 1 mg of Lovence injection. A second infusion of 0.4 mg protamine sulfate and 1 mg of Lovence 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 longer than under normal conditions. Abruption of hemorrhagic complications in all cases, the anti-factor Xa activity is never completely neutralized (maximum about 80%). Particular care should be taken to avoid overdosage with anaphylactoid reactions. Because of the vasodilator effects of Lovence injection, hypotension has been reported with protamine sulfate, it should be given only when vasopressor techniques are not available. For additional information consult the labeling of Protamine Sulfate for further information.

A single subcutaneous dose of 46.4 mg/kg enoxaparin was lethal to rats. The symptoms of acute toxicity were anorexia, decreased motility, stupor, and coma.

**DOSAGE AND ADMINISTRATION**

**Adult Dosage**: In patients undergoing hip or knee replacement surgery, the recommended dose of Lovence injection is 30 mg twice daily administered by subcutaneous injection at the initial dose given within 12-24 hours post-operatively provided hemorrhage 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 16 hours after administration, the average duration of administration is 7 to 10 days.

**Administration**: Lovence injection is administered subcutaneously. It must not be administered by intramuscular injection. Subcutaneous injection technique: Patients should be lying down and Lovence injection administered by deep subcutaneous injection. Avoid the loss of drug, do not use the air bubble from the syringe before injection. Administration should be alternated between the left and right anterolateral and left and right posterolateral axillary wall. The whole length of the needle should be introduced into a skin fold held between the thumb and
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

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 change 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
angiodyplastic 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
Consumer Safety Officer

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

1/26/96

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
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

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 anesthesia 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 hemorrrhages 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, M.D.
APPLICATION NUMBER:
NDA 20-164/S-005

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
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  KOlive 12/26/95-
Final: KO/12/26/95/c:\wpwin\karenfil\nda\20164512.0ko

SUPPLEMENT ACKNOWLEDGEMENT