General Linear Models Procedure
Class Level Information

Class	Levels	Values
PERIOD	3	1 2 3
TREAT	3	1 2 3
GENDER	2	1 2
SEQUENCE	6	1 2 3 4 5 6

Number of observations in data set = 72

[redacted]

General Linear Models Procedure

Dependent Variable: LAUC24

Source	[redacted]	Sum of Squares	Mean Square	F Value	Pr > F
Model	44	2.60985485	0.05931488	2.97	0.0018
Error	27	0.53981425	0.01999312		
Corrected Total	71	3.14966910			

R-Square	C.V.	Root MSE	LAUC24 Mean
0.828612	5.290196	0.14139703	2.67281268

Source	[redacted]	Type III SS	Mean Square	F Value	Pr > F
WEIGHT	1	0.37501592	0.37501592	18.76	0.0002
SEQUENCE	5	0.64099756	0.12819951	6.41	0.0005
GENDER	1	0.13358206	0.13358206	6.68	0.0155
GENDER*SEQUENCE	5	0.63882117	0.12776423	6.39	0.0005
SUBJECT(SEQUENCE)	6	0.64624590	0.10770765	5.39	0.0009
PERIOD	2	0.00024870	0.00012435	0.01	0.9938
TREAT	2	0.00076205	0.00038102	0.02	0.9811
TREAT*GENDER	2	0.00497196	0.00248598	0.12	0.8836
WEIGHT*TREAT	2	0.00018378	0.00009189	0.00	0.9954
PERI*TREA*GEND*SEQUE	18	0.06401382	0.00355632	0.18	0.9998

Tests of Hypotheses using the Type III MS for SUBJECT(SEQUENCE) as an error term

Source	[redacted]	Type III SS	Mean Square	F Value	Pr > F
SEQUENCE	5	0.64099756	0.12819951	1.19	0.4125

Tests of Hypotheses using the Type III MS for SUBJECT(SEQUENCE) as an error term

Source	[redacted]	Type III SS	Mean Square	F Value	Pr > F
GENDER	1	0.13358206	0.13358206	1.24	0.3080

[redacted]

[redacted] BEST POSSIBLE

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General Linear Models Procedure

Dependent Variable: LAMAX

Source	[redacted]	Sum of Squares	Mean Square	F Value	Pr > F
Model	44	1.44439660	0.03282720	2.47	0.0073
Error	27	0.35921221	0.01330416		
Corrected Total	71	1.80360881			

R-Square	C.V.	Root MSE	LAMAX Mean
0.800837	33.71504	0.11534364	0.34211329

Source	[redacted]	Type III SS	Mean Square	F Value	Pr > F
WEIGHT	1	0.15877004	0.15877004	11.93	0.0018
SEQUENCE	5	0.30421244	0.06084249	4.57	0.0038
GENDER	1	0.02054800	0.02054800	1.54	0.2246
GENDER*SEQUENCE	5	0.30251584	0.06050317	4.55	0.0039
SUBJECT(SEQUENCE)	6	0.30709504	0.05118251	3.85	0.0067
PERIOD	2	0.00172854	0.00086427	0.06	0.9372
TREAT	2	0.00796238	0.00398119	0.30	0.7438
TREAT*GENDER	2	0.01626141	0.00813071	0.61	0.5501
WEIGHT*TREAT	2	0.00556504	0.00278252	0.21	0.8126
PERI*TREA*GEND*SEQUE	18	0.09115615	0.00506423	0.38	0.9816

Tests of Hypotheses using the Type III MS for SUBJECT(SEQUENCE) as an error term

Source	[redacted]	Type III SS	Mean Square	F Value	Pr > F
SEQUENCE	5	0.30421244	0.06084249	1.19	0.4130

Tests of Hypotheses using the Type III MS for SUBJECT(SEQUENCE) as an error term

Source	[redacted]	Type III SS	Mean Square	F Value	Pr > F
GENDER	1	0.02054800	0.02054800	0.40	0.5497

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General Linear Models Procedure

