

## 5. In the WARNINGS section:

- a. "Neuroaxial Anesthesia and Post-operative Indwelling Epidural Catheter Use" subsection, the text has been revised.

**This change is ACCEPTABLE (approved January 30, 1996, supplement 005.)**

- b. In the "Thrombocytopenia" subsection, the percentage rates have been revised (as requested in the March 21, 1997 approvable letter) to include thrombocytopenia in patients receiving Lovenox for extended prophylaxis in hip replacement surgery.

**These changes were reviewed by the MEDICAL OFFICER, Dr. Nenad Markovic, and they are UNACCEPTABLE. The moderate and severe thrombocytopenia rates should be separately listed as "During clinical trials in patients following hip or knee replacement surgery..."; "During clinical trials in patients following abdominal surgery..."**

## 6. In the PRECAUTIONS section:

- a. In the "Drug Interactions" subsection, the following phrase was changed  
from: (see Laboratory Tests, PRECAUTIONS)."

to: (see **PRECAUTIONS: Laboratory Tests**)."

**This change is ACCEPTABLE.**

APPEARS THIS WAY  
ON ORIGINAL

- b. In the "Drug/Laboratory Test Interactions: *Elevations of Serum Aminotranferases*" subsection, revisions to the text approved May 6, 1997, supplement 008, are included.

**These changes are ACCEPTABLE.**

APPEARS THIS WAY  
ON ORIGINAL

- c. In the "Carcinogenesis, Mutagenesis, Impairment of Fertility:" subsection, in the second sentence of the subsection, the following phrase was changed

from: "*in vitro* rat bone marrow chromosomal aberration test"

to: "*in vivo* rat bone marrow chromosomal aberration test".

**This change is ACCEPTABLE.**

- d. In the "Pediatric Use" subsection, the word "children" was changed to "pediatric patients".

**This change is ACCEPTABLE (approved January 27, 1997 in supplement 014).**

APPEARS THIS WAY  
ON ORIGINAL

7. In the ADVERSE REACTIONS section:

- a. In the "Hemorrhage" subsection, the "Major Bleeding Episodes in Hip or Knee Replacement Surgery" table:

- (1) The table was reformatted as requested in the March 21, 1997 approvable letter.

**This change is ACCEPTABLE.**

APPEARS THIS WAY  
ON ORIGINAL

- (2) The lines defining the table columns and the box surrounding the table were deleted.

**This change is ACCEPTABLE.**

APPEARS THIS WAY  
ON ORIGINAL

- (3) In the sentence after the asterisk at the bottom of the table, the sentence was changed

from: "Bleeding complications were considered major if accompanied by a significant clinical event with hemoglobin decreased by  $\geq 2\text{g/dL}$  or transfusions of 2 or more units of blood products."

to: "Bleeding complications were considered major:(1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decreased by  $\leq 2\text{g/dL}$  or transfusion of 2 or more units of blood products."  
"Retroperitoneal and intracranial hemorrhages were always considered major."

**These changes are UNACCEPTABLE. The following phrase should be changed from " $\leq 2\text{g/dL}$  or transfusion of 2 or more units of blood products" to " $\geq 2\text{g/dL}$  or transfusion of 2 or more units of blood products".**

- (4) After the table, the following sentence was added: "The incidence of major hemorrhagic complications during the peri-operative and post-operative period was 2% (4 of 288 patients) in one study in which enoxaparin was administered as a 40 mg dose 12 hours pre-operatively."

This addition was reviewed by the **MEDICAL OFFICER, Dr. Nenad Markovic**, and it is **UNACCEPTABLE**. The firm should be requested to delete the added paragraph and incorporate the major hemorrhagic complications into the "Major Bleeding Episodes in Hip or Knee Replacement Surgery" table, the "Hip Replacement Surgery, Extended Prophylaxis" patient population group. Reporting the two studies could be differentiated as follows: Patient Group #1 (describe perioperative and postoperative dosing regimen) and Patient Group #2 (describe perioperative and postoperative dosing regimen). The appropriate statistics for each of the patient groups should be provided. The explanatory note for the groups could be included in the table as a footnote.

