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*APPLICATION NUMBER:*

**22-138**

**20-164 S-075**

**OTHER REVIEW(S)**

**Division of Medical Imaging and Hematology Products (DMIHP)**

**REGULATORY PROJECT MANAGER LABELING REVIEW**

**Name of Drug:** Lovenox<sup>®</sup> (enoxaparin sodium) Injection

**Sponsor:** Sanofi-Aventis Pharmaceuticals Inc.

**Application Number:** NDA 20-164/SLR-075

**Submission Date:** December 15, 2006

**Receipt Date:** December 18, 2006

**Application Number:** NDA 22-138

**Submission Date:** November 17, 2006

**Receipt Date:** November 17, 2006

**Materials Reviewed:** Multiple-dose Vial Package Insert (PI)  
Multiple-dose Vial Immediate Container Labeling  
Multiple-dose Vial Container Labeling

**Background and Summary**

**Background:** Lovenox was approved March 29, 1993. It is approved for the following indications:

- prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing abdominal surgery who are at risk for thromboembolic complications;
- in patients undergoing hip replacement surgery during and following hospitalization;
- in patients undergoing knee replacement surgery;
- in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness;
- prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin;
- the inpatient treatment of acute DVT with or without PE when administered in conjunction with warfarin sodium; and
- the outpatient treatment of acute DVT without PE when administered in conjunction with warfarin sodium.

Sanofi-Aventis submitted a chemistry supplement NDA 20-164/SCP-070 (S-070) on January 18, 2006 (received January 19, 2006) for a change in package insert and packaging to incorporate the statement "Do not store multiple dose vials for more than 28 days after the first use." The Division of Medical Imaging and Hematology Products (DMIHP) sent Sanofi-Aventis an approvable letter on May 26, 2006. Sanofi-Aventis resubmitted S-070 on September 8, 2006

RPM Review

Submission Date: December 15, 2006

(received September 12, 2006) and amended the supplement on January 10, 2007 (received January 11, 2007). DMIHP approved S-070 on January 12, 2007. This is the most recently approved labeling for Lovenox PI and multi-dose immediate container and carton labeling and is the labeling referenced in the review comments for the PI.

On January 24, 2006, Federal Register (FR) Notice vol. 71, No. 15 was published to list requirements on revising the content and format of labeling for human prescription drug and biological products. The ruling [also known as the Physician's Labeling Rule (PLR)] was included in 21 CFR 201.56. The new format requires sponsors to submit revised labeling according to the format described in the FR notice with new NDAs and Efficacy Supplements.

Sanofi-Aventis submitted efficacy supplement NDA 20-164/SLR-075 on November 17, 2006 for the new indication of acute ST-segment Elevation Myocardial Infarction (STEMI). The new indication also adds a new route of administration (i.e., intravenous) in addition to the approved subcutaneous route of administration. The new route uses the already approved multiple-dose presentation. The Agency expertise for review of this submission resides in the Division of Cardiovascular and Renal Products (DCRP). Therefore, a Type 6 NDA was created in DCRP as NDA 22-138. Sanofi-Aventis submitted labeling supplement NDA 20-164/SLR-075 (S-075) on December 15, 2006 (received December 18, 2006) to coincide with the (Type 6) NDA in DCRP. The labeling in both NDA 22-138 and NDA 20-164/S-075 are identical. This labeling review covers both the submission to NDA 22-138 and the submission to NDA 20-164/S-075.

## Review

### I. PACKAGE INSERT

The PI proposed for Lovenox NDA 20-164/SLR-075 submitted December 15, 2006 (received December 18, 2006) identification code "XX-XXX", was compared to the labeling in S-070 (submitted January 18, 2006; received January 19, 2006; resubmitted September 8, 2006 (received September 12, 2006); amended January 10, 2007 (received January 11, 2007) approved January 12, 2007; identifier code "XXXXX". Review comments are in bold print. The differences between the submitted PI and the approved PI are described below.

