

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020164, S015

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

**Division of Gastrointestinal & Coagulation Drug Products
CONSUMER SAFETY OFFICER REVIEW**

Application Number: NDA 20-164/S-015

Name of Drug: Lovenox® (enoxaparin sodium) Injection

Sponsor: Rhone-Poulenc Rorer Pharmaceuticals Inc.

DEC 31 1998

Material Reviewed

Submission Date(s): July 6, 1998

Receipt Date(s): July 7, 1998

Background and Summary Description: DRAFT LABELING

The sponsor submitted draft labeling July 6, 1998 in response to a February 27, 1998 approvable letter. It was noted that although there are two approved package inserts for Lovenox Injection, approved March 27, 1998 in S-016 identified as "IN-1107R, Rev. 7/98" and "IN-2828C, Rev. 7/98" only one package insert was submitted for review.

Review

Package Insert

The draft labeling, identified as IN-1107 __ Rev. __/98, was compared to the approved labeling, identified as "IN-1107R, Rev. 7/98" and the requested changes in the February 27, 1998 approvable letter (see also the February 27, 1998 CSO Labeling Review) and they are identical except for the following:

1. In the title section of the package insert:
 - a. A new company trademark logo has been added.

This change is ACCEPTABLE.

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

from: DRAFT LABELING

to: [REDACTED]

This change is ACCEPTABLE.

2. In the DESCRIPTION section, the first sentence was revised

from:

[REDACTED]

to:

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

3. The CLINICAL PHARMACOLOGY section and the "Pharmacodynamics" subsection contains multiple revisions from the approved labeling (S-016, 03/27/98) and the recommendations in the 02/27/98 approvable letter.

These revisions should be reviewed by the BIOPHARMACEUTICS reviewer (see Clinical Pharmacology and Biopharmaceutics Review dated 12/23/98).

4. In the CLINICAL TRIALS section:

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

- (1) In the first sentence, the underlined words were changed:

from:

[REDACTED]

to:

[REDACTED]

This change is UNACCEPTABLE. The 02/27/98 approvable letter specifically states that the words "post-operative" should be changed to "after surgery", EXCEPT when referencing the specific indication of prevention or treatment of post-operative DVT. The firm should be requested to revise the sentence to read:

DRAFT LABELING

- (2) In the title of the first table, and throughout the tables throughout the text, the word "Injection" was added after the word DRAFT LABELING DRAFT LABELING

This addition is ACCEPTABLE.

- (3) In the descriptive text throughout the section, the word "Injection" was added after the word DRAFT LABELING

This addition is ACCEPTABLE.

- (4) In the text throughout the section, and throughout the text of the package insert, the words DRAFT LABELING were changed to DRAFT LABELING

These changes, requested in the March 27, 1998 approvable letter, are ACCEPTABLE.

- (5) In the second sentence of the paragraph, and throughout the text of the package insert, the abbreviation was changed to read

These changes, requested in the March 27, 1998 approvable letter, are ACCEPTABLE.

- b. In the "Extended Prophylaxis in Hip Replacement Surgery" subsection, in the first sentence, the underlined words were changed

from:

DRAFT LABELING

DRAFT LABELING

to:

This change is UNACCEPTABLE. The 02/27/98 approvable letter specifically states that the words "post-operative" should be changed to "after surgery", EXCEPT when referencing the specific indication of prevention or treatment of post-operative DVT. The firm should be requested to revise the sentence to read:

DRAFT LABELING

c. In the "Treatment of Deep Vein Thrombosis and Pulmonary Embolism" subsection:

(1) In the first sentence, the underlined words were changed

from:

DRAFT LABELING

to:

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

(2) In the second sentence, and throughout the text and tables of the package insert, the word [REDACTED] was added after the word [REDACTED] to read

DRAFT LABELING

This change, requested in the March 27, 1998 approvable letter, is ACCEPTABLE.

- (3) In the subsection, and throughout the text and tables of the package insert, the word [REDACTED] was deleted before the word [REDACTED]

This change, requested in the March 27, 1998 approvable letter, is ACCEPTABLE.

