**Table 1 Studies performed before 1989 (Unfractionated heparin reference standard)**

| Study number (NDA) | Dose/Route | Number of subjects | Clearance/F (l/h) Mean ± SD and range |
|---|---|---|---|
| DN 100537 (20-164) | 20 mg/SC<br>40 mg/SC<br>60 mg/SC<br>80 mg/SC | 12 young males (cross over) | 1.85 ± 0.63 [1.20 - 3.18]<br>1.33 ± 0.32 [0.77 - 1.85]<br>1.25 ± 0.21 [0.90 - 1.60]<br>1.18 ± 0.25 [0.82 - 1.57] |
| DN 100539 (20-164) | 40 mg (day 1)/SC<br>40 mg (day 10)/SC | 12 elderly males and females | 1.38 ± 0.69 [0.75 - 3.39]<br>1.28 ± 0.82 [0.72 - 3.68] |
| DN 100541 (20-164) | 3750 IU/IV<br>7500 IU/IV | 9 young males | No Clearance data provided in the report |
| DN 100542 (20-164) | 0.25 mg/kg/IV<br>0.50 mg/kg/IV | 12 patients (dialysis) Chronic renal insufficiency | No Clearance data provided in the report |

SC = Subcutaneous administration, IV = Intravenous administration
The CL/F values corresponds to the mean ± SD obtained in each arm of the study.

**Table 2 : Studies performed after 1989 (Reference standard : WHO LMWH1)**

| Study number (NDA) or (supplement) | Dose/Route | Number of subjects | Clearance/F (l/h) Mean ± SD and range |
|---|---|---|---|
| DN 105640 (20-164) BE study (PK 122) | 40 mg (A)/SC<br>40 mg (B)/SC | 12 young males | 0.92 ± 0.180 [0.71 - 1.47]<br>0.91 ± 0.138 [0.73 - 1.28] |
| PK 123 (preliminary report) | 30 mg (day 1)/SC | 12 young males | 0.99 ± 0.20 [0.63 - 1.26] |
| PK 128 (S-004) BE study | 40 mg (A)/SC<br>40 mg (B)/SC<br>40 mg (C)/SC | 24 young males | 0.80 ± 0.10 [0.58 - 1.02]<br>0.82 ± 0.12 [0.63 - 1.12]<br>0.83 ± 0.11 [0.65 - 1.13] |
| PK 129 (S-008) BE study | 40 mg (A)/SC<br>40 mg (B)/SC | 16 young males | 0.97 ± 0.13 [0.77 - 1.28]<br>0.89 ± 0.10 [0.75 - 1.08] |
| PK 121 Collignon *et al.* Thromb. Heamostasis 1995, 73(4): 630-40 | 20 mg/SC<br>40 mg/SC | 20 young males | 1.00 ± 0.33<br>0.83 ± 0.19 |
| PK 134 (S-011) BE study (3 arms) | 40 mg (A PF syr.)/SC<br>40 mg (B MDV)/SC<br>40 mg (C MDV)/SC | 24 young<br>12 males +<br>12 females<br>No gender effect | 0.92 ± 0.18 [0.57 - 1.46]<br>1.04 ± 0.21 [0.75 - 1.67]<br>1.06 ± 0.20 [0.73 - 1.52] |
| PK 260 Patients with UA (S-016) | 60 mg (day 4)/SC | 16 Patients with UA<br>13 males + 6 females<br>No gender effect | 1.02 ± 0.33 [0.72 - 2.06] |
| PK 133 (S-015/016) BE study (3 arms) | Day 5<br>1.5 mg/kg (A)/SC<br>1.5 mg/kg (B)/SC<br>1.5 mg/kg (C)/SC | 24<br>12males+12females<br>No gender effect | 0.60 ± 0.12 [0.45 - 0.93]<br>0.58 ± 0.11 [0.39 - 0.87]<br>0.57 ± 0.11 [0.45 - 0.86] |
| K 91006 (S-015/016) Ascending dose study | 1.0 mg/kg/SC<br>1.25 mg/kg/SC<br>1.5 mg/kg/SC<br>2.0 mg/kg/SC | 16 young males | 0.72 ± 0.09 [0.59 - 0.84]<br>0.65 ± 0.06 [0.54 - 0.73]<br>0.65 ± 0.06 [0.59 - 0.81]<br>0.64 ± 0.07 [0.55 - 0.77] |
| Study 1819 (S-018) BE study (3 arms) | 1.5 mg/kg (0%)/SC<br>1.5 mg/kg (1%)/SC<br>1.5 mg/kg (2%)/SC | 18 young males | 0.84 ± 0.44 [0.60 - 2.58]<br>0.75 ± 0.13 [0.51 - 0.98]<br>0.77 ± 0.12 [0.51 - 0.98] |

