

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-164

Name of Drug: Lovenox (enoxaparin) Injection

Sponsor: Rhone-Poulenc Rorer

JAN 14

Material Reviewed

Submission Date(s): January 8, 1993

Receipt Date(s): January 11, 1993

Background and Summary Description: Final printed labeling has been submitted in response to the November 20, 1992 approvable letter to this application.

Review

Package Insert

The submitted insert, IN-1107 (Rev. 1/93), was compared to the draft insert submitted December 8, 1992 as a minor amendment to this application.

The inserts were identical except for the following:

1. Deletion from the DESCRIPTION section, of information relating to activity per syringe. This revision was done at the Agency's request (refer to teletype dated December 23, 1993).
2. The statement, "Patients with known hypersensitivity to heparin or pork products should not be treated with enoxaparin." was relocated from the PRECAUTIONS section to the CONTRAINDICATIONS section. The statement was located in the CONTRAINDICATIONS section in the draft insert included with the November 20, 1992 approvable letter.

The following difference in storage statements between the insert and product labels was noted:

Insert: Lovenox injection should be stored at or below 25°C.

Product Labels: Store at or below 25°C. Do not freeze.

Product labels and carton

1. Lot number and expiration date: The placement of the lot number and expiration date is evident on the immediate product label. The carton does not indicate the placement. Ms. Meg Martin (telephone conversation of January 14, 1993) stated that the lot number and expiration are stamped on the carton at the time of packaging on the bottom flap of the carton.
2. The carton, which holds 10 syringes, is designed with a detachable (tear-off) top. All required labeling information is located below the perforations (not lost when the top is discarded).

The labels and carton conform to the required elements for labeling under 21 CFR 201.1, 201.2, 201.5, 201.10, 201.15, 201.17, 201.18, 201.50, 201.51, 201.55, and 201.100.

Recommendations

The firm should be requested to add "Do not freeze." to the storage instructions on the package insert at the next printing.

Bronwyn Collier 1/14/93
Consumer Safety Officer

cc:
Orig NDA 20-164
~~HFD-180~~
HFD-180/CSO/BCollier
HFD-180/JGibbs
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BC/1/14/93

1/14/93

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA 20-164

Drug: Enoxaparin

MAY - 1 1992

Sponsor: Rhone-Poulenc Rorer
500 Virginia Drive,
Fort Washington, PA 19034

Class: Anticoagulant

Category: Low Molecular Weight Heparin

Indication: Prevention of Deep Vein Thrombosis following hip replacement.

Date of Initial NDA Submission: July 26, 1991

Date of Submission of Revised NDA: December 30, 1991

Reviewer: Lilia Talarico M.D.

Date of Review: April 27, 1992

On July 26, 1991, the sponsor submitted a New Drug Application for the approval of Enoxaparin injection for the prophylaxis of deep vein thrombosis in patients undergoing hip replacement surgery. The proposed regimen for enoxaparin therapy was 30 mg q12h subcutaneously beginning on the day of surgery.

The initial application was incomplete and filing was refused. On 12-30-1991, the sponsor submitted the material required to complete the application and to allow its filing for review.

Material submitted: A total of 88 volumes (1-88) were submitted with the initial NDA. Seven additional volumes were subsequently added and integrated in the resubmitted NDA. The additional volumes were labeled 2.1 through 2.22.

Data from volumes 2.1, 2.14 through 2.21 and volumes 27 through 78 of the NDA were examined for this medical review.

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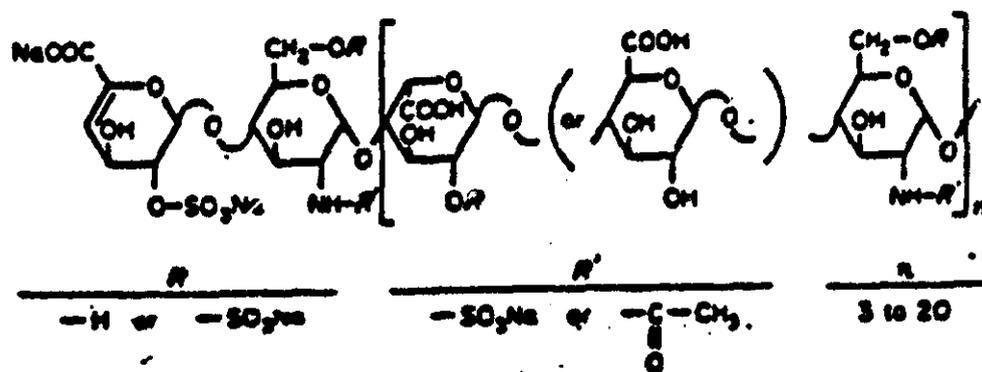
GENERAL INFORMATION

A. Name of the drug:

1. Generic Name: Enoxaparin
2. US Proprietary Name: To be established.
3. Foreign Proprietary Names: Clexane, Lovenox

B. Chemical Characteristics:

1. Description: Low Molecular Weight Heparin (LMWH)
2. Structural Formula:



3. Derivation: Depolymerized porcine mucosa heparin
4. Molecular Weight: 4500 (range 3500-5500)
5. Substance: Sodium Salt
6. Stability: 2 years at 4° RT or 45°

C. Pharmacology Category:

Anticoagulant

D. Proposed Indication:

Prophylaxis of Deep Vein Thrombosis (DVT) and pulmonary embolism (PE) in high risk orthopedic surgery patients following hip replacement.

E. Proposed Dose and Administration Regimen:

30 mg twice daily administered by subcutaneous injection, starting as soon as possible after surgery, and continued postoperatively until the risk of DVT has subsided.

F. Formulation:

The formulation proposed for marketing consists of prefilled syringes containing 30 mg of Enoxaparin with anti-Xa activity of 3000 IU in 0.3 ml of water for injection. Each prefilled syringe is affixed with a 26 gauge x1.2 inch needle.

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Enoxaparin was initially formulated with antioxidant, however, studies performed on several batches of prefilled syringes without similar stability profiles. have shown as, therefore, been eliminated from the enoxaparin formulation.

NON-CLINICAL PHARMACOLOGY and TOXICOLOGY

ADME studies were performed in rats, dogs and monkeys. Enoxaparin is completely adsorbed from subcutaneous administration, is not metabolized, does not cross the blood-brain barrier, and it is excreted unchanged in the urine. The maximum plasma radioactivity of ^{99m}Tc-enoxaparin was observed 2 to 4 hours after sc dosing and measurable radioactivity persisted for up to 22 hours. The highest radioactivity was found in the kidneys and liver. Enoxaparin was excreted primarily from the kidneys.

The kinetics of radioactivity and the biological activity (inhibition of Xa activity) of ³⁵S-enoxaparin were compared in dogs. Maximum radioactivity preceded maximal biological activity, but the elimination rates were similar. Widespread distribution of radioactivity in most organs was found, but primarily in kidneys and liver. Very low concentration was found in the brain. Enoxaparin was eliminated through the kidneys. The intravenous administration of enoxaparin to dogs showed that about 24% of plasma radioactivity was protein-bound, mainly to AT-III, and that only the protein-bound enoxaparin inhibited factor Xa activity. Repeated daily dosing did not produce accumulation of the drug. Steady state was achieved after 2-3 days with daily sc dosing of 1 mg/kg/day. The metabolism of enoxaparin was not changed with repeated administration of the drug.

