

the same age group. The incidence of DVT was twice greater than in patients after general surgery (Harkess, 1994)¹¹.

Peri-operative prophylaxis with low-dose heparin and low molecular weight heparin as enoxaparin has significantly reduced postoperative DVT incidence rates to _____ This effect was even better in combinations employing ATIII substitution with LMWH. Heparin induced anticoagulation is mediated by plasma ATIII that is usually reduced during major surgical procedures.

Most of the thromboembolic complications appear during first two to three weeks after operation. Although some authors support that the risk for VTE exists for three months, majority favor an opinion that after four weeks the incidence of VTE is neglectfully rare. Since the peri-operative prophylaxis is approved for only first two weeks, it is important to extend this prevention at least for additional _____ weeks. The extension of anticoagulation after hospital discharge must be followed with an increased awareness of hemorrhagic risks, and a readiness for an appropriate monitoring of outpatients on prophylaxis.

This supplement was submitted to support extension of prophylaxis for DVT and PE in patients who undergo a hip replacement surgery. The study ENOX 491001 may be recommended for evidence that Lovenox[®] (40 mg, sq, qd) may be used safely for 35 days (21 days outpatient). It also supports a postulate for the probability for the **new distal** DVT to appear within 21 days after hospital discharge. This prospect should be (significantly) lower in patients on enoxaparin prophylaxis than in patients on placebo or no-treatment.

Study PK-537 may be recommended as evidence that Lovenox[®] injection (40 mg, sc, qd), may be used safely for 35 days (21 days outpatient). It supports a premise on the prospects for **proximal** (includes both distal and proximal) DVT to be found at the end of 35 days period following surgery. This probability would be (significantly) lower in patients on extended prophylaxis with enoxaparin. Patients, who after the conventional perioperative prophylaxis (enoxaparin for _____ days), would be followed by placebo or no-treatment, would have a worse prognosis.

Comment: The distinction in the efficacy outcome (proximal vs. distal) encountered in this supplement gives a false impression that ENOX and PK-537 studies are contradicting. On the contrary, they presented similar efficacy for an extended prophylaxis of enoxaparin to prevent DVT after hip arthroplasty. The following comment is necessary to clarify this statement.

Most of the surgeons and hematologists still believe that the postoperative DVT are usually generated in calf veins. Unrecognized and not treated, some of them may evolve in proximal veins, and may produce PE. In few instances PE may have a fatal outcome.¹² It seems that this is the conceptual approach to postoperative DVT in this supplement.

The observed difference in the efficacy outcome between two pivotal studies is due entirely to the study design. In ENOX, the evaluation of the VTE incidence (primary efficacy variable) was done between two phlebographies (at the end of open-label and double-blind period). In PK-537, the only phlebography was done at the end of the double-blind period. Patients with "silent" DVT at the end of the open-label period have been included in the double-blind period of PK-537. This design created a different randomization and introduced a confounding variable at the beginning of the double-blind period in both studies. Such a discrepancy in design does not usually allow a meta-analytical approach (taken by the sponsor) for evaluation of efficacy. This reviewer has made several corrections in the sponsor's interpretation of data. The result of his analysis was positive regarding the similarity of both studies and efficacy of enoxaparin to protect against DVT (*vide supra* Table 8-3).

In summary on benefits, the two studies may be unequivocally considered as adequate to provide substantial evidence in support of enoxaparin efficacy for extended (up to 35 days) prophylaxis of DVT and PE in patients undergoing hip arthroplasty.

9.2 Risks

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In both studies patients were exposed to minimal risk for injury or illnesses related to enoxaparin. With relatively small number of patients involved, it created an environment for a low incidence of adverse events other than VTE(DVT) and hemorrhage. There was no statistical significant difference between frequency of such adverse events in enoxaparin and placebo groups. Detected in few laboratory testing events, thrombocytopenia was the only exception. These events were found only in enoxaparin treated patients.