SC = Subcutaneous administration, BE = Bioequivalence, Cross-over BE studies were performed, A, B and C correspond to different treatments, MDV = Multiple Dose Vial, PF=Prefilled syringe, UA = Unstable Angina. The CL/F values correspond to the mean ± SD obtained in each arm of the study.

ATTACHMENT 2

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

**Table 3 : Anti-Xa activity grouped by gender**

| Study number | Dose/Route | Number of subjects | Amax (IU/ml) Mean ± SD | AUC (h.IU/ml) Mean ± SD |
|---|---|---|---|---|
| **Healthy volunteers** | | | | |
| **PK 134 *** (S-011) BE (3 arms) | 40 mg (A PF syr.)/SC | 12 males | 0.49 ± 0.08 | 4.07 ± 1.05 |
| | 40 mg (B MDV o)/SC | | 0.47 ± 0.08 | 3.80 ± 0.83 |
| | 40 mg (C MDV7d)/SC | | 0.48 ± 0.08 | 3.75 ± 0.84 |
| | 40 mg (A PF syr.)/SC | 12 females | 0.61 ± 0.08 | 4.53 ± 0.38 |
| | 40 mg (B MDV o)/SC | | 0.58 ± 0.10 | 4.38 ± 0.48 |
| | 40 mg (C MDV7d)/SC | | 0.56 ± 0.07 | 4.28 ± 0.55 |
| **PK 133** (S-015/016) BE (3 arms) Multiple dose | Day 5 | | | |
| | 1.5 mg/kg (A)/SC | 12 males | 1.41 ± 0.27 | 17.43 ± 3.08 |
| | 1.5 mg/kg (B)/SC | | 1.45 ± 0.21 | 17.47 ± 3.12 |
| | 1.5 mg/kg (C)/SC | | 1.50 ± 0.23 | 18.31 ± 3.36 |
| | Day 5 | | | |
| | 1.5 mg/kg (A)/SC | 12 females | 1.33 ± 0.18 | 13.93 ± 3.11 |
| | 1.5 mg/kg (B)/SC | | 1.47 ± 0.23 | 14.79 ± 3.49 |
| | 1.5 mg/kg (C)/SC | | 1.39 ± 0.19 | 15.29 ± 3.24 |
| **Patients** | | | | |
| **K 91107** (S-015) - DVT treatment | Day 7 | | | |
| | 1.5 mg/kg /SC | 7 males | 1.70 ± 0.29 | 20.60 ± 3.72 |
| | Day 7 | | | |
| | 1.5 mg/kg (A)/SC | 9 females | 1.70 ± 0.38 | 19.01 ± 4.57 |
| **PK 260*** (S-016) - UA | Day 4 | | | |
| | 60mg /SC | 13 males | 0.54 ± 0.14 | 5.79 ± 1.48 |
| | Day 4 | | | |
| | 60mg /SC | 6 females | 0.67 ± 0.14 | 7.01 ± 1.10 |

* **Study 134 and 260**: Amax and AUC were not normalized to the body weight

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ATTACHMENT 3

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

LOVENOX

CLINICAL PHARMACOLOGY (Revised December 16, 1998)

Enoxaparin is a low molecular weight heparin which has antithrombotic properties. In humans, enoxaparin given at a dose of 1.5 mg/kg subcutaneously (SC) is characterized by a higher ratio of anti-Factor Xa to anti-Factor IIa activity (mean±SD, 14.0±3.1) (based on areas under anti-Factor activity versus time curves) compared to the ratios observed for heparin (mean±SD, 1.22±0.13). Increases of up to 1.8 times the control values were seen in the thrombin time (TT) and the activated partial thromboplastin time (aPTT). Enoxaparin at a 1 mg/kg dose, administered SC every 12 hours to patients in a large clinical trial resulted in aPTT values of 45 seconds or less in the majority of patients (n=1607).