In monkeys, sc administration of enoxaparin produced longer inhibition of factor Xa than of factor IIa. The degree and duration of effect were dose-dependent. Maximal inhibition of factor Xa was observed at 2-4 hours and measurable inhibition persisted for more than 12 hours. The daily administration of large dose, 100 mg/kg/day sc, produced gradual accumulation of drug effect which reached a maximum at 4 days and then plateaued. Enoxaparin and Unfractionated Heparin (UH) were evaluated in experimental animals models of thrombosis using jugular stasis/hypercoagulability or carotid/jugular shunts. In these experiments, doses of UH or enoxaparin, of similar anti-Xa

activity exhibited similar anti-thrombotic activity. The hemorrhagic activity, measured by the rabbit ear bleeding time model, was, however, greater with UH than with enoxaparin at similar anti-Xa activities.

Enoxaparin inhibited coronary thrombosis in dogs at doses that inhibited factor Xa activity without inhibition of factor IIa or prolongation of the bleeding time. Enoxaparin was as effective as heparin in preventing in vitro thrombosis in the Chandler loop and was more effective than heparin in preventing thrombosis in rabbit venous stasis test. Enoxaparin has been shown to have antithrombotic activity in rabbits, dogs and monkeys at subcutaneous doses of approximately 1 mg/kg or less. Intravenous administration of enoxaparin at doses slightly higher than those needed for antithrombotic activity can increase fibrinolysis.

Enoxaparin can induce hemorrhage because of its anticoagulant activity, however, compared to enoxaparin, heparin produced bleeding at lower doses. No prolongation of the bleeding time occurred with single doses of enoxaparin of 50 to 2000 anti-Xa units/kg. At equivalent anti-Xa activity doses, heparin prolonged the bleeding time significantly.

In summary, numerous studies have demonstrated a dissociation between the anti-thrombotic and the bleeding (hemorrhagic) activities of enoxaparin as compared to UH. Whether such dissociation of effects for enoxaparin and other low molecular heparins can be attributed exclusively to their differential anti-Xa and anti-IIa activities is unlikely, in view of the observation that heparin fractionated into lower fragments of mean MW of 2500 having almost exclusively anti-Xa activity, exhibit poor antithrombotic activity.

More likely, the reduced hemorrhagic effect may be attributed to the fact that low molecular heparins produce less inhibition of platelet function than standard heparin.

Acute toxicity was produced in rodents by the iv or sc administration of dose of enoxaparin of 6000-8000 and 2300 mg/kg respectively. Acute toxicity was manifested by ataxia, dyspnea, cyanosis, seizures and death. In subchronic and chronic toxicity studies, bleeding was the main manifestation of drug effect. Changes in hematology profile and development of extramedullary hemopoiesis were related to blood loss. The highest non toxic dose in chronic toxicity studies of 26 weeks was 3 mg/kg/day both in rats and monkeys. In the 13 week study in dogs, a possible effect on calcium metabolism secondary to enhancement of PTH secretion or activity was noted with the administration of high

doses of enoxaparin, 15 mg/kg/day. The effect of enoxaparin on calcium metabolism was not observed in rodents or monkeys. Elevation of serum urea, renal tubular necrosis and renal capsular hemorrhage were observed in rats given enoxaparin at the dose of 40 mg/kg/day iv for 26 days.

Administration of enoxaparin had no adverse effect on fertility or reproductive performance. No adverse effect on embryo/fetal development was observed. Enoxaparin was not mutagenic nor clastogenic in vitro or in vivo.

HUMAN PHARMACOKINETICS and BIOAVAILABILITY SUMMARY

The clinical pharmacology evaluation of enoxaparin included 16 studies divided in three sections: (1) Safety and Tolerance, (2) Pharmacokinetics, and (3) Pharmacodynamic.

1. Safety and Tolerance:

The safety and tolerance of enoxaparin in normal volunteers was evaluated in three open studies which are listed in the following table A,1 reproduced from vol 2.1, p.203 of the NDA:

TABLE A.1

Summary of Safety and Tolerance Studies

Report # Descriptor	Clinical Investigator (Country) Publications	Completion Status (start date)	Study Design	Number Patients (M-F)	Age Range (Mean)	Drug(s) Administered	Dose(s) (Route)	Duration	Full Report Location
100032 Single rising dose tolerance	Barragh (Ireland)	Complete (Dec. 82)	O,P Cbl	70 70:0	19-40 (26.0)	enoxaparin placebo	10, 20, 34, 60, 101 mg (i.v.)	20	2.14/164
102184 Multiple dose tolerance	Barragh (Ireland)	Complete (Unknown)	O	10 10:0	19-40 (26.5)	enoxaparin	40 mg/12h (s.c.)	7 days	2.14/230
100496 Injection site tolerance	Willer (France)	Complete (Sept. 83)	CO P	6 3:2	23-35 (NA) ²	enoxaparin enoxaparin enoxaparin enoxaparin enoxaparin	60 mg in hypertonic saline (s.c.) 60 mg in isotonic saline (s.c.) 30 mg in hypertonic saline (s.c.) 0.3 ml physiologic saline (s.c.) 0.6 ml physiologic saline (s.c.)	30 30 30 30 30	20/1

O = open; R = randomized; P = placebo; DB = double-blind; PL = parallel; CO = crossover; CN = comparative; SD = single dose.
: SD = single dose
: NA = not available

The intravenous administration of increasing single doses of enoxaparin (18, 36, 54, 69, 101 MG) produced a significant and dose-related increase of the APTT, TT, anti-Xa and anti-IIa activities. At the time of maximal activity (T^{max} = 5 minutes), the anti-Xa activity was 7 to 9 times greater than the corresponding anti-II activity. No effect on the bleeding time was noted at the highest dose.

The subcutaneous administration of 40 mg of enoxaparin twice daily for 7 days was generally safe and well tolerated. Mild local discomfort and small hematomas at the injection site were reported. There were no significant changes in APTT, PT, TT and bleeding time. Elevation of liver enzymes were noted: ALT and AST were elevated (2-3 times normal) in all subjects by day 7 and at the post-study evaluation. Alkaline phosphatase, bilirubin and GGT were normal. The transaminase levels returned to normal after discontinuation of the drug. Similar elevations of ALT and AST have been reported with administration of UH.

2. Pharmacokinetic Studies (PK):

Due to the lack of physico-chemical assay methods to measure enoxaparin in biological fluids, bioassays have been used for the PK studies. Tests used include global assessment of coagulation with both clotting tests (PT, APTT, TT, Heptest) and specific assays of anti-Xa and anti-IIa activities by clotting and amidolytic techniques.

The PK of enoxaparin were evaluated in nine studies; six in normal young volunteers, one in elderly volunteers, and one in patients with chronic renal failure. One study validated the analytical methods of assay of anti-Xa activity. The studies are listed in table A,2 reproduced from vol 2.1, p. 204 and 205 of the NDA. The administration of therapeutic dose of enoxaparin by sc injection did not prolong the PT, APTT or the TT.