# 48 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

20. NDA 20-164/SLR-075 should not be approved until NDA 22-138 is approved by the DCRP.

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cc: NDA 20-164/S-075  
drafted: dm/2.14.07  
Initialed: February 20, 2007  
Finalized: March 5, 2007

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Diane V Leaman  
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Alice Kacuba  
3/6/2007 05:57:24 PM  
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**RHPM Overview**  
**NDA 22-138/S-000**  
**Lovenox (enoxaparin sodium) Injection**

|                     |                   |
|---------------------|-------------------|
| Sponsor:            | Sanofi-Aventis    |
| Classification:     | Priority          |
| Submission Date:    | November 17, 2006 |
| Receipt Date:       | November 17, 2006 |
| User Fee Goal Date: | May 17, 2007      |

**Background**

Lovenox (enoxaparin sodium) is a low molecular weight heparin (LMWH) originally approved under NDA 20-164 for prevention of deep vein thrombosis following hip replacement surgery in the Division of Gastrointestinal and Coagulation Drug Products on March 29, 1993. Lovenox is currently approved for marketing in the US for the following indications:

- prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing abdominal surgery who are at risk for thromboembolic complications;
- in patients undergoing hip replacement surgery during and following hospitalization;
- in patients undergoing knee replacement surgery;
- in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness;
- prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin;
- inpatient treatment of acute DVT with or without PE when administered in conjunction with warfarin sodium; and
- outpatient treatment of acute DVT without PE when administered in conjunction with warfarin sodium.

This efficacy supplement was originally submitted to the Division of Medical Imaging and Hematology Products, and is intended to support an indication for enoxaparin to be used in the immediate period following myocardial infarction. The proposed indication for this NDA efficacy supplement is: "Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI) including patients to be managed medically or with subsequent Percutaneous Coronary Intervention (PCI)." The review responsibility for this supplement was administratively split and transferred to the Division of Cardiovascular and Renal Products as a Type 6 NDA (22-138). In this supplement, enoxaparin was evaluated in one well-controlled, randomized, double-blind, double-dummy, parallel-group, multinational, clinical trial: the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment – Thrombolysis In Myocardial Infarction Study 25 (the ExTRACT-TIMI 25 study).

**User Fee**

The user fee for this application was paid in full prior to the submission of the application (UFID 3006809).

**Labeling**

The original submission contained proposed draft labeling revised to include the new indication as well as changes to other sections of the package insert that reflect the formatting changes required by the

Physician's Labeling Rule. The Federal Register (FR) notice published on January 24, 2006, (vol. 71, No. 15) was published to list requirements on revising the content and format of labeling for human prescription drug and biological products. The ruling [also known as the Physician's Labeling Rule (PLR)] was included in 21 CFR 201.56. The new format requires submission of revised labeling according to the format described in the FR notice with new NDAs and Efficacy Supplements.

Based on the finding of a clinically important net beneficial effect of enoxaparin in the balance of efficacy and safety endpoint events in STEMI patients treated with enoxaparin in the ExTRACT-TIMI 25 study, Dr. U recommended that this application be approved for this indications after the recommended changes in the INDICATIONS and CLINICAL STUDIES sections of the package insert and recommended the following changes:

Other than conversion to PLR format, significant changes in label include:

- Severe renal impairment dosing adjustments appear in the Highlights section
- In section **2.1 Adult Dosage**, under *Treatment of acute ST-segment Elevation Myocardial Infarction*, the sentence reading, "An optimal duration of treatment is not known, but it is likely to be longer than 8 days."
- A new Figure 2 showing a Kaplan-Meier plot to show death or myocardial re-infarction at 30 days in the intent to treat population. Directly under this figure, the following was added:

There is a trend in favor of enoxaparin during the first 48 hours, but most of the treatment difference is attributed to a step increase in the event rate in the UFH group at 48 hours (seen in Figure 2), an effect that is more striking when comparing the event rates just prior to and just subsequent to actual times of discontinuation. These results provide evidence that UFH was effective and that it would be better if used longer than 48 hours. There is a similar increase in endpoint event rate when enoxaparin was discontinued, suggesting that it too was discontinued too soon in this study.

- A Patient Counseling Information section was added in accordance with PLR

#### **Correspondence and meetings**

1. November 20, 2001 - End of Phase 2 meeting with DMIHP
2. March 28, 2006 - pre sNDA meeting with DMIHP and DCRP – Issues leading to a Major Amendment to extend the PDUFA date were discussed
3. November 30, 2006 - Acknowledgement letter
4. January 30, 2007 - 74 Day letter outlining potential review issues
5. March 8, 2007 – Discipline Review Letter outlining review issues
6. May 11, 2007 – 2<sup>nd</sup> Discipline Review letter outlining review issues

**Divisional Memo**

Dr. Stockbridge noted in his post-approval review that there have been seven studies in the immediate period following myocardial infarction. Of these seven, four were open-label (ASSENT 3; ASSENT 3+, TIMI-23, HART II), one had an angiographic end point (AMI-SK), and one was conducted among patients not receiving thrombolysis (TETAMI). None of these 6 studies showed a reduction in death or recurrent MI. This supplement is mostly supported by the seventh study, ExTRACT or TIMI-25. He concluded in this study that the enoxaparin regimen was more effective than the heparin regimen in reduction of death and recurrent MI in patients receiving thrombolysis and enrolled within 6 hours of the index event; however, he noted that heparin is not approved for this indication. He explained that the ACC guidelines support the use of this heparin regimen, but has little evidence to support this claim. Further, he states that the usual practice of discontinuing heparin after 2 days is insufficient, as was discontinuing use of enoxaparin after 8 days. He concluded that neither agent should be discontinued as early as was done in ExTRACT, but that an optimal timeframe for use was not determined. He noted that heparin labels should be updated to incorporate the findings of ExTRACT.