**Pharmacodynamics:** Maximum anti-Factor Xa and anti-thrombin (anti-Factor IIa) activities occur 3 to 5 hours after SC injection of enoxaparin. Mean peak anti-Factor Xa activity was 0.16 IU/mL (1.58 μg/mL) and 0.38 IU/mL (3.83 μg/mL) after the 20 mg and the 40 mg clinically tested doses, respectively. Mean (n=46) peak anti-Factor Xa activity was 1.1 IU/mL at steady-state in patients with unstable angina receiving 1.0 mg/kg SC every 12 hours for 14 days. Mean absolute bioavailability of enoxaparin, given SC, based on anti-Factor Xa activity is 92% in healthy volunteers. The volume of distribution of anti-Factor Xa activity is approximately 6 L. Following intravenous (i.v.) dosing, the total body clearance of enoxaparin is 26 mL/min. After iv dosing of enoxaparin labeled with the gamma-emitter, $^{99m}$Tc, 40% of radioactivity and 8 to 20% of anti-Factor Xa activity were recovered in urine in 24 hours. Elimination half-life based on anti-Factor Xa activity was 4.5 hours after SC administration. Following a 40 mg SC once a day dose, significant anti-Factor Xa activity persists in plasma for about 12 hours.

A representative set of anti-Factor Xa activity parameters, maximum activity (Amax) and clearance (CL/F), obtained following administration of SC doses of enoxaparin sodium are presented in the following table.

Mean (SD) anti-Factor Xa activity parameters

| Study, Population | Dose | Amax (IU/mL) | | CL/F (l/h) | |
|---|---|---|---|---|---|
| | | Males | Females | Males | Females |
| PK 134, Subjects* | 40 mg enoxaparin sodium | 0.49 (0.08) | 0.61 (0.08) | 0.99 (0.23) | 0.85 (0.07) |
| PK 260, Patients** | 60 mg enoxaparin sodium with aspirin | 0.54 (0.14) | 0.67 (0.14) | 1.10 (0.38) | 0.85 (0.14) |

*: Twelve male and twelve female subjects

**: Thirteen male patients and six female patients

Clearance and $A_{max}$ derived from anti-Factor Xa values following single and multiple SC dosing in elderly subjects were close to those observed in healthy subjects. Following once a day SC dosing of 40 mg enoxaparin, the Day 10 mean area under anti-Factor Xa activity versus time curve (AUC) was approximately 15% greater than the mean Day 1 AUC value. In subjects with moderate renal impairment (creatinine clearance 30 to 80 ml/min), anti-Factor Xa CL/F values were similar to those in healthy subjects. However, mean CL/F value of subjects with severe renal impairment (creatinine clearance <30 ml/min) was approximately 30% lower than the mean CL/F value of control group subjects. Another observation in this study is that there may be a race effect in clearance of anti-Factor Xa activity. However, clinical significance of slower clearance of anti-Factor Xa activity in subjects with severe renal impairment is unknown (see PRECAUTIONS).

## PRECAUTIONS

Adjustment of enoxaparin sodium dose may be considered for patients with severe renal impairment (creatinine clearance <30 ml/min).

ATTACHMENT 4

28 pages

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DRAFT

LABELING

ATTACHMENT 5

*Original NDA 20-164 (26 July 1991).* DN 100493 Comparative study of effects of PK 10169 and a placebo on the biological parameters: coagulation, fibrinolysis. *Final Study Report.* 7 April 1986. **[Vol. 26, pages 353 to 354, 362]**

4.1.2. Anti-IIa activity (Appendix IV, table 3, page 46)

Before injection, the mean anti-IIa activity in the placebo groups was 0.03 ± 0.005 IU/ml and that in the ENOXAPARIN group was 0.03 ± 0.009 IU/ml. Analysis of variance shows that there is no difference between the 2 groups p = 0.518 (Appendix VII, table 2, page 64).