TABLE A.2

Summary of Pharmacokinetic Studies

Report # Descriptor	Clinical Investigator (Country) Publications	Completion Status (start date)	Study Design ¹	Number Patients (M-F)	Age Range (Mean)	Drug(s) Administered	Dose(s) (Route)	Duration ²	Full Report Location
105464 Analytic Methods	-	Complete (Mar. 89)	In vitro	-	-	enoxaparin ³	0-1.35 ⁴ anti-Xa IU/ml	-	2.13/1
105640 ± Metabilsulfite	Thebault (France)	Complete (Nov. 89)	O.R., CO CM	16 (16;0)	19-36 (23.1)	enoxaparin (+ metabl.) enoxaparin (- metabl.)	40 mg (s.c.) 40 mg (s.c.)	SD SD	2.12/1
100535 Bioavail. Ca ⁺⁺ vs. Na ⁺ salt	Alach (France)	Complete (Mar. 83)	O.R CO, CM	12 10;2	23-28 (24.8)	enoxaparin (sodium salt) enoxaparin (calcium salt)	60 mg (s.c.) 60 mg (s.c.)	SD SD	2.13/334
100536 Bioavailability s.c. vs. i.v.	Gulbert (France) Haemostasis (1986) 16:116 Thromb. Res. (1985) 39:631	Complete (Feb. 84)	O.R CO	8 8;0	21-33 (5.7)	enoxaparin	40 mg (i.v., s.c.)	SD	2.11/272
100537 Linear absorption	Duchier (France) J. Clin. Pharmacol. (1988) 28:609	Complete (Nov. 85)	O, CO CM, R	12	21-30 12;0	enoxaparin	20, 40, 60, 80 mg (s.c.)	SD	2.11/351

1 O = open; R = randomized; P = placebo; DS = double-blind; PL = parallel; CO = crossover; CM = comparative; SD = single dose.
 2 SD = single dose.
 3 plasma samples spiked with enoxaparin
 4 = range of enoxaparin concentrations in spiked human plasma pools

TABLE A.2 (continued)

Summary of Pharmacokinetic Studies (continued)

Report # Descriptor	Clinical Investigator (Country) Publications	Completion Status (start date)	Study Design ¹	Number Patients (M-F)	Age Range (Mean)	Drug(s) Administered	Dose(s) (Route)	Duration ²	Full Report Location
100538 Drug accumulation	Forester (France)	Complete (Apr. 83)	O, R CO	9 2:7	19-36 (26.1)	enoxaparin enoxaparin enoxaparin	0.5 mg/kg/d, (s.c.) 1.0 mg/kg/d, (s.c.) 1.5 mg/kg/d, (s.c.)	3 days 3 days 3 days	2-13/419
100541 Bioavailability heparin vs. enoxaparin	Gulbart (France)	Complete (Apr. 83)	O, CO CM, R	9 9:0	20-32 (27.0)	enoxaparin heparin	3750 U, 7500 U (i.v.) 3750 U (i.v.)	SD SD	26/1
100539 Kinetics in the elderly	Duchier (France)	Complete (Sept. 85)	O	12 5:7	73-85 (79)	enoxaparin	40 mg/d (s.c.)	10 days	26/108
100542 Kinetics in chronic renal failure	Laville Trzeciak, Pozet (France) Mazouze (1986) 16:147	Complete (Dec. 84)	O, CM PL	12 7:5	18-65 (44.30)	enoxaparin heparin	0.25, 0.5 mg/kg (i.v.) 50, 100 U/kg (i.v.)	SD SD	26/208

1 O = open; R = randomized; P = placebo; DS = double-blind; PL = parallel; CO = crossover; CM = comparative; SD = single dose.
2 SD = single dose.

Dose-dependent prolongations of the Heptest occurred, however, the anti-Xa and the anti-IIa amidolytic assays were more sensitive than the global clotting tests for quantitative determinations of enoxaparin effect in plasma.

The PK of enoxaparin administered sc and iv at the dose of 40 mg were evaluated in a cross-over design in normal subjects. The iv administration of enoxaparin resulted in maximal prolongation of the APTT at 5-15 minutes and return to normal at 2 hours post administration. The sc administration of enoxaparin resulted in maximal prolongation of the APTT at 2 hours post dose.

Anti-IIa activity was measurable only after iv administration. The mean ratio of anti-Xa AUC/anti-IIa AUC activity from iv administration of enoxaparin was 3.95 +/- 1.10 units. The bioavailability of sc enoxaparin was 92.4 +/- 22.6% with no difference between subjects or route of administration. The PK parameters of a single iv and sc 40 mg dose of enoxaparin obtained measuring anti-Xa activity, are shown in the following table:

<u>Parameter</u>	<u>Route of Administration</u>	
	<u>sc dose</u> mean ± s.d.	<u>iv dose</u> mean ± s.d.
A _{max} (ug/ml)	2.82 ± 0.53	8.14 ± 1.9
AUC _(0-∞) (h.ug.ml ⁻¹)	24.15 ± 4.43	27.17 ± 6.97
T _{1/2} (h)	5.11 ± 2.25	4.04 ± 2.46
Median T _{max} (h)	3.0	0.083

The adsorption and the PK of sc enoxaparin at doses ranging from 20 to 80 mg were studied in a cross-over design study in normal subjects. The adsorption of enoxaparin after subcutaneous administration was proportional to dose in terms of anti-Xa AUC measurement. The PK parameters for the various doses of enoxaparin are shown in the following table:

<u>Parameter</u>	<u>Enoxaparin Dose</u>			
	<u>20 mg</u>	<u>40 mg</u>	<u>60 mg</u>	<u>80 mg</u>
T _{max} (h)	2.67±1.05	3.50±1.09	3.92±1.08	3.08±0.79
A _{max} (ug/ml)	1.58±0.35	3.08±0.98	5.38±0.75	7.44±1.47
AUC _(0-∞) (h.ug.ml ⁻¹)	11.79±3.30	32.01±8.84	49.26±8.69	70.76±15.49
T _{1/2} (h)	4.18±2.21	4.36±1.07	3.70±0.82	3.46±0.86
D _p x F (L)	9.30±3.67	8.49±3.37	6.59±1.33	5.82±1.79
C _L x F (L/h)	1.86±0.63	1.33±0.32	1.25±0.21	1.18±0.25
MRT (h)	5.18±1.38	5.83±0.86	6.19±0.74	6.45±0.76

where F is absolute bioavailability factor (100%) and MRT is mean residence time or time needed to generate 50% activity.

Comparative PK of single sc doses of 60 mg of a calcium salt and a sodium salt of enoxaparin were determined. Based on anti-Xa activity analysis, the bioavailability of the calcium salt was slightly greater than that of the sodium salt. However, as the variability among individuals was less with the sodium salt, this preparation was selected for clinical studies.

The bioavailability and the disposition profile of formulations of enoxaparin with and without _____ were examined and found to be similar.

The comparative kinetics of repeated administration of three doses of enoxaparin (0.5, 1.0 and 1.5 mg/kg) were assessed in normal subjects in order to determine the risk of drug accumulation. No cumulative effect was observed following repeated doses of the drug.