**Medical Review**

In his initial review, dated March 28, 2007, Dr. U noted that from an efficacy perspective, the ExTRACT-TIMI 25 study showed that enoxaparin significantly ( $p = 0.000003$ ) reduced the incidence of the composite primary efficacy endpoint (all-cause mortality and non-fatal myocardial re-infarction within 30 days after randomization) compared to UFH (9.9% in the enoxaparin group versus 12% in the UFH group, 17% relative risk reduction). Further, from the safety perspective, enoxaparin was associated with an increase in adjudicated TIMI major bleeding at 30 days compared with UFH in patients with acute STEMI (2.1% in enoxaparin group versus 1.4% in UFH group,  $p < 0.0001$ ), without a statistically significant ( $p = 0.1443$ ) increase in intracranial hemorrhage (ICH) between the enoxaparin group (0.8%, 84 of 10,176 patients) and UFH group (0.7%, 66 of 10,151 patients).

The net clinical benefit significantly ( $p < 0.001$ ) favored enoxaparin-treated patients: for every 1000 STEMI patients treated with enoxaparin, there would be:

- 6 fewer deaths,
- 15 fewer non-fatal myocardial re-infarctions, and
- 7 fewer episodes of urgent revascularization, at a cost of an increase of 4 non-fatal major hemorrhages, with no increase in the number of non-fatal intracranial hemorrhage.

Dr. U addressed the Financial Disclosure statement on page 27 of his review. The Integrated Summary of Safety was addressed on p. 62 and the Integrated Summary of Efficacy was addressed on page 31.

**Clinical Pharmacology Review**

In his review dated April 11, 2007, Dr. Hinderling recommended the application be approved pending labeling changes. He had the following comments:

- The population PK analysis for TIMI 11A and POH0137 was adequately preformed using non-linear mixed effect modeling.
- Based on the population PK model and PK parameters derived from TIMI 11A study, the individual PK parameters are derived for patient with acute myocardial infarction, ST-segment

elevated myocardial infarction, unstable angina and non Q-wave myocardial infarction using Bayesian estimation. This approach is acceptable; however special attention needs to be paid for diagnostic plots as well as outcome interpretation.

- The population exposure-efficacy and exposure-safety model was adequately performed using logistic modeling.
- The sponsor concluded that the dosing adjustment for renal impaired patients appears to be necessary in order to reduce the risk of over-exposure and major hemorrhage. The proposed using 1mg/kg q 24 hr instead of q 12 hr for severe renal impaired patients is acceptable.

#### **Statistical Review**

In his review dated March 13, 2007, Dr. Lawrence concluded that there is strong evidence that enoxaparin is superior to unfractionated heparin in reducing the risk of myocardial re-infarction within 30 days in the population studied. There is also strong evidence that the risk of thrombolysis in myocardial infarction (TIMI) major hemorrhage within 30 days is higher in the enoxaparin treated group. Finally, there does not appear to be any particular subgroup that has an especially large treatment effect or especially small increased risk of bleeding.

#### **Environmental Assessment**

This was addressed in Dr. Srinivasachar's chemistry review dated May 11, 2007. He stated that a categorical exclusion for Environmental Assessment could be granted. He also noted that both the package insert and container (Multi-dose vial) had been revised to reflect the additional iv route administration. Further, establishment inspections were still pending and no overall recommendations were available from the Office of Compliance at the date of his review. Dr. Srinivasachar recommended this application be approvable.

#### **Division of Scientific Investigations**

Drs. Hinderling and U determined that an audit was not necessary for this application.

#### **Pediatrics**

The Division of Medical Imaging and Hematology granted a full waiver of pediatric studies in the indication of ST-segment elevation Acute Myocardial Infarction in a letter dated July 19, 2006.

#### **CSO Summary**

An approval on draft letter was drafted for Dr. Stockbridge's signature and was signed on May 16, 2007

Meg Pease-Fye, M.S.  
Regulatory Health Project Manager  
May 16, 2007

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**This is a representation of an electronic record that was signed electronically and  
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Margaret Pease-Fye  
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CSO