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**APPLICATION NUMBER: 020164, S015**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

*CSO/Oliver*

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW**

**NDA 20-164/SE1-015 and SE1-016**  
**Enoxaparin sodium injection**  
**BRAND NAME: LOVENOX®**

**SUBMISSION DATES:**  
May 19, 1998  
May 28, 1998  
June 12, 1998  
July 6, 1998  
September 24, 1998  
October 8, 1998

DEC 23 1998

**SPONSOR: Rhone-Poulenc Rorer**  
**Pharmaceuticals Inc., Collegeville, PA**

**REVIEWER: Arzu Selen, Ph.D.**

**TYPE OF SUBMISSION:**  
**Supplemental New Drug Application**

**Code: SE1**

**TITLE: Clinical Pharmacology And Biopharmaceutics Review Of the Sponsor's Responses to FDA Questions Related to Supplements to Enoxaparin Sodium NDA, NDA 20-164/SE1-15 and SE1-16**

**BACKGROUND:**

Lovenox®(enoxaparin sodium) is a low molecular weight heparin (LMWH), currently marketed for prevention of deep vein thrombosis. It is administered by subcutaneous injection, 30 mg twice daily in patients undergoing hip or knee replacement surgery and 40 mg once daily in patients who are undergoing abdominal surgery and may be at risk for thromboembolic conditions. If clinically warranted, Lovenox doses may continue for 7 to 17 days after the surgery.

In these supplements (SE1-15 and SE1-16 to NDA 20-164), the Sponsor had evaluated new indications for enoxaparin, new dosing regimens, and new packaged dosage forms of enoxaparin sodium (pre-filled enoxaparin sodium syringes). These two supplemental NDAs were initially reviewed by Dr. Lydia Kaus (July 14 1997) and certain issues were communicated to the Sponsor (July 24, 1997). The Sponsor's response (August 7, 1997), along with the recommended revisions for the labeling were reviewed by this reviewer (February 26, 1998) and were communicated to the Sponsor in Agency's February 27, 1998 dated letter. The objective of this review is to address the Sponsor's responses to the Agency's questions raised in February 1998 letter and finalize the Clinical Pharmacology Section of the package insert (PI) for the prefilled enoxaparin sodium syringe dosage forms.

The Supplement SE1-15 (NDA 20-164) is a non-priority submission for treatment of deep vein

thrombosis [REDACTED] when enoxaparin sodium is administered in conjunction with warfarin sodium. The recommended dosing regimen for enoxaparin sodium is 1.5 mg/kg qd sc or 1.0 mg/kg q12h sc. The Supplement SE1-15 (NDA 20-164) also provided information on the prefilled enoxaparin sodium syringe dosage forms (60 mg/0.6 mL, 80 mg/0.8 mL and 100 mg/mL) that are proposed for marketing.

The Supplement SE1-16 (NDA 20-164) is a priority submission for treatment of unstable angina and non-Q wave infarction with concurrent administration of aspirin. The recommended dosing regimen was 1.0 mg/kg enoxaparin sodium q 12h sc. Similarly, this supplement provided information on the pre-filled enoxaparin sodium syringe dosage forms (60 mg/0.6mL, 80 mg/0.8 mL and 100 mg/mL).

For both supplements, SE1-15 and SE1-16, the same pharmacokinetic/pharmacodynamic studies were submitted and hence, comments apply to both supplements.

In the following sections of this document, the Sponsor's responses to the questions raised in the Clinical Pharmacology and Biopharmaceutics review (dated February 26, 1998) are addressed. For ease of reference between documents (the review, the Agency letter and the Sponsor's responses), the question/request numbers are identical to those as listed in the Agency letter to the Sponsor.