The PK profile of heparin and enoxaparin administered at equal doses of anti-Xa activity were determined to establish a dose-response relationship for enoxaparin. The administration of enoxaparin was characterized by a dose proportionality based on anti-Xa activity PK parameters. Enoxaparin produced greater anti-Xa activity and longer duration of anti-Xa effect relative to heparin at same anti-Xa dose. The results are summarized in table 10054-1 reproduced from the sponsor's NDA (vol 27, p 109) The repeated administration of daily sc doses of 40 mg of enoxaparin over 10 days to elderly subjects of mean age of 79 +/- 3.5 years did not result in drug accumulation. The PK parameters in young and in elderly subjects were not significantly different.

The kinetics of anti-Xa and anti-IIa activities of iv heparin and enoxaparin were compared in patients with chronic renal failure. When compared to data from normal subjects, the effect of enoxaparin on anti-Xa activity and the elimination rate of the drugs in patients with chronic renal failure were similar.

Table 100541-1

Summary of the means and standard deviations for several pharmacokinetic parameters derived from anti-Xa activity and anti-IIa activity measurements. The administered doses of heparin and enoxaparin were based on anti-Xa units (U).

Parameter	Heparin 3750 U	Enoxaparin 3750 U	Enoxaparin 7500 U
Anti-Xa			
A_{max} (IU/ml)	0.71 ± 0.20		
(µg/ml)	4.43 ± 1.25*	7.18 ± 1.55	13.13 ± 2.49
T_{max} (minutes)	5.0	5.0	5.0
AUC(0-inf)			
h • IU • ml ⁻¹	0.74 ± 0.35		
h • µg • ml ⁻¹	4.63 ± 2.21	22.40 ± 5.26	47.07 ± 10.55
$T_{1/2}$ (h)	0.62 ± 0.16	2.99 ± 0.86	2.97 ± 0.40
Anti-IIa			
A_{max} (IU/ml)	0.59 ± 0.14		
(µg/ml)	3.68 ± 0.88	5.39 ± 2.15	11.36 ± 3.50
T_{max} (minutes)	5.0	5.0	5.0
AUC(0-6h)			
h • IU • ml ⁻¹	0.60 ± 0.26		
h • µg • ml ⁻¹		6.79 ± 3.75	21.71 ± 10.07
Mean AUC ratio anti-Xa/anti-IIa	1.22 ± 0.13	3.35 ± 0.89**	2.49 ± 0.86

* 160 IU of heparin = 1 mg of heparin
** excludes subject G''

Source of Data - Tables II to XI

3. Pharmacodynamic studies:

The PD of enoxaparin were evaluated in four single dose studies which are listed in the following table A,3 reproduced from vol 2.1, p.206 of the NDA:

TABLE 3

Summary of Pharmacologic Studies

Report # Descriptor	Clinical Investigator (Country) Publications	Completion Status (start date)	Study Design ¹	Number Patients (N-P)	Age Range (Mean)	Drug(s) Administered	Dose(s) (Route)	Duration ²	Full Report Location
100493 Coagulation fibrinolysis	Jehan-Voguo (France)	Complete (Jun. 82)	O, R CO, P	6 6:0	24-28 (24.8)	enoxaparin placebo	90 mg (s.c.)	50	31/223
100540 Coagulation fibrinolysis and platelet aggregation	Vinazer (Austria) Mazzeccato (1986) 16:106	Complete (Jan. 83)	O, CO CM	10 10:0	NA ³ (23.4)	enoxaparin heparin	90, 60, 90 mg (s.c.) 60 mg (s.c.)	50 50	31/339
100484 Fibrinolysis	Saiton, Lavy (France)	Complete (Jun. 83)	O, R CO, P	6 3:3	23-28 (26.7)	enoxaparin enoxaparin placebo	40 mg (s.c.) 2 mg/kg (s.c.)	50 50	31/349
100482 Lipolysis	Etienne Pieron (France) Dr. J. Ellis Pharmaci. (1983) 16:712	Complete (Feb. 82)	O	6 7:1 4 4:0	21-42 (28.9) 20-29 (23.0)	Phase I enoxaparin Phase II enoxaparin	60 mg (i.v. & s.c.) 60 mg (i.v.)	50	31/363

¹ O = open; R = randomized; P = placebo; DB = double-blind; PL = parallel; CO = crossover; CM = comparative; SO = single dose.
² SO = single dose.
³ NA = not available

The PD parameters that were evaluated included coagulation, fibrinolysis, platelet aggregation and lipolysis.

The effect of sc administration of 90 mg of enoxaparin on coagulation and fibrinolytic mechanisms in normal individuals were compare to placebo. Enoxaparin produced elevation of anti-Xa activity to 0.73 IU/ml with a maximal activity at 4.5 h after administration. Anti-Xa activity disappeared between 12 and 24 hours post-administration. The anti-IIa activity was lower, a maximal effect of 0.12 IU was achieved at 5 hours and returned to baseline at 12 hours. The mean maximal elevation of the APTT was 1.2 times baseline and returned to normal between 6 and 12 hours. The Thrombin Time (TT) increased to 1.5 times baseline. No changes in AT-III levels or fibrinolytic activity were detected. Comparison of the effect of equal amounts of heparin and enoxaparin in vitro showed that heparin had greater effect on TT, APTT and anti-IIa activity. The inhibition of factor Xa by heparin or enoxaparin were similar. A slightly stronger

inhibition of factor IXa, factor XII, and kallikrein were observed with enoxaparin. Fibrinolytic parameters were not changed by either heparin or enoxaparin.

In vivo studies were performed by administering single sc injections of enoxaparin (30, 60 and 90 mg) or heparin (60 mg=10,000 U). The TT was prolonged by heparin and by the highest dose of enoxaparin. Anti-IIa activity was more pronounced with heparin and it was observed only with the 90 mg dose of enoxaparin. The APTT was prolonged by the UH and by the 90 and 60 mg doses of enoxaparin. The APTT was prolonged by the heparin and by enoxaparin at the doses of 60 and 90 mg. Inhibition of factor Xa was similar at similar doses of heparin or enoxaparin, but it persisted longer with enoxaparin. Factor IXa inhibition also lasted longer with enoxaparin.

Heparin produced a slight decrease in platelet count and resulted in alteration of platelet aggregation with epinephrine and collagen, whereas enoxaparin did not alter the platelet count nor the platelet aggregability.

A single sc injection of 40 mg or of 2 mg/kg of enoxaparin had no effect on the fibrinolytic system.

Lipolytic activity was released by enoxaparin 5 minutes after iv injection and remained elevated for 5 to 15 minutes. The sc administration of enoxaparin produced less marked increase in lipolytic activity which occurred 15-30 minutes after dosing and returned to baseline between 8 and 12 hours later. The lipolytic activity released after administration of 60 mg of enoxaparin by iv or sc injection was characterized as being both lipoprotein lipase and hepatic lipase.

CONCLUSIONS

The results of the PK and PD studies showed that enoxaparin was characterized by:

1. Absolute bioavailability of almost 100% when administered subcutaneously;
2. strong anti-Xa activity and weaker anti-IIa activity than heparin resulting in anti-Xa/anti-IIa ratio of activity greater than 4, compared to that of heparin which is approximately 1;

3. dose proportionality relationship for a series of doses in the prophylactic as well as therapeutic range which enables the anti-Xa activity to be maintained for 12-24 hours following administration. These features are shared by heparin;
4. anti-Xa activity-based elimination half-life of 4 hours which is 3-4 times longer than that of heparin;
5. less active biotransformation (desulphatation and depolymerization) than heparin;
6. maintenance of anti-Xa activity over 12-24 hours;
7. minimal interaction with platelets;
8. pharmacokinetics in high risk subjects (elderly subjects and patients with renal failure) indicating no need for dose adjustment.