- (5) The underlined words in the following sentence was changed

from: "Injection site hematomas in long-term prevention trials occurred in 9% of the enoxaparin patients versus 1.8% of the placebo patients."

to: "Injection site hematomas in extended prophylaxis trials occurred in 9% of the enoxaparin patients versus 1.8% of the placebo patients."

This change is **ACCEPTABLE**.

APPEARS THIS WAY  
ON ORIGINAL

- (6) A table titled "Major Bleeding Episodes in Abdominal & Colorectal Surgery\*" was added.

This addition is **UNACCEPTABLE**. The following phrase should be changed from " $\leq 2$ g/dL or transfusion of 2 or more units of blood products" to " $\geq 2$ g/dL or transfusion of 2 or more units of blood products".

- b. In the "Local Reactions" sections, the word "ecchymosis" was added.

This addition is **ACCEPTABLE** (in the labeling approved May 6, 1997, supplement 008.)

- c. After the table titled "Adverse Events Occurring at  $\geq$  2% Incidence in Enoxaparin Treated Patients\* Undergoing Hip or Knee Replacement Surgery", the following sentence was added: "Adverse events occurring with an incidence of  $\geq$  2% with enoxaparin in one study after hip replacement surgery in which enoxaparin was administered as a 40 mg dose 12 hours pre-operatively included: anemia (16%), hemorrhage (12%), fever (8%), and peripheral edema (7%). None of the reported events were severe."

**This addition was reviewed by the MEDICAL OFFICER, Dr. Nenad Markovic, and it is UNACCEPTABLE. The firm should be requested to delete the added paragraph and incorporate the pertinent adverse events information for the patients receiving 40 mg Lovenox in the "Adverse Events Occurring at  $\geq$  2% Incidence in Enoxaparin Treated Patients\* Undergoing Hip or Knee Replacement Surgery" table in a column titled "Enoxaparin 40mg".**

- d. A table titled "Adverse Events Occurring at  $\geq$  2% Incidence in Enoxaparin Treated Patients\* Undergoing Abdominal or Colorectal Surgery" was added.

**This addition is ACCEPTABLE (in the labeling approved May 6, 1997, supplement 008.)**

- e. In the "Ongoing Safety Surveillance:" subsection, the word "Lovenox" was changed to "enoxaparin".

**This change is ACCEPTABLE.**

APPEARS THIS WAY  
ON ORIGINAL

- f. A sub-subsection titled "Other reports include:" was added.

**This addition is ACCEPTABLE (approved January 27, 1997, supplement 014).**

8. In the OVERDOSAGE section, in the "Symptoms/Treatment:" subsection, in the third sentence, the following phrase was changed

from: "Lovenox Injection"

to: "Lovenox (enoxaparin sodium) Injection".

**This change is ACCEPTABLE.**

## 9. In the DOSAGE AND ADMINISTRATION section:

- a. Prior to the "Adult Dosage:" subsection, two paragraphs were added. These paragraphs were approved in May 6, 1997, supplement 008. However, the following changes should be requested: (1) in the first paragraph, the last word in the second sentence should be changed from "values" to "baseline coagulation parameters"; and (2) Delete the second paragraph, "When patients receive...thrombosis has diminished."

**The identified portions of the added text are UNACCEPTABLE.**

## b. In the "Adult Dosage" section:

- (1) In the "Hip and Knee Replacement Surgery:" subsection, revisions approved May 6, 1997, supplement 008, have been included. However, additional revisions were also included:

- (a) The following sentences were changed:

APPEARS THIS WAY  
ON ORIGINAL

from: "Up to 14 days administration has been well tolerated in controlled clinical trials." "The average duration of administration is 7 to 10 days."

to: "Up to 14 days administration (average duration 7 to 10 days) of Lovenox 30 mg every 12 hours has been well tolerated in controlled clinical trials."

**This change was reviewed by the MEDICAL OFFICER, Dr. Nenad Markovic, and it is ACCEPTABLE.**

- (b) The March 21, 1997 approvable letter requested that several sentences regarding the 40mg administration of Lovenox be added. Proposed text was provided by the FDA. The firm revised the FDA's proposed text (the changes are underlined):

FDA Text: "For hip replacement surgery, a dose of 40 mg once daily subcutaneously, given within 12 hours prior to surgery, may be considered. Continued therapy with Lovenox Injection 40 mg once daily administered by subcutaneous injection for 3 weeks following the initial therapy is recommended."