In both studies the risk of hemorrhage (primary safety outcome) was mild and involved only minor hemorrhages (most of them injection site hematoma). Total safety was assessed by incidence rate of hemorrhage, thrombocytopenia, and other adverse events including deaths. Among "adverse events," VTE and hemorrhage had the highest incidence rate.

Thrombocytopenia was a rare event. In both studies only a mild thrombocytopenia was recorded after laboratory check-ups, not as a clinical sign. It was drug-related and resolved after withdrawal of enoxaparin. Severe thrombocytopenia with thrombosis did not occur in these studies. Due to the rarity of this event the sponsor did not elaborate further. However, the heparin-induced thrombocytopenia is inherited to all heparin-related drugs including LMWH. Enoxaparin is not an exemption. Extended prophylaxis with enoxaparin, as suggested in this supplement, may be safer if regular (weekly) check-up of platelet count is included as a part of the treatment.

In summary on risks, both studies have demonstrated that enoxaparin 40mg can be safely administered in patients up to 35 days following hip replacement surgery. In particular, those studies have demonstrated that the extension of prophylaxis with enoxaparin (40mg for 21 days) is a safe procedure for selected patients. It includes patients who have already received enoxaparin prophylaxis in the perioperative, in-hospital phase of the DVT prevention.

There is no data in these two pivotal studies, nor they are available from another study, to demonstrate that a 21-day extension of prophylaxis with enoxaparin 40mg may be as successful in populations who had other type of perioperative protection of DVT. The successful extension of prophylaxis was shown only after successful perioperative enoxaparin prophylaxis.

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9.3 Risk/Benefit Odds Ratio

The reviewer has used an Odds Ratio Test to assess how much the reduction of DVT and PE, shown in these studies, outweighs the risk of hemorrhage (Woolson, 1987)¹⁸. According to this analysis, in patients undergoing hip replacement, there was an association between enoxaparin 35-day treatment and enoxaparin 10- or 14-day treatment. This association was also present between the enoxaparin 35-day regimen and the placebo or no-treatment regimens administered to outpatients for 21 days following successful perioperative prophylaxis. The nature of this association was discussed earlier. The 35-day enoxaparin extended regimen was more effective than the 14-day perioperative regimen. The extension of prophylaxis with enoxaparin for 21 days was a more efficacious procedure than the placebo or no-treatment.

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10.0 RECOMMENDATION

This supplement is for a new indication of the Rhone-Poulenc Rorer Pharmaceuticals' Lovenox® (enoxaparin sodium) injection. The sponsor has proposed enoxaparin prophylaxis (new dose) to be extended after hospital discharge for patients who have successfully completed an initial prophylaxis with enoxaparin following hip replacement surgery (new duration).

The proposal is supported by two pivotal studies ENOX491001 and PK-527 conducted in France and Sweden on a total of 441 patients. In both studies patients were protected from perioperative development of DVT by enoxaparin 40mg, sc, qd, beginning ___ h prior to surgery and continuing for 10 (PK-537) and 14 (ENOX) days. In both studies the extension of enoxaparin (40mg, sc, qd) protection was tested versus placebo for 21 days.

Both studies are adequate and well controlled clinical trials providing substantial evidence for the following recommendation.

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Approval is recommended for:

1. **Extended prophylaxis** of DVT and PE with enoxaparin in patients undergoing elective hip arthroplasty (total hip replacement).
 - The prophylactic period should begin not before 12 hours before surgery and should last not more than 35 days after surgery. Approved commencement of prophylactic therapy: Europe ___ hours prior to surgery; USA within 24 hours after surgery.
 - Dosing: enoxaparin 40mg/0.4mL, sc, qd. for up 35 days after surgery.
2. **Extension of prophylaxis** in patients who have
 - undergone hip replacement surgery,
 - received perioperative prophylaxis (30mg/q12h or 40mg/qd following surgery up to 14 days), and
 - have been found negative for DVT by an objective method of assessment.