- (4) In the "Efficacy of Lovenox Injection In Treatment of Deep Vein Thrombosis and Pulmonary Embolism" Table:

- (a) The table, and the second table in the subsection, was revised to be consistent with the table format throughout the package insert text.

This revision, requested in the March 27, 1998 approvable letter, is ACCEPTABLE.

- (b) In the "Indication" column of the table, the indication was changed

from:

[REDACTED]
DRAFT LABELING

to:

[REDACTED]

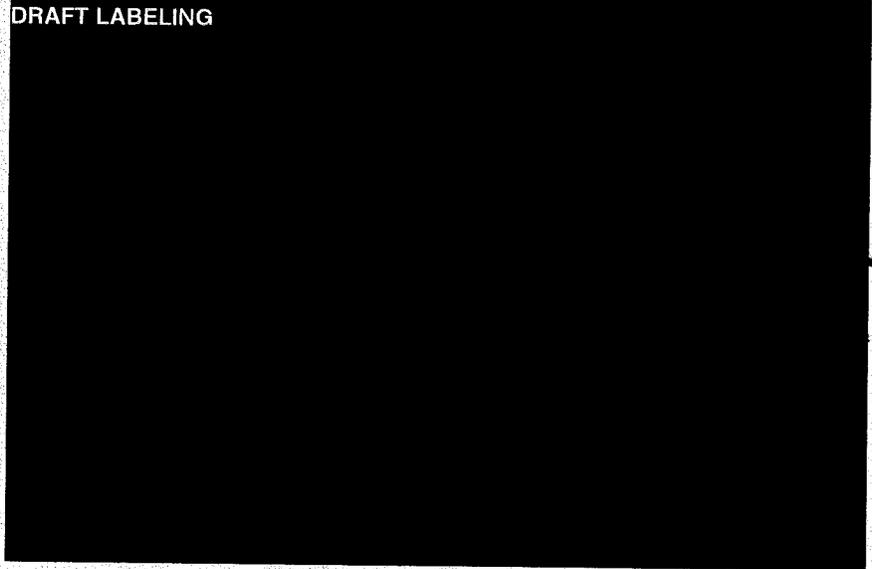
This change was reviewed by the DIVISION DIRECTOR, Dr. Lilia Talarico, and it is ACCEPTABLE.

- (5) In the paragraph describing the second study, the underlined words were changed

from:

[REDACTED]
DRAFT LABELING

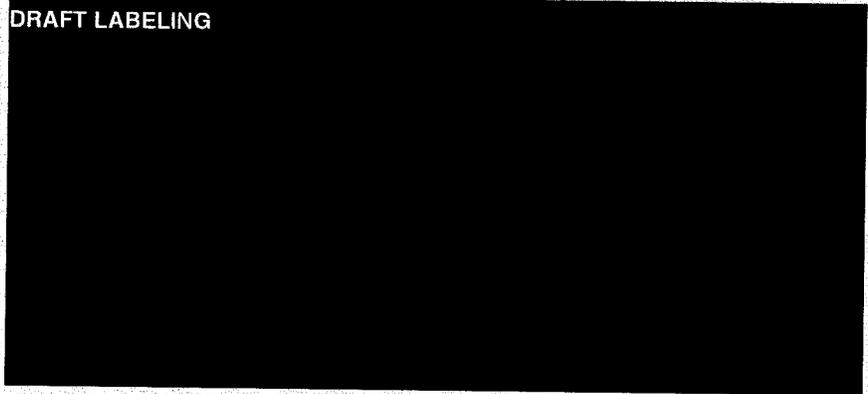
DRAFT LABELING



to:

These revisions were reviewed by the DIVISION DIRECTOR, Dr. Lilia Talarico, and they are UNACCEPTABLE. The firm should be requested to revise as follows:

DRAFT LABELING



- (6) In the table titled "Efficacy of Lovenox in Treatment of Deep Vein Thrombosis", in the "Indication" column of the table, the indication was changed

from:

DRAFT LABELING



to:

**This change was reviewed by the DIVISION DIRECTOR,
Dr. Lilia Talarico, and it is ACCEPTABLE.**

5. In the INDICATION AND USAGE section, the underlined words of the proposed new indication were changed

from:

Lovenox is also indicated for:

-

DRAFT LABELING

-

to:

Lovenox is also indicated for:

-

DRAFT LABELING

-

**This change was reviewed by the DIVISION DIRECTOR,
Dr. Lilia Talarico, and it is UNACCEPTABLE. The sponsor should be
requested to revise the indication to read:**

Lovenox is also indicated for:

DRAFT LABELING

DRAFT LABELING

6. In the WARNINGS section:

a. DRAFT LABELING

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

b. The first sentence of the subsection and the revised last paragraph of the subsection have been retained.

This is ACCEPTABLE, as it was requested in the February 27, 1998 approvable letter.

7. In the PRECAUTIONS section, in the "General" subsection, the underlined words in the last sentence were changed

from:

DRAFT LABELING

to:

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

8. In the ADVERSE EVENTS section:

a. In the "Hemorrhage" subsection:

- (1) In the "Major Bleeding Episodes in Hip or Knee Replacement Surgery" table, in footnotes 2-4, the words [REDACTED] were deleted and replaced with the word [REDACTED]

This change is ACCEPTABLE.

- (2) In the "Major Bleeding Episodes in Abdominal & Colorectal Surgery" table, the symbol [REDACTED] was replaced with the word [REDACTED]

[REDACTED]
DRAFT LABELING

This change is ACCEPTABLE.

- (3) The "Major Bleeding Episodes in Deep Vein Thrombosis and Pulmonary Embolism Treatment" table has been re-formatted as requested in the February 28, 1998 approvable letter.

These changes, requested in the February 27, 1998 approvable letter, are ACCEPTABLE.

- (4) In the "Major Bleeding Episodes in Unstable Angina and Non-Q-Wave Myocardial Infarction" table, in the first sentence of footnote 3, the last words of the sentence, [REDACTED] were deleted to read:

[REDACTED]
DRAFT LABELING

This change is ACCEPTABLE, as the sentence is now consistent with the other footnotes in tables throughout the text.

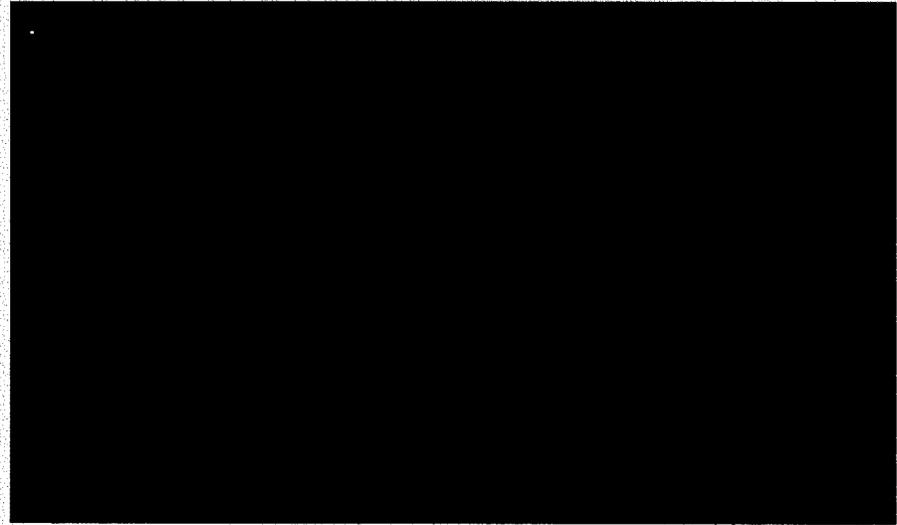
- b. In the "Elevation of Serum Aminotransferases" subsection, in the first sentence, the words "(enoxaparin sodium)" were deleted between the words Lovenox® and Injection to read: [REDACTED]

This deletion is ACCEPTABLE.

c. In the "Other" subsection:

- (1) In the first sentence, the underlined words were changed from:

to:



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

- (2) In the tables throughout the subsection, the following formatting changes were made: the word "Enoxaparin" was deleted in the table titles and replaced with the words "Lovenox Injection; the superscript [REDACTED] was deleted from above the last word of the title of the table, to above the word "Patients" in the title of each table; the words [REDACTED] were deleted from the footnotes and replaced with the word [REDACTED] and the initials [REDACTED] were changed to [REDACTED]

These formatting changes are ACCEPTABLE and provide consistency throughout the tables in the package insert.

