

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 020164/S010**

**ADMINISTRATIVE DOCUMENTS**

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: 20-164/S-010

Name of Drug: Lovenox® (enoxaparin sodium) Injection

JAN 29 1998

Sponsor: Rhone-Poulenc Rorer Pharmaceuticals Inc.

Material Reviewed

Submission Date(s): January 19, 1998  
January 27, 1998

Receipt Date(s): January 20, 1998  
January 27, 1998

APPEARS THIS WAY  
ON ORIGINAL

**Background and Summary Description:** The sponsor submitted an efficacy supplement on March 29, 1996 for a new indication: extended prophylaxis following hip replacement surgery. On July 22, 1997, the sponsor submitted draft labeling (see CSO review dated 10/09/97) in response to a March 21, 1997 approvable letter. On October 16, 1997, the firm submitted new revised labeling (see CSO review dated 12/09/97). On January 19 and January 27, 1998 the firm submitted final printed labeling (FPL) in response to the December 11, 1997 approvable letter and additional labeling revisions requested in a January 14, 1998 Agency letter.

Review

APPEARS THIS WAY  
ON ORIGINAL

Package Insert

The FPL printed at the \_\_\_\_\_, identified as "IN-1107P, Rev.1/98" and the FPL printed at the \_\_\_\_\_, identified as "IN-2828A Rev. 1/98", was compared to the draft labeling submitted October 16, 1997, the labeling approved March 7, 1997, in S-007, identified as "IN-1107N Rev.7/97" \_\_\_\_\_ and "IN-2828 Rev. 9/97" \_\_\_\_\_, the December 11, 1997, approvable letter, and the revisions requested in the January 14, 1998, Agency letter. The FPL was identical except for the following:

1. The identification number was changed.

This change is **ACCEPTABLE**.

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ON ORIGINAL

2. The following has been added to the right corner of page 1 above the identification numbers:

Lovenox®  
(enoxaparin sodium)  
Injection

**This addition is ACCEPTABLE.**

APPEARS THIS WAY  
ON ORIGINAL

3. The point size of the lettering is smaller.

**This change is ACCEPTABLE.**

4. The format has been revised from two columns to one column in the "IN-1107P" package insert.

**This change is ACCEPTABLE.**

APPEARS THIS WAY  
ON ORIGINAL

5. Page numbers have been added at the bottom of the page in the "IN-2828A" package insert.

**This change is ACCEPTABLE.**

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ON ORIGINAL

6. In the CLINICAL TRIALS section:

- a. The asterisks (\*) used to designate footnotes in the tables were changed to superscript number.

**This change is ACCEPTABLE.**

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ON ORIGINAL

- b. The phrases "Treatment Group" and "Dosing Regimen" are inaccurately placed in the column headings and the tables are inconsistently formatted throughout the text.

**Request that the firm consider revising the tables the tables at the next printing to provide a consistent format throughout the text as follows: (1) in the CLINICAL TRIALS section, delete the current first column title "Dosing Regimen" and replace with the word "Indication" (2) in the CLINICAL TRIALS section, delete the second and third column title "Treatment Group" and replace with the words "Dosing Regimen"; (3) in the ADVERSE REACTIONS section, insert the word "Indication" in the "title" section of the first column in the table titled "Major Bleeding**

Episodes in Abdominal & Colorectal Surgery"; (4) in the ADVERSE REACTIONS section, insert the title "Dosing Regimen" above the appropriate columns in all the tables; and (5) throughout the text, provide horizontal and vertical line "grids" similar to the grids in the table titled "Major Bleeding Episodes in Hip or Knee Replacement Surgery" in the ADVERSE REACTIONS section.

- 7. In the HOW SUPPLIED section, after the storage statement, the following sentence, in bolded lettering, was added: "Keep out of the reach of children."

This addition is ACCEPTABLE.

- 8. At the end of the package insert, the copyright date was changed from "© 1997" to "© 1998".

This change is ACCEPTABLE.

APPEARS THIS WAY ON ORIGINAL

Conclusions

The submitted FPL is acceptable. The firm should be requested to consistently format all tables throughout the package insert to enhance readability, clarity, and uniformity as outlined in 6.b.above.