4.1.3. Thrombin clotting time (Appendix IV, table 1, page 44)

Before injection, the mean thrombin clotting time in the placebo group was 28.3 ± 1.5 sec. and that in the ENOXAPARIN groups was 29 ± 1.4 sec The product x sequence interaction is significant p = 0.001 (Appendix VII, table 3, page 65).

Examination of the individual values shows that, in the ENOXAPARIN group, the subjects in sequence 1 (ENOXAPARIN - Placebo) had higher values ($\bar{m}$ = 32.0) than those in sequence 2 (Placebo - ENOXAPARIN) ($\bar{m}$ = 26.0). The opposite is true in the Placebo group where the sequence 1 subjects had lower values ($\bar{m}$ = 25.3) than those in sequence 2 ($\bar{m}$ = 31.3).

In the following analysis, we considered it possible to disregard this interaction since:

- all of the individual values can be considered to be normal,
- the analysis at the following times was carried out according to the difference with respect to T0,
- overall, there is no difference between the two groups nor between the two sequences,
- the separate analysis, sequence by sequence, would not have been of any interest due to the small number of subjects (n = 3).

4.1.4. Activated partial thromboplastin time (Appendix IV, table 2, page 45)

Before injection, the mean activated partial thromboplastin time in the placebo group was 32.0 ± 1.3 sec. and that in the ENOXAPARIN group was 35.5 ± 1.23 sec. The product x sequence interaction is significant p = 0.02 (Appendix VII, table 4, page 66).

As for the thrombin clotting time, this interaction is due to a difference in means between inverse sequence 1 and 2 in the ENOXAPARIN and Placebo groups.

For the same reasons cited above, we disregarded this interaction in the rest of the analysis.

4.1.5. Plasminogen (Appendix IV, table 7, page 50)

Before injection, the mean plasma plasminogen level in the placebo group was 1.0 ± 0.04 IU/ml and that for the ENOXAPARIN group was 1.01 ± 0.04 IU/ml. There is no significant difference between the 2 groups p = 0.08 (Appendix VII, table 5, page 67).

4.1.6. Tissue plasminogen activator (Total plasma fraction) (Appendix IV, table 9, page 52)

Before injection, the mean tissue plasminogen activator level in the placebo group was 0.32 ± 0.009 ng/ml and that in the ENOXAPARIN group was 0.46 ± 0.05 ng/ml. There is no significant difference between the 2 groups p = 0.06 (Appendix VII, table 6, page 68).

4.1.7. Tissue plasminogen activator (Absorbable fraction on fibrin) (Appendix IV, table 10, page 53)

Before injection, the mean level of tissue plasminogen activator absorbable on fibrin in the placebo group was 0.01 ± 0.02 ng/ml and that in the ENOXAPARIN group was 0.27 ± 0.06 ng/ml. There is no significant difference between the 2 groups p = 0.099 (Appendix VII, table 7, page 69).

The anti-Xa activity was found to very high (0.73 IU) and disappeared between hour 12 and hour 24. The anti-IIa activity remained low (0.12 IU) and disappeared more quickly between hour 6 and hour 12. These results corroborate those observed in other studies (22, 23, 24).

However, we did not observe any fibrinolytic activity with the 90 mg dose of ENOXAPARIN. Nevertheless, it is possible that the use of new assay methods that have been developed since the end of this study, with increased sensitivity, would have been able to demonstrate fibrinolytic activity.

## VI - CONCLUSION

This trial confirmed that a subcutaneous injection of 90 mg of ENOXAPARIN significantly changes the coagulation tests (activated partial thromboplastin time, thrombin clotting time). However, the observed changes are brief (at a maximum between hour 2 and hour 6) and always remain shorter than to the extensions considered to involve a risk of hemorrhage for the patient.

The administration of a single subcutaneous dose of 90 mg of ENOXAPARIN, induced a high increase in peak anti-Xa activity between hour 2 and hour 12. The anti-Xa activity values return to the base-line 24 hours after injection.

The fibrinolytic activity of the 90 mg dose of ENOXAPARINE does not differ from that of a placebo in the tests carried out in this study.



April, 7, 1986

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