Dependent Variable: LAUC36

Source	[redacted]	Sum of Squares	Mean Square	F Value	Pr > F
Model	44	2.90767918	0.06608362	3.00	0.0017
Error	27	0.59504968	0.02203888		
Corrected Total	71	3.50272886			

R-Square	C.V.	Root MSE	LAUC36 Mean
0.830118	5.423858	0.14845497	2.73707313

Source	[redacted]	Type III SS	Mean Square	F Value	Pr > F
WEIGHT	1	0.38818721	0.38818721	17.61	0.0003
SEQUENCE	5	0.73015521	0.14603104	6.63	0.0004
GENDER	1	0.15112032	0.15112032	6.86	0.0143
GENDER*SEQUENCE	5	0.72788417	0.14557683	6.61	0.0004
SUBJECT(SEQUENCE)	6	0.73984381	0.12330730	5.59	0.0007
PERIOD	2	0.00128394	0.00064197	0.03	0.9713
TREAT	2	0.00072666	0.00036333	0.02	0.9837
TREAT*GENDER	2	0.00309511	0.00154755	0.07	0.9324
WEIGHT*TREAT	2	0.00006495	0.00003248	0.00	0.9985
PERI*TREA*GEND*SEQUE	18	0.07836810	0.00435378	0.20	0.9996

Tests of Hypotheses using the Type III MS for SUBJECT(SEQUENCE) as an error term

Source	[redacted]	Type III SS	Mean Square	F Value	Pr > F
SEQUENCE	5	0.73015521	0.14603104	1.18	0.4146

Tests of Hypotheses using the Type III MS for SUBJECT(SEQUENCE) as an error term

Source	[redacted]	Type III SS	Mean Square	F Value	Pr > F
GENDER	1	0.15112032	0.15112032	1.23	0.3107

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General Linear Models Procedure

Dependent Variable: LAUC

Source	[redacted]	Sum of Squares	Mean Square	F Value	Pr > F
Model	44	3.13375178	0.07122163	3.05	0.0015
Error	27	0.63088033	0.02336594		
Corrected Total	71	3.76463210			

R-Square	C.V.	Root MSE	LAUC Mean
0.832419	5.538145	0.15285921	2.76011560

Source	[redacted]	Type III SS	Mean Square	F Value	Pr > F
WEIGHT	1	0.39209666	0.39209666	16.78	0.0003
SEQUENCE	5	0.79575495	0.15915099	6.81	0.0003
GENDER	1	0.15815452	0.15815452	6.77	0.0149
GENDER*SEQUENCE	5	0.79344510	0.15868902	6.79	0.0003
SUBJECT(SEQUENCE)	6	0.80840674	0.13473446	5.77	0.0006
PERIOD	2	0.00238183	0.00119091	0.05	0.9504
TREAT	2	0.00173389	0.00086695	0.04	0.9636
TREAT*GENDER	2	0.00193771	0.00096886	0.04	0.9594
WEIGHT*TREAT	2	0.00067549	0.00033774	0.01	0.9857
PERI*TREA*GEND*SEQUE	18	0.09149883	0.00508327	0.22	0.9993

Tests of Hypotheses using the Type III MS for SUBJECT(SEQUENCE) as an error term

Source	[redacted]	Type III SS	Mean Square	F Value	Pr > F
SEQUENCE	5	0.79575495	0.15915099	1.18	0.4158

Tests of Hypotheses using the Type III MS for SUBJECT(SEQUENCE) as an error term

Source	[redacted]	Type III SS	Mean Square	F Value	Pr > F
GENDER	1	0.15815452	0.15815452	1.17	0.3202

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[redacted]

General Linear Models Procedure

Dependent Variable: LAUC

Source	[redacted]	Sum of Squares	Mean Square	F Value	Pr > F
Model	26	3.04225294	0.11700973	7.29	0.0001
Error	45	0.72237916	0.01605287		
Corrected Total	71	3.76463210			