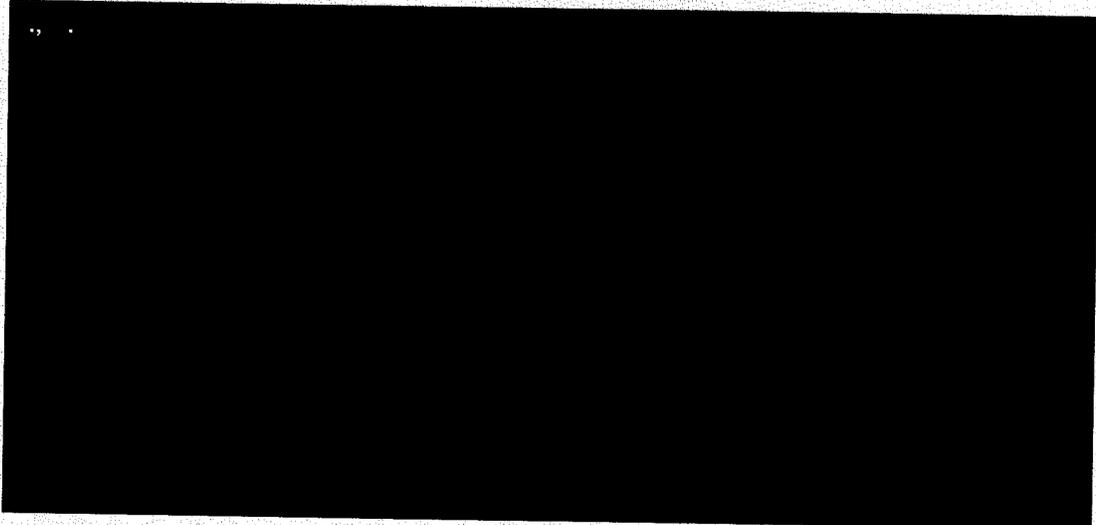
#### REVIEW OF RESPONSES TO THE QUESTIONS/REQUESTS:

1. A joint response was provided to FDA Requests 1 and 2 in the Sponsor's May 19, 1998 amendment.

**FDA Request 1:** In a July 24, 1997 dated letter, the Agency communicated to Rhone-Poulenc Rorer their concern regarding gender effect and gender and treatment interaction observed in RP54563Q-133. Possible approaches to further explore gender effect in anti-Xa derived parameters were considered and it is unclear whether these approaches were discussed with Rhone-Poulenc Rorer Pharmaceuticals. Therefore, the Agency reanalyzed the submitted data using the Type III MS from subject within sequence as the error term. The gender effect was no longer statistically significant. In future analyses, please use Type III MS from subject within sequence as the error term for evaluating gender effect.

**FDA Request 2:** During the review of the Summary Table provided in your August 7, 1997 submission, several discrepancies between the information in the table and the printouts in the attachment were noted. In the tables, it is stated that the p values are from the final model. However, based on the entry for "weight" and "Subject(gender\*sequence)" in the source column of the Summary Table, this statement appears to be incorrect. Furthermore, the sequence effect appears to be inaccurately represented in the table. Based on the SAS printouts provided in the attachment of the letter dated August 7, 1997 from Rhone-Poulenc Rorer Pharmaceuticals, the sequence effect is not significant for any one of the parameters that were tested.

**Response:** The Sponsor concurs with the points raised by the Agency in the Requests 1 and 2.



2. **FDA Request 4:** Provide ASCII data files on a disk for anti-Xa activity vs time (and pharmacokinetic parameters if available) from all subjects in RP54563Q-260 and RP54563Q-261 with the patient/subject demographics in the same file.

**Response:** The Sponsor has provided an ASCII data file as requested in the May 19, 1998 amendment.

**Action:** No further action is needed.

3. A joint response was provided to FDA Requests 3 and 5 in the Sponsor's May 19, 1998 amendment.

**FDA Request 3:** Provide the supportive data and an assessment of the correlation between anti-Xa activity and enoxaparin doses covering the studied range (40-mg to 2 mg/kg for an average body-weight of 70 kg).

**FDA Request 5:** In the response to your letter dated August 7, 1997, regarding the observation related to the CL/F values from RP54563Q-260, it is possible that the data from RP54563Q-260 is more variable compared to other studies. However, after reviewing the data, the Agency is not convinced that the differences observed in the mean CL/F values represent variability in the data or an overestimation of anti-Xa derived parameters. A review of enoxaparin sodium studies (100537, 100539, 100541, 100542, 105640, K9001006, and RP54563Q-133) has shown that the anti-Xa derived CL/F values may be lower after administration of high (1 mg/kg or higher) enoxaparin sodium doses than the CL/F values obtained after administration of low enoxaparin sodium doses (such as 60 mg in RP54563Q-260). This relationship suggesting dose-dependency in the anti-Xa derived CL/F values needs to be further investigated as requested in the response to the Supplemental NDA Submission (20-164/S-018).