Firm's Text: "For hip replacement surgery, a dose of **40 mg** once daily subcutaneously, given initially within 12 (+3) hours prior to surgery, may be considered. Following the initial phase of therapy (Lovenox 30 mg twice daily or 40 mg once daily), continued therapy with Lovenox Injection 40 mg once daily administered by subcutaneous injection for 3 weeks is recommended.

**This change was reviewed by the MEDICAL OFFICER, Dr. Nenad Markovic, and it is UNACCEPTABLE. The second sentence should be revised to read: Following the initial phase of thromboprophylaxis (Lovenox 30 mg twice daily or 40 mg once daily), continued prophylaxis with Lovenox Injection 40 mg once daily administered by subcutaneous injection for 3 weeks is recommended.**

- (2) The subsection title "Long Term Prevention Following Hip Replacement Surgery" has been deleted as requested in the May 21, 1997 approvable letter.

**This deletion is ACCEPTABLE.**

APPEARS THIS WAY  
ON ORIGINAL

- (3) A subsection titled "Abdominal Surgery" was added.

**This addition is ACCEPTABLE (in the labeling approved May 6, 1997, supplement 008.)**

- (4) In the subsection titled "Administration:"

APPEARS THIS WAY  
ON ORIGINAL

- (a) The following sentence was added: "When using Lovenox ampules, to assure withdrawal of the appropriate volume of drug, the use of a tuberculin syringe or equivalent is recommended.

**This addition is ACCEPTABLE (approved March 7, 1997, supplement 007).**

- (b) The following sentence(s) were changed

from: "An automatic injection device (TRADEMARK) is available for use with Lovenox syringes."

to: "An automatic injector, Lovenox EasyInjector™, is available for patients to administer Lovenox Injection packaged in 30 mg and 40 mg pre-filled syringes. Please see directions accompanying the Lovenox EasyInjector™ automatic injection device."

APPEARS THIS WAY ON ORIGINAL

This change is **ACCEPTABLE** (approved May 27, 1997, supplement 017).

10. In the HOW SUPPLIED section:

APPEARS THIS WAY ON ORIGINAL

a. The text and the presentation table has been modified.

The following modifications are **UNACCEPTABLE**: The firm should be requested to (1) delete the "DOSAGE AND ADMINISTRATION, Adult Dosage Reference" column; and (2) add a column with the list numbers or NDC numbers of the products.

b. In the "Caution" statement, the "(U.S.A.)" has been deleted to read: "Federal law prohibits dispensing without prescription."

This deletion is **ACCEPTABLE**.

APPEARS THIS WAY ON ORIGINAL

**Conclusions**

1. The following changes are **ACCEPTABLE**: 1., 2.d., 3.a.(1)-(2), 3.b.(1)-(2), (5)-(7 [a-b]), 3.c., 4.a.-b., 5.a., 6.a.-d., 7.a.(1)-(2)(5), b., d.-f., 8., 9.b.(1)(a), (2)-(4[a-b]), and 10.b.
2. The following changes are **UNACCEPTABLE** and the firm should be requested to make the suggested revisions: 2.a.-c., 3.a.(3), 3.b.(3),(4)(a)-(b), 5.b., 7.a.(3)-(4),(6), 7.c., 9.a., 9.b.(1)(b) and 10.a.
3. The firm should be requested to make the revisions requested in the CSO Review.