Contrary to the sponsor's conclusions that the kidneys play a minimal role in the excretion of enoxaparin and that the risk of accumulation of enoxaparin in patients with renal failure is minimal, a recent publication by Y. Cadroy et al in *Thrombosis Research* 63; 385-390, 1991 indicate that the elimination of enoxaparin in patients with renal failure is delayed independently of the degree of renal failure. The total clearance of enoxaparin was decreased two-fold and the apparent resorption and elimination half-lives of the drug were prolonged 1.7 times.

A total of 191 subjects received enoxaparin in the course of the Clinical Pharmacology studies. The drug was well tolerated and appeared safe. Aside from the pharmacological effect on the coagulation tests, reversible elevation of the transaminases represented the only laboratory abnormality attributable to the administration of the drug.

BACKGROUND AND RATIONALE FOR THE CLINICAL USE OF ENOXAPARIN:

Venous thromboembolism is a frequent complication in patients undergoing hip surgery, and particularly in patients undergoing elective hip replacement because of the direct trauma imposed on the femoral vein during the procedure. In the absence of prophylaxis or early diagnostic surveillance, the risk of DVT with hip replacement can be as high as 50 to 80%. The incidence

of proximal DVT is about 20% and that of pulmonary embolism (PE) is 5 to 10%. The frequency of fatal PE based on clinical diagnosis or post-mortem findings has been reported at 0.3% and 10% respectively.

Several regimens of prophylactic anticoagulation have been used in orthopedic surgery, including aspirin, dextran, warfarin and heparin. All, however, have shown limitations. Aspirin was found to reduce the incidence of DVT from 45% in the placebo control to 20% in the treated group, but this effect has been reported only in men. Dextran reduced the risk of DVT, but it can produce bleeding and fluid overload. Warfarin therapy started pre-operatively reduced the incidence of DVT to about 25-30%, however, the risk of severe bleeding complications has limited its use. When started after surgery warfarin may effectively reduce the occurrence of DVT with less bleeding complications. Although adequate dosing of sc heparin has been shown to effectively reduce the risks of thromboembolic complications, its use has not become firmly established because adjusted dosing may be needed and because of the concerns for intra- or peri-operative hemorrhagic complications.

Depolymerization of heparin yields various fractions of reduced molecular weight. Compared to the parent molecule, these low molecular heparins, such as enoxaparin, exhibit a higher anti-Xa/anti-IIa activity ratio, produce less inhibition of platelet function, have higher bioavailability and longer duration of effect. The dissociation between the anti-Xa and the anti-IIa activities has suggested that these low molecular weight compounds may have greater anti-thrombotic than anti-coagulant effect and that their administration for the prophylaxis and treatment of thromboembolic disorders may carry less risk of bleeding complications.

Animal experiments have indeed demonstrated that LMWHs retain the antithrombotic activity of the parent compound with lower anticoagulant activity. The complete bioavailability of LMWHs and the elimination half-life of their anti-Xa activity in excess of 4 hours indicated that these compounds may be suitable for prophylaxis of DVT in high risk patients when administered once or twice daily subcutaneously.

Enoxaparin is approved in Europe for: 1) prophylaxis of venous thromboembolism in high risk orthopedic surgery and in moderate risk general surgery patients, and 2) for the prevention of thrombus formation in extracorporeal circulation.

Three European clinical trials were conducted to demonstrate the effectiveness of presurgical administration of enoxaparin in the prevention of DVT in orthopedic surgery.

The first trial evaluated different doses of enoxaparin and showed that the dose of 40 mg QD sc was both effective and well tolerated when compared to 60 mg QD sc, 30 mg q12h sc and 20 mg q12h sc.

The second trial demonstrated that both regimens of 40 mg QD sc or 20 mg q12h enoxaparin sc were effective in preventing post-operative DVT.

The third trial showed that enoxaparin at the dose of 40 mg QD sc was more effective than UH at the dose of 5000 U q8h in reducing the incidence of DVT in high risk patients.

Four controlled clinical trials have been conducted in North-America to demonstrate the effectiveness and safety of enoxaparin in the prevention of DVT in orthopedic surgery, namely elective total hip replacement. The dosage and schedule of administration used in the North-American clinical trials were based on the results of the preclinical and pharmacological studies, on the prior experience from the European clinical trials, and on current clinical practice of orthopedic surgery in North-America. A regimen with fixed dose of 30 mg enoxaparin sc twice daily starting 12 to 24 hours after surgery was selected for the North-American clinical trials for the following reasons: 1). North-American orthopedic practice favors postoperative initiation of antithrombotic prophylaxis in order to reduce the risk of perioperative bleeding; 2). as the preoperative dose of enoxaparin was omitted, the twice daily administration of enoxaparin was selected in place of the 40 mg qd used in Europe in the attempt to reduce the thromboembolic risks from early, intra-operative thrombus formation; 3). the administration of fixed dose of enoxaparin would not require laboratory monitoring of anticoagulation or dose adjustments.

CLINICAL STUDIES

Four controlled clinical studies have been submitted under this NDA to document the safety and effectiveness of enoxaparin in the prevention of deep vein thrombosis (DVT) in patients undergoing elective hip replacement surgery.

The four studies are listed in the following table 1.1 reproduced from the NDA:vol 77, p.10.

TABLE 1.1

OVERVIEW OF STUDIES IN THE PREVENTION OF DEEP VEIN THROMBOSIS IN HIP REPLACEMENT SURGERY

Protocol Number	Study Design	Location	Length of Treatment Start	Duration	Treatment Group	Dose mg/units	Regimen
ENO 664	Placebo Controlled Double Blind	Canada	Within 12-24 hr Post-surgery	Up to 14 Days Post-surgery	Placebo Control Enoxaparin	30 mg	q12h q12h
PK 523	Controlled Double Blind	Canada	Within 12-24 hr Post-surgery	Up to 14 Days Post-surgery	Calcium Heparin Control Enoxaparin	7500 IU 30 mg	q12h q12h
PK 526	Dose Ranging Double Blind	United States	Within 2 Days Post-surgery	Up to 7 Days Post-surgery	Enoxaparin Enoxaparin Enoxaparin	10 mg 40 mg 30 mg	QD QD q12h
PK 525	Controlled Open Label	United States	Within 2 Days Post-surgery	Up to 7 Days Post-surgery	Sodium Heparin Control Enoxaparin Enoxaparin	5000 U 40 mg 30 mg	q8h QD q12h

STUDY NUMBER: ENO 884

STUDY TITLE: Evaluation of enoxaparin efficacy and safety for the prevention of deep vein thrombosis in patients undergoing elective total hip replacement.