**Response:** The Sponsor has indicated that the data from studies conducted before 1989 (100537, 100539, 100541 and 100542) and the data from more recent studies (105640, K91006 and RP54563Q-133) are not comparable because of the differences in the reference

standards used in determining potency of enoxaparin sodium (WHO LMWH1 versus WHO 3<sup>rd</sup> and 4<sup>th</sup> International Standards of Heparin) and the differences in analytical sensitivity for anti-Xa activity (0.113 IU anti-Xa activity versus 0.025 IU anti-Xa activity).

The mean clearance parameters from the pre-1989 and post-1989 studies summarized by the Sponsor is included in Attachment 1.

The Sponsor states that the above two reasons in part explain the differences observed in CL/F values and also comments that the variability in CL/F in fixed dose studies may be higher than the CL/F in studies where enoxaparin dose was adjusted by body-weight. The Agency considers it is acceptable that the studies conducted before and after 1989 are not comparable, however, it is also important to recognize that the studies conducted before- and after 1989 are not linked.

In response to the relationship between dose and anti-Xa activity, the Sponsor refers to two studies, DN100537 (conducted before 1989) and K91006 (conducted after 1989) to support dose proportionality claim. In Study DN100537, the enoxaparin sodium doses of 20-, 40-, 60- and 80-mg were administered sc to 12 young male subjects. In Study K91006, 1.0-, 1.25-, 1.5- and 2.0 mg/kg doses of enoxaparin sodium were administered sc to 16 young male subjects. In addition to the comparison of these studies, the Sponsor also provides results from a pooled analysis of data from three studies which will be discussed later in this section.

The two studies, DN100537 and K91006, referred to support the claim that enoxaparin anti-Xa activity is dose-independent over the 40 mg to 2.0 mg/kg enoxaparin sodium dose range, were conducted years apart with different reference standards and analytical methods. The Sponsor indicates that the studies can be linked because of the overlap observed in parameter values after high doses of DN100537 and low doses of K91006. This approach is considered to be unacceptable if the studies conducted before and after 1989 are considered to be incomparable as the validity of the "overlap" is questionable.

Furthermore, if only the post-1989 studies were considered, in Studies where enoxaparin sodium doses ranged from 20 mg to 60 mg (Studies DN 105640, PK 123, PK 128, PK 129, PK 134 and PK 260), the mean CL/F values were higher than those observed in studies where enoxaparin sodium doses ranged from 1 mg/kg to 2 mg/kg (PK 133, K91006 and Study 1819). These results are consistent with the trend observed when the results were viewed in their entirety and not grouped as before- and after-1989 data.

Another concern is that majority of these studies did not include female subjects. Pharmacokinetic data were obtained from female subjects or patients in studies PK 134 (12 males and 12 females), PK 260 (13 male and 6 female patients), and PK 133 (12 male and 12 female subjects).

The Sponsor's next approach, as mentioned above, involved pooled data analysis to demonstrate dose-proportionality of enoxaparin anti-Xa activity over the 40 mg to 2.0 mg/kg dose range. The anti-Xa activity parameters (A<sub>max</sub> and AUC) were pooled from three studies (preliminary report from PK 123, PK 128 and K91006, all conducted after 1989). In PK 123, 30 mg single dose of enoxaparin sodium was administered sc to 12 young male volunteers, in PK 128, 40 mg single dose of enoxaparin sodium was administered sc to 24 young male

volunteers and in K91006, several doses of enoxaparin sodium (single 1.0 mg/kg, 1.25 mg/kg, 1.5 mg/kg and 2.0 mg/kg) were administered sc to 16 young male volunteers. The data (Amax and AUC values) for each subject in PK 123 and 128 were converted to mg/kg enoxaparin sodium dose for comparison with the data from K91006. The parameter values were either adjusted to mean body weight or adjusted to 70 kg body weight for linear regression analysis of data across studies.