- Extension of prophylaxis should begin within 24h of the last enoxaparin injection, and should last not more than 21 days.
- Dosing: enoxaparin 40mg/0.4mL, sc, qd, from the beginning of the extension period for up to 35 days after surgery.

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Approval is not recommended for:

- "Long term prevention following hip replacement surgery" (citation from Labeling Annotated). This is a vague statement that may lead to misinterpretation.

The presented evidence is not supporting a separate outpatient treatment of patients who, during the perioperative, in-hospital phase of prophylaxis against DVT and PE,

- have been protected by therapies other than enoxaparin, or
- have developed asymptomatic DVT, but left undiagnosed at hospital discharge.

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In addition, the new **Labeling** should:

- Adopt terms extended prophylaxis (5 weeks) and extension of prophylaxis (21 days) rather than to employ terms such as long-term, chronic, continuous or similar with undetermined duration. These terms should define the two prophylactic options more precisely. Alternative terminology with the same meaning may also be considered.

In the Section "Clinical Trials", subsection "Long Term Prevention Following Hip Replacement Surgery", change "Long Term . . ." into "Extended . . ."

On Table "Efficacy of Lovenox in Long Term Prevention . . ." change ". . . Long Term . . ." into ". . . Extended . . ."

In the last paragraph of the same section "Clinical Trials", 2d line from bottom, change ". . . during long term prevention . . ." into ". . . during extension of prevention . . ."

In the Section "Indications and Usage" instead of the proposed phrase add the following paragraph: "In addition, Lovenox is indicated for extended prevention of deep vein thrombosis following hip replacement surgery. Prophylactic period to begin not prior to 12 hours before surgery and to last not more than 35 days after surgery. Lovenox can also be used for extension of prophylaxis following a successful perioperative prophylaxis (free of DVT as assessed by an objective measurement) with the same drug but another dosing regimen."

In the Section "Dosage and Administration" change the title of subsection from "Long Term . . ." into "Extended . . ."

In the subsection "Hip or Knee Replacement Surgery", first paragraph, first sentence, after the phrase ". . . has been established . . ." add ", or 40 mg qd started preoperatively."

- Avoid terms that may confuse reader to consider that Lovenox may be used after any perioperative prophylaxis. In the paragraph following the subtitle "Extended Prevention following Hip Replacement Surgery", change the word "therapy" for "enoxaparin perioperative prophylaxis"
- Change the title of the subsection "Local Irritation" into "Local Reaction" and in the first paragraph of this subsection add the word "ecchymoses" after ". . . hematoma".
- Instruct outpatients to check platelet count frequently while on enoxaparin prophylaxis and to report any suspicion for a bleeding tendency or the hemorrhagic event. In the section "Dosage and Administration," after the phrase ending ". . . coagulation parameters." add a new sentence: "Weekly monitoring (including platelet count) is required for outpatients on extended prophylaxis."

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These suggestions are to be included in the new Labeling and do not require Phase IV commitments.

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(Nenad Markovic, M.D.)

cc:

NDA 20-164

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HFD-180/NMarkovic

HFD-181/CSO

HFD-180/JChoudary

HFD-180/EDuffy

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11.0

APPENDIX

- 11.1 Content of the Supplement
- 11.2 Literature Cited
- 11.3 Labeling Annotated

11.1

INDEX (CONTENT OF THE SUBMISSION)