NDA Volumes: 32; 33; 2,15

<u>Investigators:</u>	<u>Study Center</u>	<u>Patients enrolled</u>
Jack Hirsh, M.D.	Hamilton Gen.Hos. Hamilton	42
A.G. Turpie, M.D.	Hamilton, Ontario,	
M. Levine, M.D.	Henderson Gen. Hospital	33
C.J. Carter, M.D.	Hamilton, Ontario	
R.M. Jay, M.D.	St. Joseph's Hospital	25
P.J.Powers, M.D.	Hamilton, Ontario	

STUDY OBJECTIVE; The objective of the study was to compare the safety and efficacy of enoxaparin, administered at the dose of 30 mg q12h sc postoperatively for up to 14 days, to similarly administered placebo, for the prophylaxis of postoperative DVT in patients undergoing elective total hip replacement (THR).

STUDY DESIGN; The study was randomized, double-blind, parallel-group, placebo-controlled, multicenter study to assess the safety and efficacy of enoxaparin in the prevention of DVT in patients undergoing elective hip replacement.

The study endpoint was represented by the development of DVT (efficacy failure). Surveillance for DVT (efficacy assessment) was performed initially by ¹²⁵I-fibrinogen scans and Impending Plethysmography (IPG). If either of these tests was abnormal, definitive diagnosis of DVT was made by contrast venography. However, the incidence of DVT in the first 24 patients enrolled in the study was unexpectedly low due to the limited sensitivity of the non-invasive diagnostic methods employed initially. Thereafter, the protocol was changed to include mandatory bilateral venogram for the assessment of efficacy.

Safety was evaluated daily throughout the duration of the study. The results of the venograms and the bleeding episodes reported during the trial were interpreted by an independent committee blinded to treatment allocation.

STUDY POPULATION; Male and female patients, aged 40 or older, who were scheduled for elective hip replacement and had signed informed consent were eligible for the study.

Exclusion criteria were: child-bearing potential, pregnancy and lactation, previous hip replacement, history of bleeding disorder, allergy to iodine or contrast dye, treatment with aspirin during the hospitalization, history of disease or treatment that would interfere with the kinetics of enoxaparin, participation in a study of other experimental drugs within 4 weeks.

No concomitant medications were allowed other than those necessary for the patient's welfare. The use of aspirin and other medications the week prior to the study were recorded. All concomitant medications used during the study were recorded in the case report form.

REASONS FOR DISCONTINUATION OF PATIENTS FROM THE STUDY: Patients could be discontinued from the study for any of the following reasons:

- Lost to follow up.
- Treatment emergent symptom(s).
- Ineffectiveness.
- Improvement.
- Found not to meet inclusion criteria.
- Dosage/medication error or violation.
- Administrative.
- Intercurrent illness.

The reason for premature discontinuation from treatment was recorded by the investigator in the CRF and reviewed by the sponsor in order to identify the one event that directly resulted in early study termination or to reassign the cause of termination. For example, if a patient developed venogram proven DVT and had been terminated as "adverse reaction" by the investigator, the patient would be reassigned by the sponsor to "ineffectiveness".

If several possible reasons for early study termination existed for any patient, the sponsor would attempt to find the event which led most directly to study discontinuation.

DOSING SCHEDULE Patients were randomly assigned in a 1:1 ratio in blocks of 10 to receive either enoxaparin 30 mg q12h sc or placebo q12h sc. Both injections were 0.3 ml. The first dose was given at 8 am the day after surgery. If surgical hemostasis had not been achieved by then, the initiation of the treatment was postponed. Treatment with study medication was continued for 14 days or until the end of study.

EVALUATION AND SCHEDULING; The study procedures and the schedule are outlined in Table I reproduced from vol 33 of the NDA.

TABLE I
STUDY SCHEMATIC - OVERVIEW

Evaluation/Procedure	Prior to Surgery	Periodosing Interval														End of Study ⁷
		Calendar/Treatment Day ¹														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Informed Consent	X															
Complete Medical History	X															
Complete Physical Examination	X															
Laboratory Tests: Hematology and Coagulation, Serum Chemistry and Urinalysis	X															
Vital Signs	X															
Impedance Plethysmography (IPG)	X					X		X		X		X		X		X
¹²⁵ I-Fibrinogen Leg Scan	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lung Scan	X										X	X	X	X	X	X
Pulmonary Angiography ⁵											X	X	X	X	X	X
Anti-Factor Xa Activity ⁶		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bleeding Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hemoglobin, Hematocrit, RBC		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Tests (PT, APTT)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Experience Evaluation		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dosing											X	X	X	X	X	X
Bilateral venography ⁷											X	X	X	X	X	X
Concomitant Medications																X
Assessment of Operative Site																X

¹ Day 1 was the first post-operative day; the next calendar day was Day 2.
² Or at time of discontinuation of study medication.
³ ¹²⁵I-fibrinogen was injected immediately following surgery (study day 0); scans were performed daily post-operatively.
⁴ At entry and between days 10 and 14.
⁵ Selective pulmonary angiography performed to establish definitive diagnosis of pulmonary embolism, if necessary.
⁶ Plasma samples to be obtained 6 hours after first daily dose.
⁷ Mandatory venography was strictly enforced for the last 76 patients enrolled.

EFFICACY PROCEDURES; Because of the low incidence of DVT detected in the first 24 patients in whom surveillance of DVT had been carried out with ¹²⁵I-fibrinogen leg scanning and IPG, bilateral venograms were made mandatory in the rest of patients. The VG was obtained between day 10 and 14 of study or at the time of patient's discontinuation from the study. VGs were reviewed blindly by qualified physicians at the study site. The results were reported separately for each leg as "positive" "negative" or "inadequate". The location of the obstruction was noted in the positive VGs. A unilaterally obtained negative VG was classified as inadequate. Factors affecting the reading of the VG were recorded and their location was noted.

¹²⁵I-fibrinogen leg scans were performed at study entry and daily post-operatively. The scans were read blindly and were classified as "positive", "negative" or "inadequate". IPG was performed on day 5, 7, 9 11 and 13 post-operatively and were read blindly.

The protocol states that a lung scan would be performed at entry and between days 10 and 14 of study, and that a pulmonary angiogram would be obtained if the lung scan was positive. However, routine lung scans were not performed during the study.

Clinical signs and symptoms of DVT were reassessed in patients who developed pulmonary embolism (PE) or received contra-active concomitant medications (therapeutic anticoagulation) without having had VG, IPG or ¹²⁵I-fibrinogen scan performed.

SAFETY PROCEDURES;

Laboratory Tests: Laboratory tests performed during the study included Hematology (complete CBC with WBC differential counts and platelet count), Coagulation (PT, APTT, anti-Xa activity), Serum Chemistry (SMA 16) Urinalysis (including microscopic examination of sediment).

Bleeding Assessment: Bleeding was assessed for intensity (none, minor or major) and for relationship to study medication (none, remote, possible, probable or definite). Any action taken as result of bleeding was noted. The data were reviewed by a panel of physicians to identify overt and/or severe bleeding. Bleeding was classified as major (retroperitoneal, intracranial, prosthetic joint, overt and leading to transfusion of 2 or more units of blood or to drop in hemoglobin of 2 gm/dL or more) or minor (overt but not meeting above criteria). Time to onset of bleeding in relation to surgery was noted.

Vital signs recorded included blood pressure, pulse rate and respiratory rate.