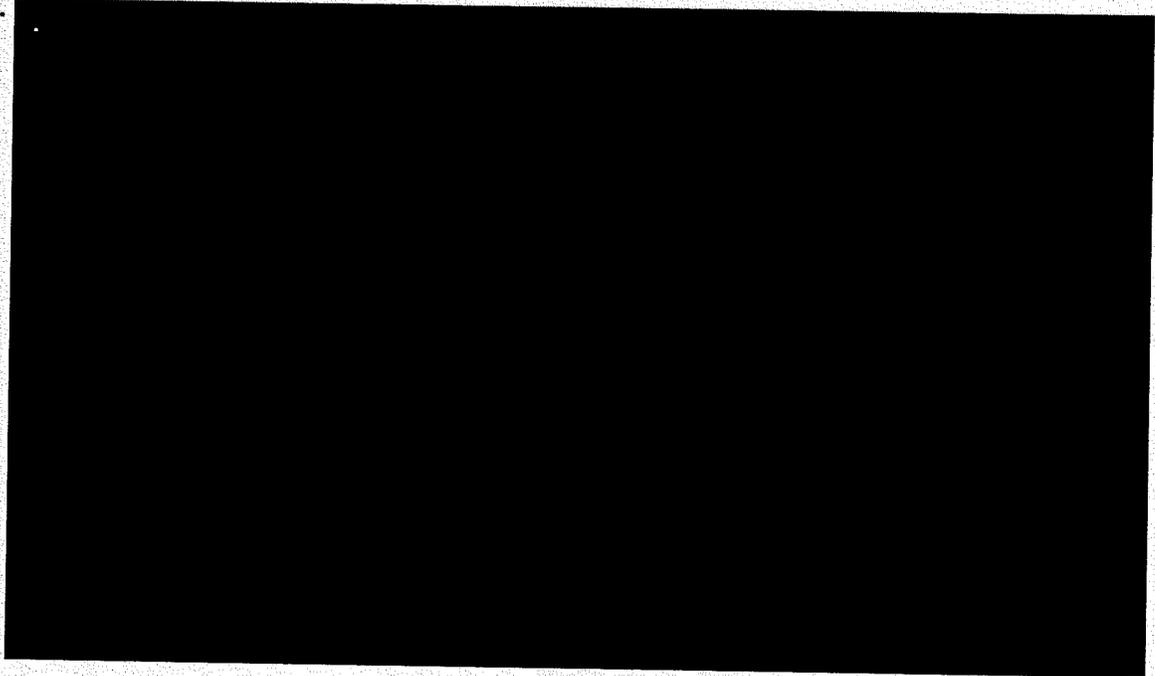
Although linear regression equations were obtained for Amax and AUC values as a function of enoxaparin dose, many issues need to be considered and addressed to justify pooling data from across studies (such as selection criteria of studies). Furthermore, dose-proportionality assessment is usually performed in a single study where subjects receive all of the doses. As a result, the presented information for this response is not considered to be sufficient evidence to support dose-proportionality of anti-Xa activity of enoxaparin over 40 mg to 2.0 mg/kg dose range.

**Action:** The response provided by the Sponsor to support that the results from before- and after-1989 studies are incomparable is accepted.

