

- b. The words [REDACTED] were added to the bottom flap.

This addition, requested in the February 28, 1998 approvable letter, is ACCEPTABLE.

- c. The "Caution" statement, located below the [REDACTED] section, was deleted and replaced with the phrase: [REDACTED] located below the storage statement.

This change is ACCEPTABLE.

- d. The following phrase was added, in bolded type-face, after the "Directions for Use" statement: [REDACTED]

This change is ACCEPTABLE.

- e. The "Made in France" statement was moved from below the "Rhone-Poulenc Rorer Pharmaceuticals Inc., Collegeville, PA" statement, to above the statement.

This change is ACCEPTABLE.

- f. The storage statement was changed

from:

[REDACTED]
DRAFT LABELING

to:

[REDACTED]
This change, requested in the February 28, 1998 approvable letter, is ACCEPTABLE.

- g. The [REDACTED] DRAFT LABELING

This change is ACCEPTABLE.

13. On the blister packs:

- a. The format of the drug name has been changed

from: DRAFT LABELING

to:

This change is ACCEPTABLE.

- b. The storage statement was changed

from:

DRAFT LABELING

to:

This change, requested in the March 27, 1998 approval letter for S-016, is ACCEPTABLE.

- c. The " " statement was deleted and replaced with the phrase: " ".

This change is ACCEPTABLE.

- d. The "Made in France" statement was moved from above the "Rhone-Poulenc Rorer Pharmaceuticals Inc." statement, to the right of the NDC number.

This change is ACCEPTABLE.

14. On the immediate container label:

- a. The orientation information on the syringe barrel.

This information is ACCEPTABLE.

- b. The words [REDACTED] were added.

This addition, requested in the February 28, 1998 approvable letter, is ACCEPTABLE.

- c. The sponsor stated that there will be no graduation numbers on the label itself, but there are graduation numbers on the barrel of the syringe.

This information is ACCEPTABLE.

Conclusions

1. The following changes are ACCEPTABLE: 1.a.-b., 2., 4.a.(2)-(5), 4.c.(1)-(3), 4.c.(4)(a)-(b), 4.c.(6), 6.a.-b., 7., 8.a.(1)-(4), 8.b., 8.c.(1)-(2),(3)(a)-(c), 9., 10.a.-c., 11., 12.a.-g., 13.a.-d., and 14.a-c.
2. The following changes are UNACCEPTABLE: 4.a.(1), 4.b., 4.c.(5), 5., and 8.c.(3)(d).
3. The following changes should be reviewed by the BIOPHARMACEUTICS REVIEWER: 3.

/s/ [REDACTED]

Karen Oliver
Regulatory Health Project Manager

12/30/98

/s/ [REDACTED]

12-31-98

APPEARS THIS WAY ON ORIGINAL
[REDACTED]

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-164/S-015

Name of Drug: Lovenox® (enoxaparin sodium) Injection

FEB 27 1998

Sponsor: Rhone-Poulenc Rorer Pharmaceuticals Inc.

Material Reviewed

Submission Date(s): February 10, 1998

Receipt Date(s): February 10, 1998

Background and Summary Description: DRAFT LABELING

DRAFT LABELING

On February 10, 1998, the sponsor submitted revised draft labeling using the current approved labeling (S-010, approved 01/30/98) with the changes pertinent to S-015 added. It was noted that although there are two approved package inserts for Lovenox Injection, approved January 30, 1998 in S-010 identified as "IN-1107P, Rev. 1/98" and "IN-2828A, Rev. 1/98" only one package insert was submitted with this supplemental application for review.

Review

Package Insert

The draft labeling, identified as IN-1107__ Rev. __/98, was compared to the approved labeling, identified as "IN-1107P, Rev. 1/98" and to the changes reviewed in S-016 (an approvable letter was issued 09/08/97) that were common to both supplements S-015 and S-016.