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*/S/*  
*01/20/98*  
Karen Oliver  
Regulatory Health Project Manager

cc:

- Original NDA 20-164/S-010
- HFD-180/Div. Files
- HFD-180/L.Talarico */S/ 29-98*
- HFD-180/N.Markovic
- HFD-180/K.Oliver
- HFD-180/E.Duffy
- HFD-180/J.Sieczkowski
- HFD-720/A.J.Sankoh

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HFD-720/M.Rashid  
r/d init: L.Talarico 01/26/98  
draft: KO/January 23, 1998  
final: KO/01/28/98/c:\wpwin\karenfil\rev\20164801.1ko

CSO REVIEW

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**Division of Gastrointestinal & Coagulation Drug Products**

**CONSUMER SAFETY OFFICER REVIEW**

**Application Number:** 20-164/S-010

DEC - 3 1997

**Name of Drug:** Lovenox® (enoxaparin sodium) Injection

**Sponsor:** Rhone-Poulenc Rorer Pharmaceuticals Inc.

**Material Reviewed**

**Submission Date(s):** October 16, 1997

APPEARS THIS WAY  
ON ORIGINAL

**Receipt Date(s):** October 17, 1997

**Background and Summary Description:** The sponsor submitted an efficacy supplement on March 29, 1996 for a new indication: extended prophylaxis following hip replacement surgery. On July 22, 1997, the sponsor submitted draft labeling in response to a March 21, 1997 approvable letter (see CSO review dated 10/09/97). On October 16, 1997, the firm submitted new revised labeling in response to the recommendations in the 10/09/97 CSO labeling review.

**Review**

The new revised draft labeling, identified as "IN-1107 \_\_, Rev. \_\_/97" was compared to the draft labeling submitted July 22, 1997, and the recommendations in the 10/09/97 CSO labeling review. The draft labeling are identical except for the following:

1. In the CLINICAL PHARMACOLOGY section:
  - a. The first reference to "subcutaneous" route of drug administration, was changed to "subcutaneous (s.c)", with subsequent references throughout the text of the package insert consistently changed to the initials "s.c.", and the first reference to "intravenous" route of drug administration was changed to "intravenous (i.v)", with subsequent references throughout the text of the package insert consistently changed to the initials "i.v."

**These changes, as requested in the 10/09/97 CSO Review, are ACCEPTABLE.**

- b. In the "Pharmacodynamics" subsection, the word "administration" was changed to "dosing".

**This change, as requested in the 10/09/97 CSO Review, is ACCEPTABLE.**

- c. In the "Pharmacodynamics" subsection the words "once-daily" was changed to "once daily" in this subsection.

**This change, as requested in the 10/09/97 CSO Review, is ACCEPTABLE.**

2. In the CLINICAL TRIALS section:

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

- (1) In the first table titled "Efficacy of Lovenox in Hip Replacement Surgery", the subsection title was changed from "All Treated Patients" to "All Hip Replacement Patients". The subsection titles were consistently changed to reflect the specific patient population treated.

**These changes, as requested in the 10/09/97 CSO Review, are ACCEPTABLE.**

- (2) In the first table titled "Efficacy of Lovenox in Hip Replacement Surgery", the subsection title "Treatment Group Dosing Regimen" was changed to "Dosing Regimen". The subsection titles were consistently changed in the tables throughout the text.

**This change is ACCEPTABLE.**

- (3) In the second table titled "Efficacy of Lovenox in Hip Replacement Surgery", the subsection title "Dosing Regimen" was re-instated and used consistently throughout the text of the package insert tables.

**This change, as requested in the 10/09/97 CSO Review, is ACCEPTABLE.**

- (4) In the second table titled "Efficacy of Lovenox in Hip Replacement Surgery", the initials "QD" were changed to "q.d." and "BID" to "b.i.d." and these initials were used consistently throughout the text of the package insert.

**These changes, as requested in the 10/09/97 CSO Review, are ACCEPTABLE.**

- (5) In the second table titled "Efficacy of Lovenox in Hip Replacement Surgery", in the body of the table, there is only one asterisk (\*) referencing a "\*p" value. The second "\*\*\*p" value is not referenced by a "\*\*\*" in the body of the table.