- Vol.1 Cover letter and Administrative History. Form FDA 356. Patent Information. Index to the Application. Proposed Text for Labeling-Annotated. Pharmacological Class, Scientific Rationale, Intended Use, and Potential Benefits; Foreign Marketing History; Chemistry, Manufacturing and Control Summary; Clinical Data Summary and Results of Statistical analysis; Integrated Summary of Benefits and Risks.
- Vol.2 Table of Controlled Clinical Trials. List of clinical investigators, INDs and NDAs; Background and Overview of Clinical Investigations. Clinical Studies: **Study ENOX 491001**, Comprehensive medical report, Study Documents, Protocol and List of investigators, Sample case report forms. CV of Investigators.
- Vol.3 Ethics Committee approval. Certificates of Analysis. Randomization scheme and Codes. Statistical Appendix: Methods and results, Statistical tables.
- Vol.4 Statistical tables (cont)
- Vol.5 Statistical tables (cont). Documentation: Data Analysis, Statistical analysis Plan; Documentation of derived variables.
- Vol.6 Patient data Listings and Summaries. Master decode list, randomization list, data evaluability document, population description at randomization, efficacy parameters, safety-laboratory parameters, prior and concomitant medication, treatment, follow-up of the patients, three months follow-up.
- Vol.7 Patients profiles.
- Vol.8 Publications referenced in the report. Consensus Conference: Prevention of venous thrombosis and PE (JAMA, 286:745-9,1986. Imperiale et al. A meta-analysis of methods to prevent venous thromboembolism following total hip replacement. JAMA, 271:1780-85,1994. Leizerovitz et al. Low molecular weight heparin in prevention of perioperative thrombosis. BMJ, 305:913-20,1992. Nurmohamed et al. LMWH vs standard heparin in general and orthopedic surgery:a meta-analysis. Lancet, 340:152-56,1992, etc.

- Vol.9 **Study PK-537.** *Nicolas et al. A double-blind, placebo-controlled, two-parallel group, randomized trial to evaluate the efficacy and safety of prolonged administration of enoxaparin 40 mg sc od during the first three post-discharge weeks in the prevention of deep venous thrombosis in 260 patients undergoing elective total hip replacement.* Comprehensive medical report. Study documents: Protocol, Amendments and administrative changes; sample case report forms and consent form, primary investigators Cvs, Ethics Committee approval, Randomization Scheme and Codes.
- Vol.10 Statistical Appendix. Statistical analysis plan. Summary tables. Statistical report. Patient data listings.
- Vol.11 Patient data listings (con't)
- Vol.12 Patient data listings (con't)
- Vol.13 Patient Profiles
- Vol.14 Integrated summary of efficacy. Integrated summary of safety. Statistical analysis plan. Statistical report.
- Vol.15 Statistical analysis of the integrated summaries of efficacy and safety (con't). Drug abuse and overdose (no changes to original NDA). Integrated summary of benefits and risks.
- Vol.16 Case reports. ENOX: pt No. 103, 063; PK-537: pt No. 1225, 1231, 1299, 1234, 1260, 1318.
- Vol.17 Case reports. ENOX: pt No.1131, 1176, 1298, 1003,1057,1069,
- Vol.18 Case reports. PK-537 pt No..1165,1206, 1002, 1063.

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11.2 LITERATURE CITED

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11.3 LABELING ANNOTATED

(see under separate cover)

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DIVISION OF GASTROINTESTINAL AND COAGULATION PRODUCTS
MEDICAL OFFICER'S REVIEW

August 21, 1997

NDA: 20-164
Supplement: S-010
Submission: SAFETY UPDATE
Drug: Lovenox® (enoxaparin sodium) injection.
Category: Anticoagulant
Indication: Perioperative prophylaxis of DVT and PE following orthopedic (hip and knee) and abdominal surgery, and extended prophylaxis in hip surgery.

AUG 26 1997

Sponsor: Rhone-Poulenc Rorer, Pharmaceuticals (RPR),
 Collegette, PA.

Date received: 07/09/97
Due date: 01/09/98
Date completed: 08/21/97

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Action Proposed: No Change of Labeling (Version July 8, 1997).
 Advice to add more information on injection site hemorrhage.