R-Square	C.V.	Root MSE	LAUC Mean
0.808114	4.590385	0.12669992	2.76011560

Source	[redacted]	Type III SS	Mean Square	F Value	Pr > F
WEIGHT	1	0.39209666	0.39209666	24.43	0.0001
SEQUENCE	5	0.79575495	0.15915099	9.91	0.0001
GENDER	1	0.15815452	0.15815452	9.85	0.0030
GENDER*SEQUENCE	5	0.79344510	0.15868902	9.89	0.0001
SUBJECT(SEQUENCE)	6	0.80840674	0.13473446	8.39	0.0001
PERIOD	2	0.00232779	0.00116389	0.07	0.9302
TREAT	2	0.00022830	0.00011415	0.01	0.9929
TREAT*GENDER	2	0.00943724	0.00471862	0.29	0.7467
WEIGHT*TREAT	2	0.00155713	0.00077856	0.05	0.9527

Tests of Hypotheses using the Type III MS for SUBJECT(SEQUENCE) as an error term

Source	[redacted]	Type III SS	Mean Square	F Value	Pr > F
SEQUENCE	5	0.79575495	0.15915099	1.18	0.4158

Tests of Hypotheses using the Type III MS for SUBJECT(SEQUENCE) as an error term

Source	[redacted]	Type III SS	Mean Square	F Value	Pr > F
GENDER	1	0.15815452	0.15815452	1.17	0.3202

[redacted]

Oliver

JUL 14 1997 ✓

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20-164 SE1-15 and SE1-16 **Submission Dates**: February 28th, 1997
Enoxaparin Injection (SC) March 18th, 1997.
Lovenox
Rhone Poulenc Rorer

Reviewer: Lydia C. Kaus
Type of Submission: Supplements for two new indications and new dosing regimens.

SYNOPSIS:
The sponsors have approved labeling for prevention of deep vein thrombosis, which may lead to pulmonary embolism, following hip or knee replacement surgery. The recommended dose is 30 mg every 12 hours administered by SC injection up to 14 days. The currently marketed formulation has a concentration of 100mg/1mL enoxaparin sodium. A 0.5 mL pre-filled syringe is approved. In these submissions the concentration of enoxaparin sodium remains the same, the formulation is the same, however there is a new size of the pre-filled syringe, 1.0 mL.

This is a joint review for two supplements (SE1-15 and SE1-16) since the same pharmacokinetic/pharmacodynamic studies were submitted for both supplements.
Supplement SE1-16 is a priority submission with information on

- a new indication - the treatment of unstable angina and non-Q-wave infarction with concurrent administered with aspirin
- a new dosing regimen of 1.0 mg/Kg q 12h SC
- new packages 60 mg/0.6 mL, 80 mg/0.8mL and 100 mg/1.0 mL in pre-filled syringes
- a new manufacturing line

Supplement SE1-15 is a nonpriority submission with information on

- a new indication, the treatment of deep vein thrombosis [redacted]
- new packages 60 mg/0.6 mL, 80 mg/0.8mL and 100 mg/1 mL in pre-filled syringes
- a new manufacturing line
- new dosing regimens, 1.5 mg/Kg qd SC or 1.0 mg/Kg q12h SC

The new packages and new manufacturing line provide the same information in both supplements. The new dosing regimen of 1.0 mg/Kg q 12h SC is common to both submissions, although it is for different patient populations.

An open single ascending dose pharmacokinetic study (Protocol Report K 9001006) of enoxaparin after subcutaneous administration of 1.0 mg/Kg, 1.25 mg/Kg, 1.5 mg/Kg and 2.0 mg/Kg in 16 healthy volunteers shows approximate dose proportionality for Anti-Xa activity based on clearance, normalized AUC and normalized Amax. Enoxaparin showed approximate dose proportionality for Anti-IIa activity based on clearance except at the 1.0 mg/Kg dose. This deviation at the lower dose may be related to the lower levels being measured rather than some other mechanism such as induction. The original submission for enoxaparin showed dose proportionality for anti-Xa activity from 20 to 80 mg given S.C. In this study the ratio of the AUC of anti-Xa to anti-IIa activity is 3 to 5.5 times higher than the potency ratio of 3.56 reported in the original submission for enoxaparin.