1. Throughout the text of the package insert:
 - a. The abbreviation [REDACTED] should be changed to [REDACTED] except for the initial time the word [REDACTED] is used in the CLINICAL PHARMACOLOGY section which should read: [REDACTED]
 - b. The phrase [REDACTED] should be deleted and replaced with the word [REDACTED]

- c. All the tables should be revised to provide a consistent format throughout the text as requested in the January 30, 1998 approval letter for S-010.
 - d. Except when referencing the specific indication of prevention or treatment of post-operative DVT, change the words [REDACTED]
 - e. Delete the hyphen between time elements and replace with the word [REDACTED]
DRAFT LABELING [REDACTED]
 - f. Change the abbreviation [REDACTED]
 - g. Change the abbreviation [REDACTED]
 - h. Change the words [REDACTED]
 - i. Insert the appropriate route of administration to the "dosing regimen" listed in the tables.
2. In the DESCRIPTION section, the firm made multiple changes that are supported in identical chemistry submissions to S-015 and S-016. The changes in this section were reviewed in S-016.

The firm should be requested to revise the DESCRIPTION section as requested in the September 8, 1997 approvable letter for S-016 with the following additional requests:

- (1) Change the first sentence in the section to read: [REDACTED]
DRAFT LABELING [REDACTED]
- (2) Change the reference to DRAFT LABELING [REDACTED]
[REDACTED] in the draft labeling for S-015 to [REDACTED]
- (3) Retain the reference to the 30 and 40 mg prefilled syringes in the first paragraph in S-015.
- (4) Retain the added reference to the DOSAGE AND ADMINISTRATION section in the first paragraph in S-015.

3. In the CLINICAL PHARMACOLOGY section, the firm made multiple changes that were supported in identical biopharmaceutics submissions to S-015 and S-016. In addition, changes pertinent to S-015 were identified.

These changes should be reviewed by the BIOPHARMACEUTICS REVIEWER, Dr. Arzu Selen (see Clinical Pharmacology and Biopharmaceutics Review dated 02/26/98).

4. In the CLINICAL TRIALS section:

- a. In the "Hip or Knee Replacement Surgery" subsection:

The firm should be requested to revise the subsection as requested in the September 8, 1997 approvable letter for S-016.

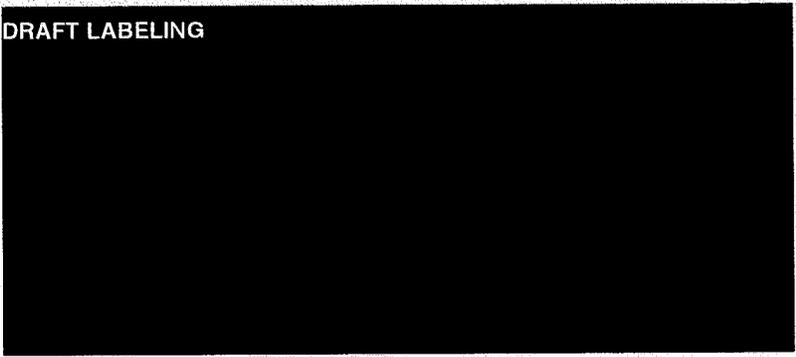
- b. A subsection titled "Treatment of Deep Vein Thrombosis and Pulmonary Embolism" was added.

The information in this subsection was reviewed by the MEDICAL OFFICER, Dr. Nenad Markovic, and the DIVISION DIRECTOR, Dr. Lilia Talarico, and it is UNACCEPTABLE.

- **The firm should be requested to revise the description of the first clinical study:**

- (1) **Revise the first sentence to read:**

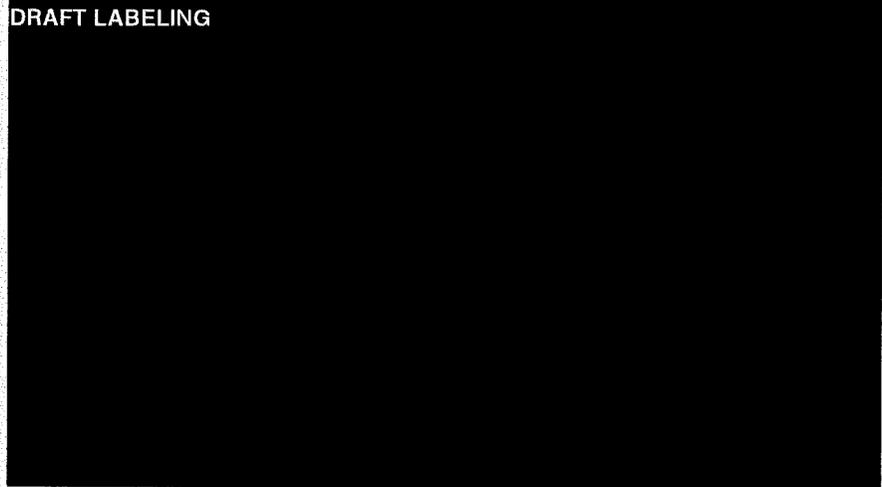
DRAFT LABELING



- (2) **Insert the word [REDACTED] after the word [REDACTED] in the sentence referencing [REDACTED] to read: [REDACTED]**