Medical reviewer: Nenad Markovic, M.D.
Review File: LOV10S3R.R28

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1.0 MATERIAL UTILIZED IN THIS REVIEW

- Rhone-Poulenc Rorer's Safety Update Report . Submission: July 8, 1997. Post-Marketing Safety Information from 12/01/96 to 03/31/97.
- Rhone-Poulenc Rorer's Draft Labeling for Lovenox® injection (revision July 8, 1997). It is a part of the same submission with the Safety Update Report, and a prerequisite for approval of Supplement-10.
- FDA Spontaneous Reporting System (SRS). Selected information from MedWatch, 15-Day MFR, and Manufacturer's Periodic Reports.
- MEDLINE EXPRESS database. Period 01/97-06/97. Search terms enoxaparin, Lovenox, Clexane, and LMWH. Abstracts of articles are attached in Appendix M-35 (enoxaparin) and M-50 (LMWH).
- DGCDP Documentation.
 - Rhone-Poulenc Rorer's Annual Report for _____ (Lovenox Injection). All adverse events in all indications. Period 05/19/96 through 05/18/97. Submission: July 28, 1997).
 - Rhone-Poulenc Rorer's recent Adverse Event Reports. Submissions: SE1/BM010 (07/29/97), D-reports (07/24/97), D-reports (07/21/97), and Response to FDA Request (07/23/97).
 - Rhone-Poulenc Rorer's General Correspondence. Letter from August 15, 1997.

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2.0 BACKGROUND

On April 5, 1996, the Rhone-Poulenc Rorer, Pharmaceuticals, submitted a supplement (NDA#20-164/S-010) for a new dose (40 mg qd) and duration (2-week perioperative treatment and 21 days after hospital discharge) of enoxaparin (Lovenox® Injection) treatment in hip replacement surgery. The review was completed on December 30, 1996, and Lovenox® Injection was appraised as *safe and effective for extended prophylaxis of DVT and PE following hip replacement surgery.*

On March 21, 1997, the Agency informed the sponsor that the Draft Labeling, submitted with the supplemental application, was approvable. As a prerequisite for the approval, the Agency requested submission of a new Draft Labeling with recommended changes, and a Safety Update Report (all indications). The sponsor has submitted both documents as a single package on July 8, 1997.

3.0 SAFETY UPDATE REPORT (Rhone-Poulenc Rorer, July 28, 1997)

3.1 Descriptive of Reviewed Material

The submitted document includes (1) Cover Letter and (2) Attachment.

- 3.1.1 In the Cover Letter, the sponsor presents that the report contains only the Post-Marketing Safety Information from 12/01/96 to 03/31/97. None of ongoing clinical trials was completed during this period.

The sponsor's summary of the data shows a total of 304 spontaneous, post-marketing events involving 172 patients treated with Lovenox Injection. The most frequently reported adverse event was hemorrhage, followed by thrombocytopenia and anemia. Other, less frequently reported events include pulmonary embolism, thrombophlebitis, thrombocytosis, and rash. According to the sponsor, these events were expected, and no new adverse event was reported.

The sponsor concludes: "A review of the information in these tables and listings by RPR reveals no new information that would significantly affect the safety profile of the risk/benefit ratio of enoxaparin."

- 3.1.2 The Attachment includes:

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- Adverse Event Count by *Body System* of Post-Marketing Events for all Enoxaparin doses combined (Attachment 2/1, pp 3-9),
- Adverse Event *Line Listing* by Country (Attachment 2/2, pp. 2-19),
- *Line Listing* of venous thromboembolism (VTE) reports (Attachment 2/3, p.1),
- *Line Listing* of hemorrhage (Attachment 2/4, pp.1-3), and
- *Line Listing* of thrombocytopenia (Attachment 2/5, p.1)

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- 3.1.2.1 The Body System tables contain information on a total of 304 spontaneous, post-marketing events involving 172 patients treated with Lovenox® injection.