A randomized, three period crossover study (Protocol Report RP 54563Q-133) compared the pharmacokinetic profile of two formulations of enoxaparin: single concentration (100 mg/mL) enoxaparin in ampoules (1 shot vs. 2 shots) versus double concentration (200 mg/mL) enoxaparin in ampoules, administered as 1.5 mg/Kg once a day subcutaneous treatment for 5 days to healthy males and females. Single strength vs. double strength enoxaparin was shown to be bioequivalent in a single dose study, PK129, reviewed in April 1996 (NDA 20-164/SE1 (008)). The present study uses doses of enoxaparin (1.5 mg/Kg) likely to be used in the treatment of thrombosis or unstable angina. Gender effect was tested in an ANOVA model incorporating the terms treatment, period, sequence, gender and subject(sequence). In terms of anti-Xa: the Amin activities comparing Day 3 to Day 5 were not significantly different for the three treatment groups. Steady-state has probably been reached by Day 3. A gender effect was noticed in terms of the AUC being lower in females, but not on Amax nor AUC(0-24h), $p<0.05$. A statistically significant gender effect ($p<0.0001$) was noticed on parameters such as volume of distribution and terminal half-life, but not on total body clearance. In terms of anti-IIa: steady-state based on Amin was evident by Day 3. No significant gender effects were noticed on pharmacokinetic parameters except a borderline significance for AUC_{0-t} ($p=0.0324$). In terms of [redacted] there was a significantly lower extent of absorption ($p<0.001$) in females vs. males and the MRT of [redacted] activity was significantly longer in males vs. females ($p<0.001$). The average exposure in females is lower than in males ($p<0.001$) and the apparent elimination half-life is prolonged in males vs. females. No significant gender effects were observed for aPTT. The results from the two one-sided test show that many of the parameter comparisons had the lower bound of the 90% CI greater than 100%. This lends some doubt as to the conclusions of bioequivalence, however, as stated previously, an earlier submission showed bioequivalence of the single to double strength enoxaparin (PK129, reviewed in April 1996 (NDA 20-164/SE1 (008)).

[redacted] APPEARS THIS WAY ON ORIGINAL

A randomized pilot trial (Protocol Report RP 54563Q-260) of 5 weeks enoxaparin 60 mg sc plus aspirin alone following conventional medical therapy was undertaken in patients admitted to hospital with diagnosis of unstable angina or acute non-Q-wave myocardial infarction. The

sponsors concluded that the clearance in Study RP54563-260 is within that found in earlier studies, however the study shows a mean clearance about 70% longer than that reported in previous studies (mean 1.02 L/hr vs. mean 0.6 L/hr).

A multi center trial of safety and tolerability of two doses of enoxaparin was undertaken in patients with unstable angina and non-Q-wave myocardial infarction (Protocol Report RP 54563Q-261). The trough anti-Xa activities were 20 to 33% higher in the 1.25 mg/Kg group compared to the 1.0 mg/Kg group. Also "peak" anti-Xa activities were 45 to 50% higher in the 1.25 mg/Kg group compared to the 1.0 mg/Kg group. The "peak" activity is not an exact figure since single samples were taken approximately 3 hours postdose, however Protocol Report K 9001006 in this submission showed that there was dose linearity between 1.0 to 2.0 mg/Kg in healthy adults. After the third dose of 1.25 mg/Kg there was a statistically significant higher "peak" anti-Xa activity ($p<0.01$) in patients experiencing major hemorrhage than those without major hemorrhage. Also, the rate of major hemorrhage was 6.5 % in the 1.25 mg/Kg group compared to a rate of 1.9% in the 1.0 mg/Kg group of patients. Comparison of median trough and peak levels for the third vs. last dose showed similar values, indicating lack of accumulation for bid dosing.