- The firm should be requested to revise the description of the second study to read:

DRAFT LABELING

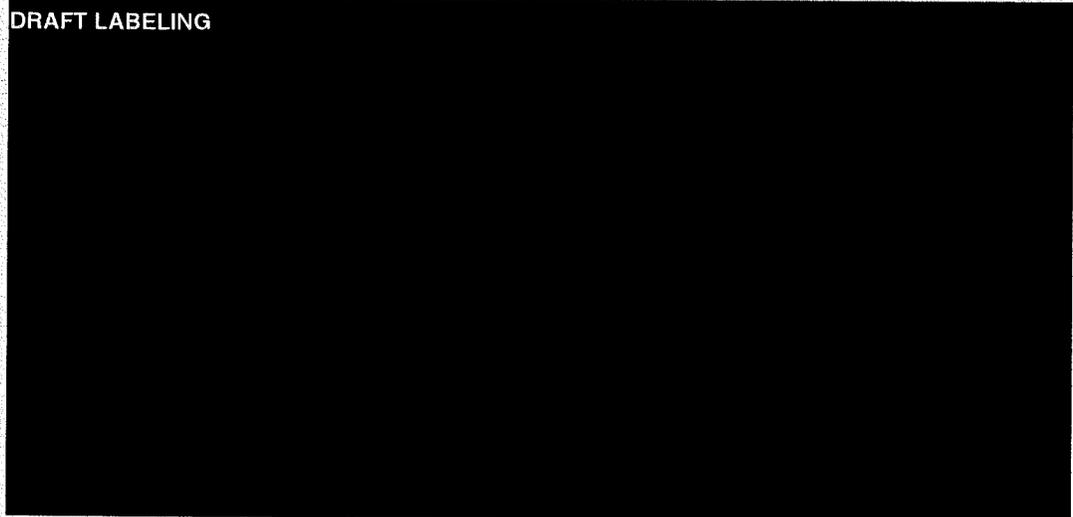
A large black rectangular redaction box covers the majority of the page content below the first bullet point. The text "DRAFT LABELING" is visible in the top left corner of this redacted area.

- The firm should be requested to revise the data table for the second study to be consistent with the table format requested in the January 30, 1998 approval letter for S-010.

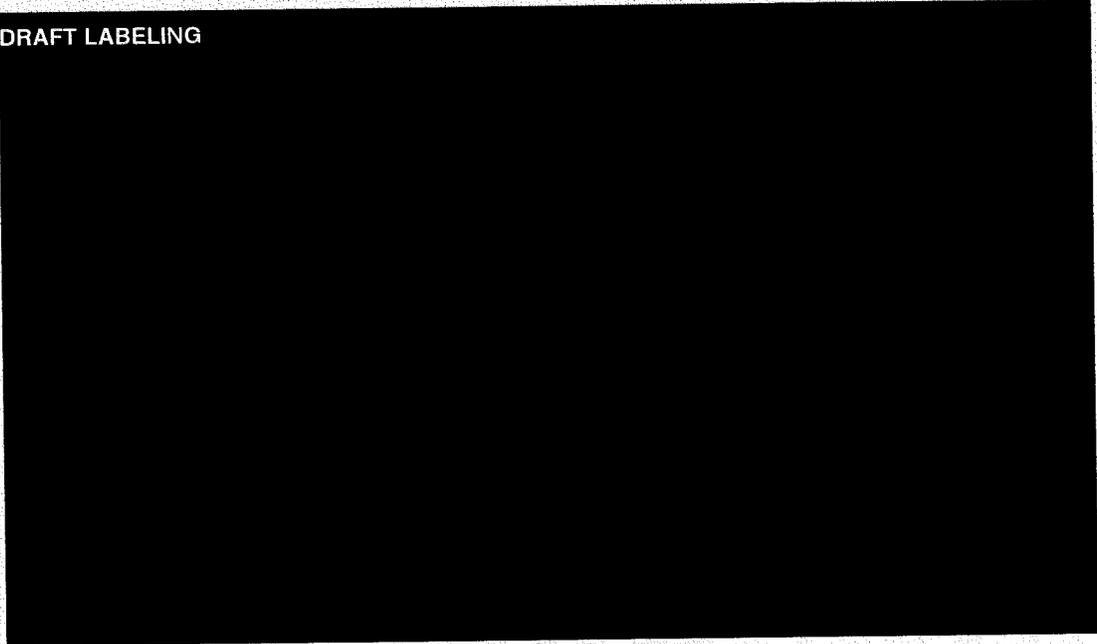
5. The INDICATIONS AND USAGE section has been revised.