- 3.1.2.2 Adverse Event Line Listing of Post-Marketing Events by Country contains a total of 345 adverse events that occurred in 185 patients. The *Listing* contains reports of 318 adverse events in 177 patients treated with Lovenox® injection. Inadvertently, 27 events and 8 patients are erroneously reported from subjects receiving Enoxacin (quinolone antibiotic).
- 3.1.2.3 *Line Listing on VTE* contains information on 12 patients who experienced serious VTE adverse events. Eight of them were classified as PE, remaining as DVT.
- 3.1.2.4 *Line Listing of Hemorrhage* includes reports of 77 events, 28 (36%) classified as "not serious."
- 3.1.2.5 *Line Listing of Thrombocytopenia* includes reports of 22 events. Two event were classified as HIT (MFR No. DE01-03466, AT51-00049).

3.2 Reviewer's Comment on the Safety Update Report

- 3.2.1 This report does not contain information of any unexpected adverse event, or of unexplained and/or increased frequency of the expected events.
- 3.2.2 The three most frequently described adverse events are hemorrhage, thrombocytopenia and anemia. They are well recognized enoxaparin related events and appropriate warnings, and/or precautions are present in the Labeling.
- 3.2.3 The following three adverse events need further comment. The first two are only for notation. The third should be considered for Labeling.

• THROMBOCYTOPENIA: In a separate listing, thrombocytopenia was reported 22 times. In five instances the event was classified as not serious. All other cases were classified as serious. Two events of heparin-induced thrombocytopenia (one HIT-AT51-00049, another HIT-DE01-03466) were reported. This information justifies separate listing.

- NEUTROPENIA: Two cases of agranulocytosis, three of leukopenia and one of pancytopenia were reported. What is the probability for enoxaparin to induce any of these events (to cause neutropenia) has not been reported. FDA DPE is monitoring the incidence of this event.
- HEMORRHAGE AT INJECTION SITE AND OTHER INJECTION SITE REACTIONS: Injection site burning, bruising, hematoma, hemorrhage, mass and/or reaction, is an adverse event frequently seen with subcutaneous administration of enoxaparin. However, prior pharmacological studies have reported its incidence in about one third of injections. Clinical experience shows a frequency below 10%.

To disclose if this event has been under-reported, the sponsor was asked for more details on the subject. According to the answer (sponsor's letter from August 15, 1997) ecchymosis/hematoma "is always classified as a minor hemorrhage unless it occurs together with a drop of hemoglobin of >30g/L and transfusion of 2 units of whole blood or packeted cells. Ecchymosis/hematoma <5cm is only counted as an event if it is termed clinically significant." Ecchymosis/hematoma >5cm is subsequently categorized as minor hemorrhage.

In the Annual Report (submission July 28, 1997) the sponsor reported that in the recent study 308, TIMI-11B, patients with unstable angina, receiving enoxaparin 40mg or 60mg qd for 14 days, experienced bleeding associated with injection in 113/1454 (7.7%). In this group, ecchymosis/hematoma >5cm occurred in 89/1454 (6.1%) patients (Annual Report, p.95). Apparently one event was calculated per patient. Possibility that one patient could have more than one event cannot be seen from this report. It seems that a calculated risk for ecchymosis/hematoma >5cm could be larger than 1:20.

Enoxaparin subcutaneous injection has always been associated with injection site hemorrhage (minor). It has not caused safety consideration because these events almost never needed an investigator to intervene for patient protection. Usually, this event was included in reports of "any" or "minor" hemorrhage.

However, this reviewer believes that extension of enoxaparin administration for 21 days (Supplement-10) could increase the probability for occurrence of larger injection site ecchymosis/hematoma. It is particularly important because of increasing number of patients who self-administer enoxaparin in the outpatient settings. Information about this risk should be made available to patients and their physicians. Therefore, this risk should be identified in the Labeling.