**This is UNACCEPTABLE. The firm should be requested to provide the appropriate footnote information for the "\*\*\*" in the body of the table.**

- (6) In the "Extended Prophylaxis in Hip Replacement Surgery" subsection, in the paragraph beginning with the words "In a second study, patients undergoing...". the phrase "placebo 35" is incorrect.

**This is UNACCEPTABLE. As requested by the MEDICAL OFFICER, Dr. Nenad Markovic, the firm should change the phrase to "placebo 45".**

- b. In the "*Extended Prophylaxis in Hip Replacement Surgery*:" subsection:

- (1) In the first sentence of the text describing the first study, the dosing regimen for the perioperative period was added in the first sentence and the following words were added to the second sentence of the paragraph: "At the end of the perioperative period, all patients..."

**These changes were reviewed by the MEDICAL OFFICER, Dr. Nenad Markovic, and they are ACCEPTABLE.**

- (2) In the paragraph describing the second study:

- (a) In the first sentence, the dosing regimen was added.

**This addition was reviewed by the MEDICAL OFFICER, Dr. Nenad Markovic, and they are ACCEPTABLE.**

- (b) In the last sentence, the number of deep vein thrombosis events during extended prophylaxis for the enoxaparin and placebo patient groups were added.

**This addition was reviewed by the MEDICAL OFFICER,**



**Dr. Nenad Markovic, and they are ACCEPTABLE.**

- (3) The black box outline the table titled "Efficacy of Lovenox in Long Term Prevention Following Hip Replacement Surgery" was deleted.

**This deletion is ACCEPTABLE. However, there are inconsistencies in the package insert regarding the black line outlining of the tables. Throughout the package insert, the firm should be requested to format tables consistently, by containing or not containing a black box outline.**

- c. In the "Abdominal Surgery" subsection, the word "once-daily" was used.

**This is UNACCEPTABLE. the words "once only" should be re-instated and used consistently throughout the text.**

3. In the WARNINGS section, the "Thrombocytopenia" subsection, the percentage rates have been revised, separately listing the moderate and severe thrombocytopenia rates for patients undergoing hip or knee replacement surgery.

**These changes, requested in the 10/09/97 CSO Review, were reviewed by the MEDICAL OFFICER, Dr. Nenad Markovic, and they are ACCEPTABLE.**

4. 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 revised to include information regarding the peri-operative period and the extended prophylaxis period in the "Hip Replacement Surgery, Extended Prophylaxis" subheading.

**This additional information, requested in the 10/09/97 CSO review, was reviewed by the MEDICAL OFFICER, Dr. Nenad Markovic, and it is UNACCEPTABLE. The firm should be requested to delete the headings in the first column and replace with the following: "Hip Replacement Surgery Without Extended Prophylaxis\*\*" and "Hip Replacement Surgery With Extended Prophylaxis\*\*\*\*" and provide appropriate information for the column headings. In the footnotes for the asterisks, state all the dosing regimens used in the clinical trials.**

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

from: "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."

to: "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."

**This change, requested in the 10/09/97 CSO Review, is ACCEPTABLE.**

- (3) Horizontal and vertical grid lines were added to the table.

**This addition is ACCEPTABLE. Request that the firm add grid lines to all the tables to enhance readability, clarity and uniformity.**

- (4) After the table, the following sentence was deleted as requested in the 10/09/97 CSO review: "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 deletion is ACCEPTABLE.**

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

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

to: "Injection site hematomas during the extended prophylaxis period after hip replacement surgery occurred in 9% of the enoxaparin patients versus 1.8% of the placebo patients."

**These changes were reviewed by the MEDICAL OFFICER, Dr. Nenad Markovic, and they are ACCEPTABLE.**

- (6) In the table titled "Major Bleeding Episodes in Abdominal & Colorectal Surgery\*", as requested in the 10/09/97 CSO Review, the following phrase was changed:

from: "...≤2g/dL or transfusion of 2 or more units of blood products."

to: "...≥2g/dL or transfusion of 2 or more units of blood products."

**This change is ACCEPTABLE.**

- b. The table titled "Adverse Events Occurring at ≥ 2% Incidence in Enoxaparin Treated Patients\* Undergoing Hip or Knee Replacement Surgery", was revised to include adverse events information for the patients receiving 40 mg Lovenox as requested in the 10/08/97 CSO review.