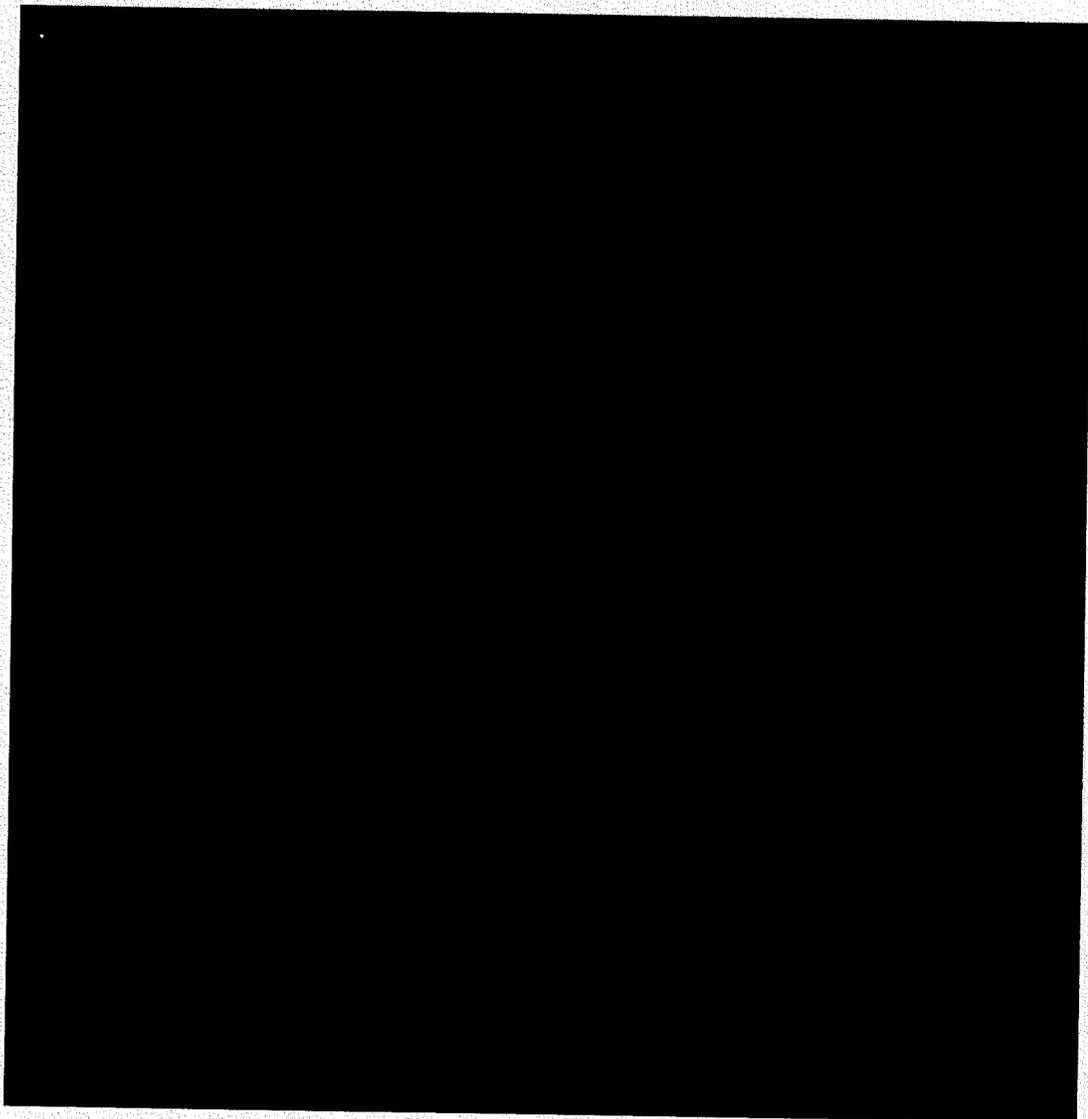
However, the claim for dose-proportionality over the 40-mg to 2.0mg/kg dose range of enoxaparin sodium is not acceptable. Should the Sponsor wish to have this claim, a dose-proportionality study in male and female, body-weight matched subjects with body-weights within 10-15% of the "normal" range, would be suggested. This could be further discussed with the Sponsor if the Medical Division would like the Sponsor to conduct an additional study to determine dose-proportionality of enoxaparin sodium.

The comments under the action item of this section, if considered to be significant for safe and effective use of enoxaparin by the Medical Division, may be communicated to the Sponsor.

4.



5.



6. **FDA Request 8:** Provide an annotated, tabulated summary of anti-Xa derived pharmacokinetic parameters (grouped by gender) over the studied dose ranges. This table will be reviewed by the Agency for possible inclusion in the package insert.

**Response:** The Sponsor has provided a summary of some of the pharmacokinetic parameters (Amax and AUC for anti-Xa activity) for post-1989 studies and this table is included in Attachment 2.

The Sponsor does not agree in including a table of anti-Xa activity parameters in the PI.

**Action:** Including a table of Amax and AUC values is not considered to be as informative as including the CL/F values for anti-Xa activity across dose groups and also, in male and female subjects. A table is constructed by the reviewer that represents typical mean CL/F values from two studies and is included in the revised PI (in Attachment 3).

## LABELING COMMENTS (CLINICAL PHARMACOLOGY SECTION)

The Sponsor has provided a revised label (July 2, 1998) to address comments that were raised in the Agency's earlier letter (February 27, 1998) and the Sponsor's revised and proposed draft PI is included as Attachment 4. In this Section, the comments raised by the Agency, the Sponsor's responses and our proposed action for the labeling are presented. A completely revised "Clinical Pharmacology Section" for the label is in Attachment 3.