This subsection was reviewed by the MEDICAL OFFICER, Dr. Nenad Markovic, and the DIVISION DIRECTOR, Dr. Lilia Talarico, and it is UNACCEPTABLE. The firm should be requested to revise the section to read:

DRAFT LABELING

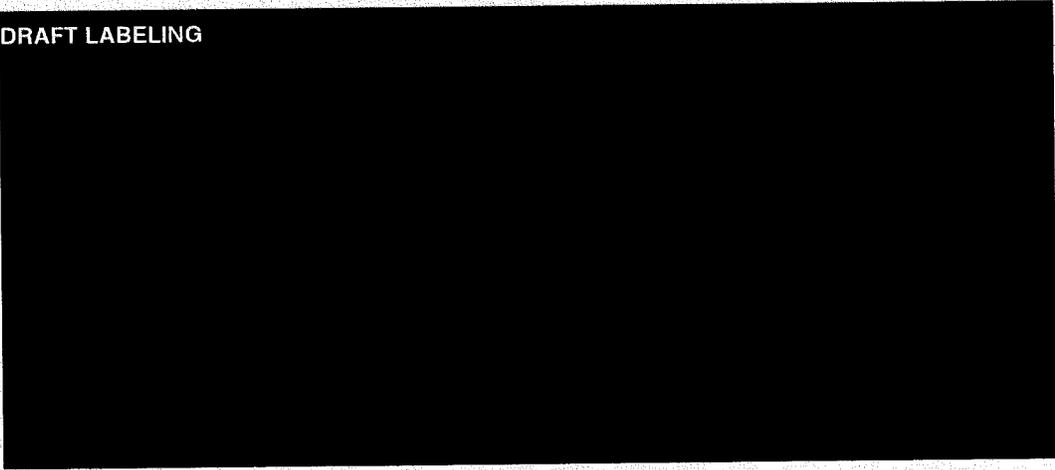
A large black rectangular redaction box covers the majority of the page content below the second bullet point and the numbered item. The text "DRAFT LABELING" is visible in the top left corner of this redacted area.

DRAFT LABELING



6. In the WARNINGS section:
 - a. **The firm should be requested to revise the second paragraph as requested in the September 8, 1997 approvable letter.**
 - b. In the "Thrombocytopenia" subsection:

DRAFT LABELING



- (3) The firm should be requested to retain the last paragraph of the subsection, with revisions, to read:

DRAFT LABELING

7. In the PRECAUTIONS section:

- a. In the "General" subsection, the last sentence in the subsection was deleted:

DRAFT LABELING

BEST POSSIBLE

This is UNACCEPTABLE. The firm should be requested to re-instate the sentence to read:

- b. In the "Laboratory Tests" subsection, the phrase [REDACTED] was changed to [REDACTED]

This change is ACCEPTABLE.

- c. In the "Drug Interactions" subsection:

The firm should be requested to revise the subsection as requested in the September 8, 1997 approvable letter.

- d. The "Drug/Laboratory Test Interactions":

- (1) The subsection was deleted from the PRECAUTIONS section, and placed in the ADVERSE REACTIONS section, after the "Thrombocytopenia" subsection.

This change is ACCEPTABLE.