3.2.3 FDA Spontaneous Reporting System Database.

The reviewer contacted the Division for Pharmacovigilance and Epidemiologic (DPE). There was no report in this Division of any unexpected adverse event or any increased frequency of expected adverse events with use of enoxaparin (all indications) between the latest search (02/97) and the cut-of-date August 1, 1997. DPE monitors events reported as enoxaparin associated neutropenia, and reports on enoxaparin and epidural hematoma.

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3.2.4 MEDLINE EXPRESS (01/97-07/97)

MEDLINE was browsed for search terms enoxaparin, Lovenox, Clexane, and LMWH. Thirty-five articles on enoxaparin, and 50 articles on LMWH were found (Appendix 1). They were surveyed for reports of adverse events. No unexpected adverse event, or an increased frequency of expected adverse events were reported.

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4.0 REVISED LABELING DRAFT (RPR, Version July 8, 1997)

4.1 SAFETY CONSIDERATION: A draft for revised Labeling is included in the same submission with the Safety Update Report (NDA#20-164/S-010; July 8, 1997). This text is taken out from the approved Labeling (1997 PDR, RPR, Lovenox® Injection) and, in the parts related to safety (contraindications, warnings, precautions, and adverse reactions) it does not contain proposal for any change.

4.2 REVIEWER'S COMMENTS ON SAFETY IN LABELING: The Supplement-10 is for "extended prophylaxis of DVT and PE in patients following hip surgery." For the first time in the U.S., enoxaparin will be approved for a continuous prophylaxis of DVT and PE for about five weeks (≤ 35 days) following hip surgery. Prior approvals were granted only for period of about two weeks following surgery (hip, knee and abdominal). These additional three weeks of Lovenox treatment increase the risk of bleeding including injection site bleeding (ecchymosis/hematoma), a type of adverse event not sufficiently described in the current Labeling. Therefore, I would suggest the following change of the proposed Labeling:

Page 9. Section Adverse Reactions, subsection Local Reactions:
- Change from . . . pain, hematoma, echymosis, . . . into: . . .
pain, large hematoma and/or ecchymosis, . . .

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5.0 REVIEW SUMMARY

5.1 This is a review of recent information for safety of Lovenox® Injection. The Safety Update is due for approval of the Supplement-10 (NDA#20-164/S-010). Six independent sources of information were used for this review:

- The sponsor's submission on July 8, 1997:
 - a. Safety Update Report, and
 - b. Revised Labeling Draft
- DGCDP documents:
 - a. The most recent sponsor's 15-Day Alert Reports and MedWatch Reports.
 - b. The sponsor's submission on May 28, 1997: Annual Report
- FDA Spontaneous Reporting System Database.
- MEDLINE EXPRESS Database (01/97-07/97).

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5.2 Safety in General: None of these sources show any unexpected adverse event, or increased frequency of expected adverse events, that may be considered for inclusion in the Labeling.

5.3 Safety of Patients who will be exposed to Extended Prophylaxis (Supplement-10): With respect to the safety aspects in the submitted Revised Labeling Draft (version July 8, 1997), it appears that information on Injection Site Hemorrhage is insufficient to illustrate the risks of patients undergoing extended prophylaxis (3 weeks following 2-week perioperative prophylaxis). The text in the proposed Labeling Draft is based on a 2-week enoxaparin administration. This should be corrected in the next Labeling.

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6.0 RECOMMENDATION

1. The safety information in the current Labeling (version July 8, 1997) should include the statement concerning the occurrence of injection site hemorrhage. The

sponsor should be asked to add a new phrase: "large hematoma and/or ecchymosis" on page 9, subsection Local Reactions.

7.0 APPENDIX APPEARS THIS WAY
(Attached) ON ORIGINAL

/S/

Nenad Markovic, M.D.

cc:

NDA 20-164

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HFD-180/NMarkovic

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HFD-180/JChoudary

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f/t 8/25/97 jgw

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Appendix 1