### CLINICAL PHARMACOLOGY SECTION

a) **FDA Request:** As requested in the September 8, 1997 letter, revise the second sentence of the first paragraph to indicate that the reported anti-Xa/anti-IIa ratio is based on activity derived following iv dosing of enoxaparin sodium. In addition, provide the anti-Xa to anti-IIa activity ratio (median value across studies) after the sc dosing.

**Response:** In response, the Sponsor has indicated that since anti-Xa/anti-IIa ratio after sc dose is more relevant, the package insert dated July 2, 1998 (submitted on July 6, 1998) is revised to reflect the ratio after the sc dose. As requested, the Sponsor has provided the median ratios of AUC values (13.3) but has also indicated a preference to report the mean (SD) values for the AUC ratios which is 14.0 (3.1)

**Action:** The Sponsor's proposed revision is accepted and is incorporated in the revised PI (Attachment 3), no further action is needed.

b) **FDA Request:** Provide the data to support the third and fourth sentences of the first paragraph related to changes in coagulation parameters.

**Response:** The Sponsor has provided relevant sections from 4 reports to support the following sentences which were the third and the fourth sentences in the draft PI (dated February 10, 1998). The information provided by the Sponsor to support these sentences is included in Attachment 5. These reports were issued in 1986, 1994, 1996 and 1997.

In the July 2, 1998 draft PI, for the third sentence, the Sponsor has revised the observed increases in TT and aPTT to 1.6 times the control value and has altered the 5<sup>th</sup> sentence and moved it before the 4<sup>th</sup> sentence in the February version of the draft PI.

**Action:** The revision made by the Sponsor to indicate "1.6 times" should be "1.8 times". In addition, the information provided in the reports to support the sentence regarding the "fibrinogen level" and "parameters of fibrinolysis" (the 5<sup>th</sup> sentence in the July 1998 version of the draft PI) is not considered to be as conclusive as it may seem from this sentence and is redundant with respect to information provided under dosage and administration. Therefore, the revised Sentence 5 is deleted.

The revisions are made in the CLINICAL PHARMACOLOGY Section of the PI (Attachment 3).

c) **FDA Request:** Provide a tabular summary of data (including study number, design,

enoxaparin sodium dose, dosing frequency, patient population, aPTT results) that support the last sentence of the first paragraph related to the effects of dosing on aPTT measurements. Clarify if any other studies were used to support this sentence as both reports K9001006 (taken to be the report listed as PK91006:RP54563) and PK 91007 listed in footnote 9 are single dose studies.

**Response:** The Sponsor clarifies that PK91007, although listed as a single dose study in the February 10, 1998 PI, is a multiple dose study and has provided a table summarizing mean aPTT measures across studies. This table is included in Attachment 6.

**Action:** No further action.

**d) In the Pharmacodynamics Subsection:**

1. **FDA Request:** Provide the reference and the information supporting the fifth sentence of the first paragraph related to clearance of enoxaparin including the enoxaparin sodium dose at which this estimate was obtained.

**Response:** The Sponsor has indicated that the clearance value reported is after an iv dose of enoxaparin sodium. While this information is considered to be significant, it is important to include the CL/F value after sc administration of enoxaparin sodium.

**Action:** The additional information on CL/F after sc dosing of enoxaparin is included in the Agency's revised package insert (Attachment 3). No further action.

2. **FDA request:** Provide the reference and the information supporting the first sentence of the second paragraph related to clearance and Cmax derived from anti-Xa activity after single and multiple doses in elderly subjects and in subjects with renal impairment.

**Response:** The Sponsor has indicated that the existing statement in the February 10, 1998 draft PI regarding the mean anti-Xa AUC values on "Day 10 being 25% higher (possibly in comparison to single dose)" is incorrect.

**Action:** The information provided by the Sponsor is accepted and incorporated into the revised PI (Attachment 3).

3. **FDA request:** Provide the data and the method used for calculation of the AUC values that are indicated to be 25% higher on Day 10 compared to Day 1 in the third sentence of second paragraph.