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

5. In the DOSAGE AND ADMINISTRATION section:

- a. Prior to the "Adult Dosage:" subsection, the last word in the second sentence was changed from "values" to "baseline coagulation parameters"; and (2) the second paragraph, "When patients receive...thrombosis has diminished." was deleted.

**These changes, requested in the 10/09/97 CSO Review, are ACCEPTABLE.**

- b. In the "Adult Dosage" section:

- (1) In the "Hip and Knee Replacement Surgery:" subsection, the underlined words in the following sentence were added:

From FDA's Text: "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."

Firm's Proposal: "Following the initial phase of thromboprophylaxis in hip replacement surgery patients (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."

**This addition is ACCEPTABLE.**

6. In the HOW SUPPLIED section, the text and the presentation table, as requested in the 10/09/97 CSO Review, was modified as follows: (1) "DOSAGE AND ADMINISTRATION, Adult Dosage Reference" column was deleted; (2) a column with the NDC numbers of the products was added; and (3) the word "Presentation" as a column heading was deleted.

**These changes are ACCEPTABLE.**

**Conclusions**

1. The following changes are ACCEPTABLE: 1.a.-c., 2.a.(1)-(4), 2.b.(1)-(2), 3., 4.a.(2)-(6), 4.b., 5.a.-b., and 6.
2. The following changes are UNACCEPTABLE and the firm should be requested to make the suggested revisions: 2.a.(5)-(6), 2.c, and 4.a.(1).
3. The following inconsistencies should be conveyed to the firm: 2.b.(3) and 4.a.(3).
4. The Agency has received more than 30 spontaneous safety reports describing patients who have developed epidural or spinal hematomas with the concurrent use of Lovenox® Injection and spinal/epidural anesthesia or spinal puncture. Many of the hematomas caused neurologic injury, including long-term or permanent paralysis. As a result of these reports, the Agency is requesting that all manufacturers of low molecular weight heparins and heparinoids make changes in their package insert labeling so as to furnish adequate information for the safe and effective use of the drug. To address these safety concerns in the Lovenox package insert, the approvable letter for this supplement will include revisions to the PRECAUTIONS, WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections.

APPEARS THIS WAY  
ON ORIGINAL

*/S/*  
*12/09/97*  
Karen Oliver  
Regulatory Health Project Manager

APPEARS THIS WAY  
ON ORIGINAL

cc:

Original NDA 20-164/S-010  
HFD-180/Div. Files  
HFD-180/L.Talarico  
HFD-180/N.Markovic  
HFD-180/K.Oliver  
HFD-180/E.Duffy  
HFD-180/J.Sieczkowski  
HFD-720/M.Huque  
HFD-720/M.Rashid

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ON ORIGINAL

draft: KO/October 26, 1997

r/d Initials: N.Markovic 10/29/97

r/d Initials: L.Talarico 11/03/97

final: KO/12/09/97/c:\wpwin\karenfil\rev\20164710.0ko

CSO REVIEW

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ON ORIGINAL

*Oliver*

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: 20-164/S-010

Name of Drug: Lovenox® (enoxaparin sodium) Injection

OCT - 9 1997

Sponsor: Rhone-Poulenc Rorer Pharmaceuticals Inc.

Material Reviewed

APPEARS THIS WAY  
ON ORIGINAL

Submission Date(s): July 22, 1997

Receipt Date(s): July 24, 1997

**Background and Summary Description:** The sponsor submitted an efficacy supplement on March 29, 1996 for a new indication: extended prophylaxis following hip replacement surgery. The sponsor submitted draft labeling in response to a March 21, 1997 approvable letter.