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APPENDIX II

Contains the following information relating to clinical studies listed in APPENDIX I:
* dose proportionality data
* graphs

ABBREVIATIONS:

AUC	area under the plasma concentration versus time profile
CL/F	total body clearance for anti-Xa activity
Amax	maximum plasma concentration
MRT	mean residence time
t1/2β	half-life for anti-Xa activity
SS	steady-state
Tmax	time when Amax observed
Vdss	volume of distribution at steady-state
Vdβ	volume of distribution
aPTT	activated partial thromboplastin time
PT	prothrombin time
s.c or SC	subcutaneous

BACKGROUND

Enoxaparin is a low molecular weight heparin (LMWH) obtained by partial and controlled depolymerization of benzyl ester of porcine heparin. The antithrombotic activity of enoxaparin depends on anti-Xa activity derived from short and highly bioavailable glycosaminoglycan fragments (M.Wt. <5400 daltons), anti-IIa activity derived from fragments with M.Wt. in the 5400-10000 dalton range and release of TFPI (tissue factor pathway inhibitor) from the vessel wall. This results in a delay and a decrease in prothrombinase activity and thrombin generation. Anti-Xa activity is mostly used to define the antithrombotic and anticoagulant effects.

Rationale for Selection of Starting Dose and Treatment Regimen:
The selection of 1.0 mg/Kg every 12 hours is based on a preliminary safety study where patients were on a dose of 1.0 mg/Kg or 1.25 mg/Kg. Patients dosed at 1.25 mg/Kg had a greater incidence of major hemorrhagic events.

Comments (to send to sponsors):
1. An alternate model to use for gender analysis would be:

Y = Weight sequence gender sequence*gender subject(sequence*gender)
period product product*gender weight*product
*sequence*product*period*gender*

Using this model, if the interaction term *"sequence*product*period*gender"* is not significant at the $p<0.1$ level, this term could be dropped from the model and the data re-analyzed. If no terms show significance at the 0.05 level then the analysis could then be repeated dropping the weight term. It is noted that to some extent weight is taken into account through the dose being given on a weight basis. The model further explores gender effects in terms of the gender*product interaction.

The sponsors are requested to carry out the above statistical analysis on the data in Study RP 54563Q-133 and to forward the SAS code and ASCII data set to the Agency.

2. The sponsors need to address the difference in mean clearance of anti-Xa activity in the population studied under Protocol Report RP 54563Q-260 as compared to earlier studies. The sponsors should be aware of consistency in units when comparing mean clearance across studies i.e. whether clearance is a based on IU anti-Xa or mg enoxaparin. Comparison of ranges should be avoided since these are dependent on the number of subjects used in the analyses. The present study suggests that clearance is 70% higher than shown previously in healthy subjects.

3. The sponsors may want to consider a drug-interaction study in healthy elderly subjects with two treatment arms: enoxaparin and enoxaparin with aspirin.

4. The sponsors are encouraged to undertake non-linear mixed effect modeling of the data in this study and studies where sampling for determination of anti-Xa activity etc. has occurred. If undertaken correctly this would give a much better picture of the handling of enoxaparin by different populations and the influence of cofactors such as age, co-administered drugs.

Labeling Comments (to be sent to sponsor):

1. The sponsors should consider updating the labeling to include information on the *in vitro* potency vs. the *in vivo* ratio of anti-Factor Xa to IIa activity. The statement should reflect the more recent information on the higher *in vivo* ratio of anti-Factor Xa to IIa activity shown in the submission. A possible statement in the labeling would be:

DRAFT LABELING

[redacted]

2. The sponsors should consider incorporating the gender differences shown in the healthy volunteer study. A possible statement in the labeling would be:

DRAFT LABELING

[redacted]

enter Tabulated results here. "

RECOMMENDATION:
The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II finds NDA20-164 SEI-15 and SE1-16 satisfactory. The comments and labeling comments should be forwarded to the sponsors.

APPEARS THIS WAY ON ORIGINAL

/S/ [redacted] 6/9/97

Lydia C. Kaus, M.S., Ph.D. 7/14/97
Team Leader, Gastrointestinal and Coagulation Drug Products, Division of Pharmaceutical Evaluation II.

/S/ [redacted]
FT initialed by
Mei-Ling Chen, Ph.D. 7/8/97
Director, DPEII

cc:NDA 20-164, HFD-180, HFD-870 (Chen, Kaus), HFD-850 (Lesko), Central Document Room (Barbara Murphy).

APPEARS THIS WAY ON ORIGINAL