ADVERSE EVENTS: Adverse events, either observed by the physician or reported by the patient, were recorded with date of onset, severity (mild, moderate or severe), action taken (change of dose, discontinuation of medication, contra-active treatments) and investigator's assessment of relationship to study regimen (definitely, probably, possibly, remotely related or unrelated)

PACKAGING, BLINDING AND LABELING PROCEDURES: Study medication was supplied in 1 ml ampuls containing 100 mg of enoxaparin. Placebo was supplied in identical 1 ml ampules containing saline solution. The volume of each dose was 0.3 ml.

Each patients was supplied with a box containing 30 ampules. Each box and each ampules were labeled with the number according to the randomization code. Individual sealed envelopes were provided for every patient to allow unblinding if necessary. All data regarding the administration of the medication were recorded in the CRF.

The lot numbers of enoxaparin used for this study were recorded.

STATISTICAL SAMPLE SIZE AND HOW IT WAS DETERMINED: Assuming a rate of thrombosis of 15% and 50% for the enoxaparin and placebo groups respectively, and using a significance level of 0.05, a sample size of 100 evaluable patients (50 in each group) was calculated to provide a power of more than 95%.

EFFICACY EVALUATION;

Definition of efficacy outcome: Efficacy was assessed by the incidence rate of DVT. The diagnosis of DVT by venogram had absolute priority. A positive VG was defined by a positive finding in either the operative or non-operative limb or both limbs. A negative VG was defined as a negative bilateral VG. An inadequate VG was one in which the diagnosis of DVT could not be made nor excluded. A unilateral negative VG was classified as inadequate.

Diagnosis of DVT by either a positive ¹²⁵I-fibrinogen scan or IPG had second priority. Clinical evidence of DVT was defined as either a positive result of fibrinogen scan or IPG or other clinical evidence such as PE or administration of anticoagulant therapy for DVT.

All treated patients who had received any study medication and had had at least one clinical evaluation were classified into one of the following outcome groups:

Group	Venography	-----Clinical Evidence of DVT-----	
		¹²⁵ I-Fibrinogen or IPG	Other Clinical Evidence of DVT
1	+	All	All
2	-	All	All
3	IN/ND	+	All
4	IN/ND	-, IN/ND	+
5	IN/ND	-, IN/ND	Not +

IN/ND indicate that the VG was inadequate or not done
All indicate all situations: +, -, IN/ND.

- Group 1 included patients with positive VG (unilateral or bilateral), regardless of the results of the other evaluations.
- Group 2 included patients with negative bilateral VG, regardless of the results of the other evaluations.

- Groups 3 and 4 included patients in whom VG was not done or it was inadequate and who had the diagnosis of DVT was made by noninvasive tests or other clinical evidence.
- Group 5 included patients in whom VG was inadequate or not done, noninvasive vascular tests were negative, inadequate or not done and in whom there was no clinical evidence of DVT.

STUDY POPULATION

The study population included in the efficacy analysis was represented by:

1. all randomized patients: this included all randomized patients regardless of whether they had efficacy data.
2. all treated patients with efficacy data; this included all treated patients with at least one post-treatment efficacy evaluation.
3. evaluable patients: this included the patients from the second group for whom none of the following occurred during the study:
 - enrollment prior to enforcement of mandatory VG.
 - administration of disallowed concomitant therapy.
 - insufficient therapy, i.e., less than 3 day treatment
 - no definitive VG results obtained.
4. unevaluable patients: this include all patients in each treatment group who were the complement of evaluable patients with respect to the all treated population. In this study all randomized patients were treated, therefore, there were no unevaluable patients.

EFFICACY ANALYSES

INTENT-TO-TREAT ANALYSES: ALL TREATED PATIENTS WITH EFFICACY DATA:

For this patient population, the efficacy endpoint, i.e., the incidence of treatment failure was defined as:

Groups 1, 3, 4 (positive)
Groups 1, 3, 4, (positive) + Groups 2, 5 (negative)

Within this patient population, the incidence of DVT was also summarized within the subsets of type of surgery (primary hip replacement or revision), use of surgical cement, use of graduate compression stockings (GCS), gender, age, and race.

ALL RANDOMIZED PATIENTS

In this study all randomized patients were treated and were included in the all treated patient population.

EVALUABLE PATIENTS EFFICACY DATA:

All evaluable patients had definitive VG, therefore, the efficacy endpoint (treatment failure) was defined as:

Group 1 (positive)
Group 1 (positive) + Group 2 (negative)

Group 3 (noninvasive vascular test evidence of DVT) and group 4 (clinical evidence of DVT) were not considered in the evaluation of efficacy for the evaluable patients.

Within the evaluable patient population, the incidence of DVT was also summarized for the subsets of type of surgery, type of anesthesia, use of surgical cement, use of GCS, gender, age, and race.

SAFETY EVALUATION;

PATIENT POPULATION: All patients who received at least one dose of study medication were included in the safety evaluation.

SAFETY ANALYSES; The primary safety endpoints determined for each of the treatment groups were:

- Incidence of death, premature discontinuation from treatment, adverse events (according to severity and relationship to study medication)
- Incidence of patients with major or minor bleeding episodes and day of onset of major bleeding episodes
- The mean number of total units of blood transfused on study (aside from operative and recovery room units), and the incidence of 0, 1-2, and more than 2 units of blood transfused on study.

-The incidence of abnormal values of clinical concern for selected laboratory tests from day 1 through the end of the study, including:

Platelets: Thrombocytopenia-

mild: equal or greater than $1 \times 10^5/\text{mm}^3$ and less than the investigator's lower limit of normal

moderate: equal or greater than $10^4/\text{mm}^3$ and lower than $1 \times 10^5/\text{mm}^3$

severe: lower than $10^4/\text{mm}^3$

Platelets: Thrombocytosis-

mild: greater than the investigator's upper limit of normal and lower than $6 \times 10^5/\text{mm}^3$

moderate: higher than $6 \times 10^5/\text{mm}^3$ and lower than $1 \times 10^6/\text{mm}^3$

severe: higher than $1 \times 10^6/\text{mm}^3$

Hemoglobin: Values lower than 8 gm/dL or a decrease equal or greater than 2 gm/dL from baseline.

SGOT and SGPT: 3- to 6-fold increase and more than 6-fold higher than the investigator's upper limit of normal.

Total Bilirubin: Values greater than 2 mg/dL.

Alkaline Phosphatase: Any value greater than 2-fold higher than the investigator's upper limits of normal.

Creatinine: Any value greater than 2 mg/dL.

BUN: Any value greater than 30 mg/dL.

-The mean changes from baseline for hematology laboratory tests at day 4, 7 and at the end of study and follow-up and end of study and follow-up for serum chemistry tests. The post-surgical, pre-treatment value was the baseline for CBC and coagulation tests. The baseline for all the other values was the pre-surgical values.

-Shifts in the percentage of patients with hematology and chemistry laboratory values outside the normal range at the end of the study relative to baseline.

- The mean change from pre-surgery baseline for systolic and diastolic blood pressure, pulse rate, and temperature at day 4, 7 and at end of study.

PHARMACOKINETIC ANALYSES

Fibrinopeptide A, Anti-Xa and Anti-IIa Activities

The assay of FPA was found to be unreliable, therefore no analysis of the data was performed. Plasma levels of anti-Xa and anti-IIa activity were obtained at selected centers.