**Response:** The Sponsor has provided Day 10 and Day 1 anti-Xa activity AUC values and has also shown that mean Day 10 anti-Xa AUC value is 15% higher than the mean anti-Xa AUC values on Day 1 (instead of the "25%" difference as reported in the February 1998 draft PI). The Sponsor has compared AUC(0-24) values on Day 10 and Day 1. One would expect a comparison of Day 10 AUC(0-24) with Day 1 AUC(0-∞), however, given the anti-Xa disposition characteristics, AUC(0-24) and AUC(0-∞) values should be similar, so an approximate 15% increase is an acceptable revision.

**Action:** The correction is indicated in the revised PI (Attachment 3).

**4. FDA request:** Provide the data that supports the third paragraph related to decline of total radioactivity and anti-Factor Xa activity.

**Response:** The Sponsor has provided a copy of the literature article that relates the total radioactivity in plasma to anti-Xa activity measured in plasma after iv administration of radiolabeled enoxaparin sodium dose and enoxaparin sodium dose, respectively.

This article is included in Attachment 7.

**Action:** No further clarification/action is needed.

### **RECOMMENDATION**

The Office of Clinical Pharmacology and Biopharmaceutics/Divisions of Pharmaceutical Evaluation II and III have reviewed the Sponsor's responses to questions raised during clinical pharmacology and biopharmaceutics review of the supplements (SE1-015 and SE1-016) to the Lovenox NDA (NDA 20-164). The Sponsor has addressed the questions that were raised by the Agency.

One of the concerns has been possible dose- and gender-related differences in enoxaparin disposition, as assessed by anti-Xa activity. Although a typical dose-proportionality study with both male and female subjects over the range of enoxaparin doses studied (20-mg to 2.0 mg/kg) has not been conducted, across studies, there appears to be a gender-related difference with respect to enoxaparin dose and the anti-Xa activity. In general, the anti-Xa clearance (CL/F) values in male subjects seem consistently higher than the values observed in female subjects. This concern has been communicated to the Sponsor who has indicated that there are no clinically significant gender effects. The Sponsor attributes the observed gender effects to differences in body-weight and recommends enoxaparin doses that are adjusted by body-weight for the indications evaluated in these supplements (SE1-015 and SE1-016). This approach may be adequate to provide a safe and effective dosing scheme for indications and the enoxaparin doses indicated in these supplements. However, the impact of possible gender related differences in CL/F values may need to be further considered in situations where fixed doses of enoxaparin sodium is used such as in knee and hip replacement surgeries. If the Medical Division concurs, further investigation of the gender- and dose-dependent effects in anti-Xa activity may be warranted to ensure safe and effective use of enoxaparin. It is interesting to note that the risk for spinal/epidural hematomas after use of enoxaparin seems to be higher than expected in female patients (based on National Center for Health Statistics, 1996 National Hospital Discharge Survey, per Dr. Diane Wysowski). This suggests that further investigation of body-weight adjusted dosing of enoxaparin in this patient population may be warranted.

The changes proposed by the Sponsor for the PI are mostly acceptable and the revised draft Clinical Pharmacology Section of the PI is included in Attachment 3 of this document.

In addition, the Sponsor would like to include in the PI results from a renal impairment study where mean CL/F of anti-Xa activity was approximately 30% lower in patients with severe

renal impairment compared to the mean CL/F value of control subjects. In this renal impairment study, a race effect was also observed because there were nine black subjects in the group of ten subjects with severe renal impairment. Given these results, the Sponsor is requested to conduct a Phase 4 study to further investigate the effects observed in the patients with severe renal impairment. Furthermore, since 9 out of 10 volunteers with severe renal impairment were black, it is also important to determine whether the observed difference also signifies a race-related difference in anti-Xa activity. The renal impairment study may be conducted according to the CDER guidance (Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function- Study Design, Data Analysis and Impact on Dosing and Labeling) in control subjects and in patients with severe renal impairment, preferably both in black and caucasian body-weight matched subjects.

Further investigation of race-, dose- and gender-dependent effects as well as the effect of renal impairment on disposition of anti-Xa and anti-IIa activity is recommended.

ISI  
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12/23/98

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cc: NDA 20-873, HFD-180 (Talarico, Oliver),  
HFD-870 (Chen, Hunt, Lee), HFD-880 (Selen), HFD-850 (Lesko)  
HFD-340 (Viswanathan), Central Document Room (Barbara Murphy)

ATTACHMENT I

Lovenox  
Supplemental NDA 20-164/SE1-015 and SE1-016