APPEARS THIS WAY ON ORIGINAL

*/S/*  
\_\_\_\_\_  
Karen Oliver  
Regulatory Health Project Manager  
*10/27/97*



cc:

Original NDA 20-164/S-010

HFD-180/Div. Files

HFD-180/L.Talarico /S/10-9-97

HFD-180/N.Markovic

HFD-180/K.Oliver

HFD-180/E.Duffy

HFD-180/J.Sieczkowski

HFD-720/M.Huque

HFD-720/M.Rashid

draft: KO/September 29, 1997

r/d Initials: N.Markovic 10/07/97

r/d Initials: L.Talarico 10/07/97

final: KO/10/09/97/c:\wpwin\karenfil\rev\20164709.1ko

CSO REVIEW

APPEARS THIS WAY  
ON ORIGINAL

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ON ORIGINAL



**EXCLUSIVITY SUMMARY for NDA # 20-164 SUPPL # 010**

**Trade Name** Lovenox Inj. **Generic Name** Enoxaparin Sodium  
**Applicant Name** Rhone-Poulenc Rorer **HFD-** 180

**Approval Date** 01/30/98

APPEARS THIS WAY  
ON ORIGINAL

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA?  
YES /     / NO / X /

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ON ORIGINAL

b) Is it an effectiveness supplement?

YES / X / NO /     /

If yes, what type? (SE1, SE2, etc.)

SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / X / NO /     /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

\_\_\_\_\_  
\_\_\_\_\_  
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:  
  
\_\_\_\_\_  
\_\_\_\_\_

Form OGD-011347 Revised 8/7/95; edited 8/8/95  
cc: Original NDA    Division File    HFD-85 Mary Ann Holovac

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ON ORIGINAL

d) Did the applicant request exclusivity?

YES / x / NO / \_\_\_ /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES / \_\_\_ / NO / x /

If yes, NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

3. Is this drug product or indication a DESI upgrade?

YES / \_\_\_ / NO / x /

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).**

APPEARS THIS WAY  
ON ORIGINAL

APPEARS THIS WAY  
ON ORIGINAL

**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / x / NO / \_\_\_ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-164 \_\_\_\_\_

NDA # \_\_\_\_\_

NDA # \_\_\_\_\_

APPEARS THIS WAY  
ON ORIGINAL

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / \_\_\_ / NO / \_\_\_ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # \_\_\_\_\_

NDA # \_\_\_\_\_

NDA # \_\_\_\_\_

APPEARS THIS WAY  
ON ORIGINAL

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.**

**PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / x / NO / \_\_\_ /

APPEARS THIS WAY  
ON ORIGINAL

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / x / NO / \_\_\_ /

APPEARS THIS WAY  
ON ORIGINAL

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

\_\_\_\_\_  
\_\_\_\_\_

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /  / NO /  /

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /  / NO /  /

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /  / NO /  /

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # PK 537

Investigation #2, Study # ENX 49001

Investigation #3, Study # \_\_\_\_\_

APPEARS THIS WAY  
ON ORIGINAL

APPEARS THIS WAY  
ON ORIGINAL

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #2	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #3	YES / <input type="checkbox"/> /	NO / <input type="checkbox"/> /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
 NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
 NDA # \_\_\_\_\_ Study # \_\_\_\_\_

APPEARS THIS WAY  
ON ORIGINAL

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #2	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #3	YES / <input type="checkbox"/> /	NO / <input type="checkbox"/> /

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
 NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
 NDA # \_\_\_\_\_ Study # \_\_\_\_\_

APPEARS THIS WAY  
ON ORIGINAL

- c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # PK 537

Investigation #2, Study # ENX 49001

Investigation #\_, Study # \_\_\_\_\_

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

- a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
 IND # \_\_\_\_\_ YES / \_\_\_ / ! NO / \_\_\_ / Explain: \_\_\_\_\_  
 ! \_\_\_\_\_

Investigation #2 !  
 IND # \_\_\_\_\_ YES / \_\_\_ / ! NO / \_\_\_ / Explain: \_\_\_\_\_  
 ! \_\_\_\_\_

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ON ORIGINAL

- (b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !  
 YES / x / Explain \_\_\_\_\_ ! NO / \_\_\_ / Explain \_\_\_\_\_  
PK 537 conducted in Sweden ! \_\_\_\_\_  
 \_\_\_\_\_ ! \_\_\_\_\_