- (3) In the "Adverse Events in enoxaparin Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction" subsection:
- (a) In the second paragraph, the words [REDACTED] were deleted between the words Lovenox® and Injection to read: [REDACTED]

This change is ACCEPTABLE.

- (b) In the table, throughout the subsection, the following formatting changes were made: the word [REDACTED] was deleted in the table title and replaced with the words [REDACTED] the superscript [REDACTED] was deleted from above the last word of the title of the table, to above the word [REDACTED] in the title of each table; the words [REDACTED] were deleted from the footnotes and replaced with the word [REDACTED] and the initials [REDACTED]
DRAFT LABELING

These formatting changes are ACCEPTABLE and provide consistency throughout the tables in the package insert.

- (c) In the "Ongoing Safety Surveillance" subsection, the number of epidural or spinal hematomas has been changed from [REDACTED]
DRAFT LABELING

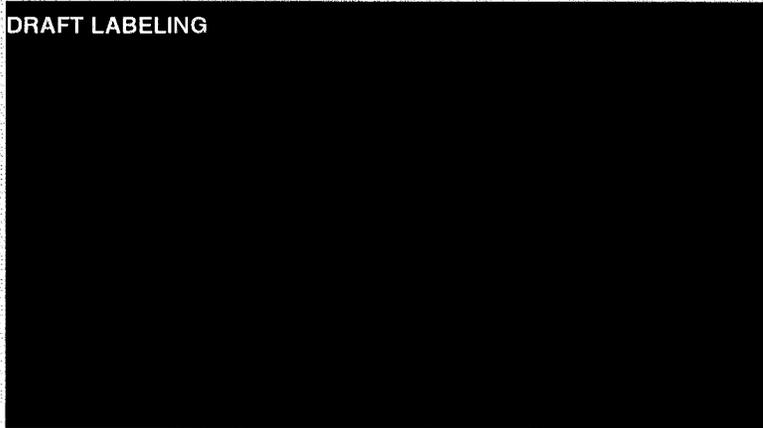
This change was reviewed by the DIVISION DIRECTOR, Dr. Lilia Talarico, and it is ACCEPTABLE.

- (d) In the "Other reports include" subsection, the underlined words were changed

from:

DRAFT LABELING

to:



This change was reviewed by the DIVISION DIRECTOR, Dr. Lilia Talarico, and it is UNACCEPTABLE. The sponsor should be requested to revise the text to read:

DRAFT LABELING

9. In the OVERDOSAGE section, in the second paragraph, the words "(enoxaparin sodium)" were deleted between the words Lovenox® and Injection to read: [REDACTED]

This change is ACCEPTABLE.

10. In the DOSAGE AND ADMINISTRATION section:

- a. The underlined words in the first sentence of the first paragraph has been changed

from:

DRAFT LABELING

to:

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

- b. In the "Adult Dosage" subsection, in the second sentence, the word [REDACTED]

DRAFT LABELING

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

- c. In the "Treatment of Deep Vein Thrombosis and Pulmonary Embolism" subsection, in the second sentence, the underlined words have been changed

from:

DRAFT LABELING

to:

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

11. After the HOW SUPPLIED section, the [REDACTED] statement has been deleted and replaced with the phrase: [REDACTED]

This change is ACCEPTABLE.

Immediate Container Labels and Cartons

In a May 19, 1998 submission, the sponsor submitted mock-up copies of the labels for the 60, 80, and 100 mg immediate container labels, blister packets, and cartons. The copies were compared to the mock-up labeling submitted February 28, 1997 (also see the February 27, 1998 CSO labeling review) and the requests in the February 28, 1998 approvable letter, and they are identical except for the following:

12. On the cartons:
 - a. The format of the drug name has been changed

from:

to:

This change is ACCEPTABLE.