Review

The draft labeling, identified as "IN-1107\_\_\_, Rev. \_\_\_/97" was compared to the draft labeling submitted March 29, 1996, identified as IN-XXXXX, Rev.MM/YY", and to the revisions listed in the March 21, 1997 approvable letter. The draft labels are identical except for the following:

1. In the DESCRIPTION section, the following sentences were changed

from: "It is available in prefilled syringes and ampules each containing 10 mg enoxaparin sodium per 0.1 mL Water for Injection." "The approximate anti-Factor Xa activity is 1000 IU per every 10 mg of drug (with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard (see HOW SUPPLIED for presentation descriptions)."

to: "It is available in: prefilled syringes containing 30 mg enoxaparin sodium per 0.3 mL Water for Injection or 40 mg enoxaparin sodium per 0.4 mL Water for Injection, and ampules containing 30 mg enoxaparin sodium per 0.3 mL Water for Injection (see DOSAGE AND ADMINISTRATION and HOW SUPPLIED)." "The approximate anti-Factor Xa activity is 1000 IU per every 10 mg of drug (with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard)."

These changes were reviewed by the **REVIEW CHEMIST**,  
**Dr. Joseph Sieczkowski**, and they are **ACCEPTABLE**.

2. In the **CLINICAL PHARMACOLOGY** section, the "Pharmacodynamics" subsection:

- a. In several sentences the word "intravenous" was changed to "i.v.", although in other sentences, the word "intravenous" was retained.

**This is UNACCEPTABLE. In first reference to "intravenous" route of drug administration in the text, the words "intravenous (i.v.)" should be used. Additional references throughout the text of the package insert should consistently use the initials "i.v."**

- b. The word "subcutaneous" was changed to the abbreviation "s.c."

**This is UNACCEPTABLE. In first reference to "subcutaneous" route of drug administration in the text, the words "subcutaneous (s.c.)" should be used. Additional references throughout the text of the package insert should consistently use the initials "s.c."**

- c. The word "dosing" was changed to "administration".

**This change is UNACCEPTABLE. The word "dosing" should be re-instated in this section and throughout the text.**

- d. An hyphen was added between the following two words to read: "once-daily".

**This change is ACCEPTABLE. The phrase "once-daily" should be used consistently throughout the text of the package insert.**

3. In the **CLINICAL TRIALS** section:

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

- (1) The second sentence in the second paragraph was changed

from: "Treatment was initiated 12-24 hours post-surgery and was continued for 10-14 days post-operatively."

to: "Provided that hemostasis was established, treatment was initiated 12-24 hours post-surgery and was continued for 10-14 days post-operatively."

This change is **ACCEPTABLE** (approved May 6, 1997, supplement 008).

- (2) In the first and second table titled "Efficacy of Lovenox in Hip Replacement Surgery", several editorial changes were initiated including: removing the "box" enclosure around the table; underlining headings and subheadings within the table; and bolding headings within the table.

**These changes are ACCEPTABLE.**

- (3) In the second table titled "Efficacy of Lovenox in Hip Replacement Surgery", the subsection titled "Dosing Regimen" was changed to "Dose".

This change is **UNACCEPTABLE** as it is inconsistent with the other tables. The title "Dosing Regimen" should be re-instated and used consistently throughout the text of the package insert tables.

- b. In the "*Extended Prophylaxis in Hip Replacement Surgery:*" subsection:

- (1) The title of the subsection was changed and the text of the subsection was inserted after the table and text for the "Efficacy of Lovenox in Hip Replacement Surgery" table as requested in the March 21, 1997 approvable letter.

**This change is ACCEPTABLE.**

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ON ORIGINAL

- (2) The text of the subsection was changed, such that the second study (a double blind design, those with no venous thromboembolic disease were randomized to a post-discharge regimen of either enoxaparin 40 mg [n=90] once daily or to placebo [n=89]) was listed first, the first study (a double-blind design, patients without venous thromboembolic disease, by clinical examination, were randomized to a post-discharge regimen of either enoxaparin 40 mg once daily sc or to placebo for 3 weeks) was listed second.

**These changes were reviewed by the MEDICAL OFFICER, Dr. Nenad Markovic, and they are ACCEPTABLE.**

- (3) In the first sentence of the text describing the first study, the dosing regimen is not included.



This change is **ACCEPTABLE** (approved May 6, 1997, supplement 008).

- (2) In the first and second table titled "Efficacy of Lovenox in Hip Replacement Surgery", several editorial changes were initiated including: removing the "box" enclosure around the table; underlining headings and subheadings within the table; and bolding headings within the table.