- (2) The percent of patients with greater than three times the upper limit of normal laboratory reference for AST and ALT have been changed.

This change was reviewed by the MEDICAL OFFICER, Dr. Nenad Markovic, and the DIVISION DIRECTOR, Dr. Lilia Talarico, and it is ACCEPTABLE.

- (3) The changes requested in the September 8, 1997 approvable letter for S-016 were not incorporated.

This is UNACCEPTABLE. The firm should be requested to incorporate the changes.

- e. In the "Carcinogenesis, Mutagenesis, Impairment of Fertility" subsection:

- (1) The firm should be requested to revise the subsection as requested in the September 8, 1997 approvable letter.

- (2) The firm should be requested to provide the re-calculation, including related formulas and all mathematical processes, for the maximum human dose in clinical trials.

- f. In the "Pregnancy" subsection, the "*Teratogenic Effects*" and "*Non-teratogenic Effects*" sub-subsections:

The firm should be requested to revise the subsection as requested in the September 8, 1997 approvable letter.

8. In the ADVERSE EVENTS section, in the "Hemorrhage" subsection:

- a. The word [REDACTED] has been deleted in the first sentence of the subsection.

This is UNACCEPTABLE. The firm should be requested to insert the word "major" in the first sentence of the subsection to read:

[REDACTED] DRAFT LABELING [REDACTED]

- b. The "Major Bleeding Episodes" tables for the various indications have been combined into one large table integrating all of the indications with the bleeding definition at the introduction to the table. In addition, the major bleeding events for "Deep Vein Thrombosis and Pulmonary Embolism" treatment were added.

These changes were reviewed by the MEDICAL OFFICER, Dr. Nenad Markovic, and the DIVISION DIRECTOR, Dr. Lilia Talarico, and they are UNACCEPTABLE.

- The firm should be requested to delete the one large table and insert the table approved in S-010 on January 10, 1998 with the request revisions.
 - Regarding the table for major bleeding episodes in "Deep Vein Thrombosis and Pulmonary Embolism Treatment"
 - (1) The table should be formatted in a manner consistent with the other tables.
 - (2) All major bleeding criteria should be referenced in the footnote.
 - (3) Insert the word "sodium" after the word "warfarin" in the sentence referencing "warfarin" to read: "warfarin sodium".
- c. The subsection titled "Elevations of Serum Aminotransferases" was inserted after the "Thrombocytopenia" subsection.

This information, and the placement of the information, was reviewed by the MEDICAL OFFICER, Dr. Nenad Markovic, and the DIVISION DIRECTOR, Dr. Lilia Talarico, and it is UNACCEPTABLE. The firm should be requested to make the following changes:

- (1) Re-insert the second paragraph of the subsection: [REDACTED]
 - (2) Implement the changes requested in the September 8, 1997 approvable letter for S-016.
- d. In the "Other" subsection:

The firm should be requested to incorporate the information approved in January 30, 1998, in S-010, including the modifications to the tables requested in that letter. Note: Changing the phrase DRAFT LABELING [REDACTED]

- e. In the "Other" subsection, information regarding adverse events at $\geq 2\%$ incidence in enoxaparin treated patients undergoing treatment for deep vein thrombosis and pulmonary embolism was added.

This information should be reviewed by the MEDICAL OFFICER, Dr. Nenad Markovic, and DIVISION DIRECTOR, Dr. Lilia Talarico, and the information is ACCEPTABLE. The firm should be requested to modify the table as requested in the January 30, 1998, in S-010.

9. In the OVERDOSAGE section, the "Symptoms/Treatment" subsection:

The firm should be requested to initiate the changes requested in the September 8, 1997 approvable letter for S-016.

10. In the DOSAGE AND ADMINISTRATION section:

- a. The first paragraph has been changed

from (S-010) **DRAFT LABELING**

from (S-016):

to (S-015):

This information should be reviewed by the MEDICAL OFFICER, Dr. Nenad Markovic, and DIVISION DIRECTOR, Dr. Lilia Talarico, and the information is UNACCEPTABLE. The firm should be requested to delete the first paragraph and insert the following to read:

All patients should be screened prior to administration of Lovenox to rule out a bleeding disorder. Since coagulation parameters are unsuitable for monitoring Lovenox activity, routine monitoring of