APPEARS THIS WAY  
ON ORIGINAL



Investigation #2

YES / x / Explain \_\_\_\_\_ ! NO / \_\_\_ / Explain \_\_\_\_\_

ENX 49001 conducted in France

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / \_\_\_ / NO / x /

If yes, explain: \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

/S/ \_\_\_\_\_ 01/26/98  
Signature Date  
Title: Project Manager

APPEARS THIS WAY  
ON ORIGINAL

/S/ \_\_\_\_\_ 1-29-98  
Signature of Division Director Date

APPEARS THIS WAY  
ON ORIGINAL

cc: Original NDA      Division File      HFD-85 Mary Ann Holovac

# PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

**NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.**

NDA/PLA/PMA # NDA 20-164 Supplement # 010 Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-180 Trade and generic names/dosage form: Lovenox (enoxaparin sodium) Injection Action: AP AE NA 01/30/98

Applicant Rhone-Poulenc Therapeutic Class Anticoagulant; Low Molecular Weight Heparin

Indication(s) previously approved prevention of DVT in hip/knee replacement surgery and abd. surgery

Pediatric information in labeling of approved indication(s) is adequate X inadequate    

Proposed indication in this application prevention of DVT during and following hospitalization in hip replacement patients.

**FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.**

**IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS?**     Yes (Continue with questions) X No (Sign and return the form)

**WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED?** (Check all that apply)

    Neonates (Birth-1month)     Infants (1month-2yrs)     Children (2-12yrs)     Adolescents(12-16yrs)

1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.
- a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- c. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing,
- (2) Protocols were submitted and approved.
- (3) Protocols were submitted and are under review.
- (4) If no protocol has been submitted, attach memo describing status of discussions.
- d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
- X 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
5. **PEDIATRIC LABELING MAY NOT BE ADEQUATE.**
- a. Pediatric studies are needed.
- b. Pediatric studies may not be needed but a pediatric supplement is needed.
6. If none of the above apply, attach an explanation, as necessary.

**ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER?**     Yes     No

**ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.**

IS/ Project Manager 01/26/98  
Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA # NDA 20-164/5-010

HFD-180/Div File

NDA/PLA Action Package

HFD-006/ KRoberts (include labeling for all NME approvals; either draft or final)

(revised 9/15/97)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)**

APPEARS THIS WAY  
ON ORIGINAL

MEMORANDUM

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

DATE: January 26, 1998  
FROM: Lilia Talarico, M.D.  
Division Director, HFD-180  
SUBJECT: Pediatric Studies  
TO: NDA 20-164/S-010

/s/

1-29-98

APPEARS THIS WAY  
ON ORIGINAL

Lovenox® (enoxaparin sodium) Injection us a low molecular weight heparin with a proposed indication of prevention of deep venous thrombosis DVT), which may lead to pulmonary embolism (PE), in patients undergoing hip replacement surgery, during and following hospitalization.

Additional approved indications include the prevention of DVT, which may lead to PE, following knee replacement surgery and abdominal surgery.

These indication have little, if any, potential for use in pediatric patients and generally, the pediatric population has a relatively low risk of DVT.

APPEARS THIS WAY  
ON ORIGINAL

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# PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # NDA 20-164/S-010 Supplement # 010 Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HF D-180 Trade and generic names/dosage form: Lovenox (enoxaparin sodium) Action: AP AE NA

Applicant Rhone-Poulenc Rorer Therapeutic Class \_\_\_\_\_

Indication(s) previously approved Prophylaxis of DVT following hip and knee replacement surgery  
Pediatric information in labeling of approved indication(s) is adequate \_\_\_ inadequate \_\_\_

Indication in this application \_\_\_\_\_ (For supplements, answer the following questions in relation to the proposed indication.)

1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.
  - a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
  - b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
  - c. The applicant has committed to doing such studies as will be required.
    - (1) Studies are ongoing,
    - (2) Protocols were submitted and approved.
    - (3) Protocols were submitted and are under review.
    - (4) If no protocol has been submitted, attach memo describing status of discussions.
  - d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed. *not a pediatric condition /S/*
5. If none of the above apply, attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/  
Signature of Preparer and Title

3/19/97  
Date

cc: Orig NDA/PLA/PMA # NDA 20-164/S-010  
HF D-180 /Div File  
NDA/PLA Action Package  
HFD-006/ SOLmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)