**These changes are ACCEPTABLE.**

APPEARS THIS WAY  
ON ORIGINAL

- (3) In the second table titled "Efficacy of Lovenox in Hip Replacement Surgery", the subsection titled "Dosing Regimen" was changed to "Dose".

This change is **UNACCEPTABLE** as it is inconsistent with the other tables. The title "Dosing Regimen" should be re-instated and used consistently throughout the text of the package insert tables.

b. In the "*Extended Prophylaxis in Hip Replacement Surgery*:" subsection:

- (1) The title of the subsection was changed and the text of the subsection was inserted after the table and text for the "Efficacy of Lovenox in Hip Replacement Surgery" table as requested in the March 21, 1997 approvable letter.

**This change is ACCEPTABLE.**

APPEARS THIS WAY  
ON ORIGINAL

- (2) The text of the subsection was changed, such that the second study (a double blind design, those with no venous thromboembolic disease were randomized to a post-discharge regimen of either enoxaparin 40 mg [n=90] once daily or to placebo [n=89]) was listed first, the first study (a double-blind design, patients without venous thromboembolic disease, by clinical examination, were randomized to a post-discharge regimen of either enoxaparin 40 mg once daily sc or to placebo for 3 weeks) was listed second.

**These changes were reviewed by the MEDICAL OFFICER, Dr. Nenad Markovic, and they are ACCEPTABLE.**

- (3) In the first sentence of the text describing the first study, the dosing regimen is not included.

**This is UNACCEPTABLE. The sponsor should be requested to include the dosing regimen for the perioperative period in the first sentence and add the following words to the second sentence of the paragraph: "At the end of the perioperative period, all patients..."**

- (4) In the paragraph describing the second study:
- (a) In the first sentence, the dosing regimen of the study is not included.

**This is UNACCEPTABLE. The sponsor should be requested to include the dosing regimen for the second study, including the perioperative and post operative periods.**

- (b) In the last sentence, only the p-values for both total DVT and proximal DVT are included.

**This is UNACCEPTABLE. The sponsor should be requested to also provide the number of deep vein thrombosis events during extended prophylaxis for the enoxaparin and placebo patient groups.**

- (5) The table titled "Efficacy of Lovenox in Long Term Prevention Following Hip Replacement Surgery", which illustrated the results from the study in which all patients were examined for clinical signs and symptoms of DVT disease prior to randomization was deleted and replaced with a table titled "Efficacy of Lovenox with Extended Prophylaxis Following Hip Replacement Surgery". The replacement table illustrates results from the study in which all patients underwent bilateral venography prior to randomization.

**These changes were reviewed by the MEDICAL OFFICER, Dr. Nenad Markovic, and they are ACCEPTABLE.**

- (6) In the description of the first knee replacement surgery study, the following sentence was changed

from: "Treatment was initiated with 12-24 hours post-operatively and was continued up to 15 days post-operatively."

to: "Provided that hemostasis was established, treatment was initiated with 12-24 hours post-operatively and was continued up to 15 days post-operatively."

**This change is ACCEPTABLE (approved May 6, 1997, supplement 008.**

(7) In the table titled "Efficacy of Lovenox in Knee Replacement Surgery":

(a) Several editorial changes were initiated including: removing the "box" enclosure around the table; underlining headings and subheadings within the table; and bolding headings within the table.

APPEARS THIS WAY  
ON ORIGINAL

**These changes are ACCEPTABLE.**

(b) The subheading within the table "All Treated Patients" was changed to "All Knee Replacement Patients".

**This change is ACCEPTABLE. The sponsor should be requested to make similar changes in the other tables, identifying the patient population being treated, i.e., "All Hip Replacement Patients."**

c. A subsection titled "Abdominal Surgery:" as added.

**This addition is ACCEPTABLE (abdominal surgery indication approved May 6, 1997, supplement 008.)**

4. In the INDICATIONS AND USAGE section:

APPEARS THIS WAY  
ON ORIGINAL

a. The indication for "Abdominal Surgery" was added.

**This addition is ACCEPTABLE (abdominal surgery indication approved May 6, 1997, supplement 008.)**

b. The wording of the "hip replacement surgery" indication was changed as requested in the March 21, 1997 approvable letter.

**This change is ACCEPTABLE.**