STATISTICAL ANALYSIS

Demographic and Baseline Characteristics

The two treatment groups were compared at baseline for categorical variables (sex) and other demographic variables (age, weight, BP, medical and surgical histories, transfusions) using descriptive statistics. Each variable was summarized for all treated and all evaluable patients. As all randomized patients were treated, the treated and the randomized groups are the same.

Efficacy Analyses

The endpoint was represented by development of DVT (treatment failure).

The incidence of DVT was analyzed for both all treated patients with efficacy data and for the evaluable patients. Justification for pooling across centers was investigated using a two-way logistic regression model. The results were also summarized by center to provide a qualitative assessment of the presence of interactions.

A two-way logistic regression model was used to compare the treatment groups. The treatment comparison between the two treatment groups was based on a 5% significance level. All tests were two-sided. An approximate 95% confidence interval for the odds ratio of treatment failure in placebo versus enoxaparin was computed. The odds of a treatment failure are defined as estimated incidence rate of treatment failure/estimated incidence rate of treatment success. The incidence rate of treatment failure by treatment group was summarized in patients subpopulations by sex and age.

ADVERSE EVENTS

The COSTART dictionary was used to classify the adverse events. Events for a particular COSTART occurring more than once were counted only once. Repeated reporting of the same adverse event in a patient was reported only as the most severe. Each type of event occurring within a body system was counted.

Adverse events incidence rates (all events excluding those unrelated to study medication) were summarized by treatment group. The adverse events were summarized for each body system and overall. Overall indices reflected the number of patients reporting any adverse event.

Fisher's exact test was performed for the statistical comparison of the enoxaparin and the placebo groups for total adverse events in each body system, for each event with an incidence of 5% or higher, for all adverse reactions, and for each event with an incidence of 5% or higher for all adverse events excluding those unrelated to study medication. These analyses were requested by the Agency at a pre-NDA meeting in March 1991.

Bleeding Assessment

The overall incidence of major bleeding, minor bleeding, absence of bleeding and the percentage of patients who experienced any major or minor bleeding during the study period was determined for each treatment group. A two-way logistic regression model with factors for treatment group and center was used.

Laboratory Data

Mean changes from baseline were determined on Day 14 or at the end of the study for all laboratory parameters, except CBC and coagulation which were measured daily and whose changes were assessed daily and at the end of study. The mean changes from pooled parameters across investigators were summarized for the two treatment groups using descriptive statistics. No formal statistical analyses were performed for these laboratory data. Fisher's exact test was performed for the statistical comparison between the two groups of the selected laboratory values of clinical concern. Shift tables were generated that summarize the distribution (below, within, above normal or unknown categories) of baseline and end of study hematology and chemistry values. Statistical analysis of the daily determinations of anti-Xa activity was not available at the time of the NDA submission. If more than one laboratory or vital sign determination was available for a parameter, the first evaluation was used for analysis.

Vital Signs

The mean changes from baseline for systolic and diastolic pressure were summarized for the two treatment groups. No formal statistical test of hypothesis was performed.

DATA QUALITY CONTROL

The study was performed in Canada and the original database was created in Canada. The sponsor prepared the NDA report from the database recreated from the CRFs.

The Central Adjudicating Committees for Venography and Bleeding reviewed the major endpoint of the trial. The entire database was verified against the results of the Committees' adjudication. Supportive analyses contained in this report were prepared by the sponsor in US and verified against CRFs and source documentation in 10% of cases.

RESULTS

One hundred patients were randomized for the study and all were treated: 50 patients received enoxaparin 30 mg q12h and 50 patients received placebo q12h. A total of 48% of all patients (50% of enoxaparin and 46% of placebo) completed the study. Fifty-two percent (52%) of patients (50% of the enoxaparin and 54% of the placebo patients) were prematurely discontinued. Fifty-eight percent (58%) of patients (54% of the enoxaparin and 62% of the placebo patients) had definitive VG results, met all other evaluability criteria and constituted the evaluable patient population.

All 100 randomized patients received at least one dose of study medication and were included in the safety evaluation.

The patients disposition and availability are summarized in the following table:

<u>Patients</u> <u>Disposition</u>	<u>Treatment Group</u>		
	<u>Enoxaparin</u>	<u>Placebo</u>	<u>Overall</u>
	n (%)	n (%)	n (%)
Patients Randomized	50	50	100
Patients Treated	50 (100%)	50 (100%)	100 (100%)
Completed	25 (50%)	23 (46%)	48 (48%)
Discontinued	25 (50%)	27 (54%)	52 (52%)
Patients Evaluated for Efficacy:			
All treated Patients	50 (100%)	50 (100%)	100 (100%)
Evaluable Patients	27 (54%)	31 (62%)	58 (58%)

PATIENT DISCONTINUATION

Fifty-two treated patients were prematurely discontinued from the study: 25 in the enoxaparin and 27 in the placebo group. The primary reason for discontinuation was improvement for the enoxaparin group and failure for the placebo group. A summary of the discontinued patients is shown in the following table:

<u>Reason for Withdrawal</u>	<u>Treatment Group</u>		
	<u>Enoxaparin</u> n (%)	<u>Placebo</u> n (%)	<u>Overall</u> n (%)
Patients Randomized	50	50	100
Patients Treated	50 (100%)	50 (100%)	100 (100%)
Patients Discontinued	25 (50%)	27 (54%)	52 (52%)
Failure of Treatment	3 (6%)	16 (32%)	19 (19%)
Improvement	12 (24%)	4 (8%)	16 (16%)
Adverse Events	2 (4%)	4 (8%)	6 (6%)
Lost to Follow-up	3 (6%)	1 (2%)	4 (4%)
Intercurrent Illness	3 (6%)	0	3 (3%)
Treatment Error	0	1 (2%)	2 (1%)
Other	2 (4%)	1 (2%)	3 (3%)

PATIENT EVALUABILITY

Fifty-eight of the 100 patients were fully evaluable (completed venography), including 27 or 54% of the enoxaparin group and 31 or 62% of the placebo group. The most common reason for exclusion from evaluability was enrollment prior to mandatory venography (VG). This affected 24 of the 100 treated patients equally distributed between the two treatment groups. The data on patient evaluability and reason for exclusion are summarized in the following table:

<u>Patients</u>	<u>Treatment Group</u>		
	<u>Enoxaparin</u> n (%)	<u>Placebo</u> n (%)	<u>Overall</u> n (%)
Patients Randomized	50	50	100
Patients Treated	50 (100%)	50 (100%)	100 (100%)
Patients Evaluable	27 (54%)	31 (62%)	58 (58%)
Patients not Evaluable	23 (46%)	19 (38%)	42 (42%)
Prior to mandatory VG	13 (26%)	11 (22%)	24 (24%)
Mandatory VG not done	5 (10%)	6 (12%)	11 (11%)
VG not interpretable	1 (2%)	0 (0%)	1 (1%)
Unallowed Medications	4 (8%)	2 (4%)	6 (6%)

STUDY COMPLETION AND EVALUABILITY

The distribution of the patients between those who completed the study and those who were discontinued is shown in the following table:

<u>Patients</u>	<u>Treatment Group</u>		
	<u>Enoxaparin</u>	<u>Placebo</u>	<u>Overall</u>
	n (%)	n (%)	n (%)
Patients Randomized	50	50	100
Patients Completed	25 (100%)	23 (100%)	48 (100%)
Completed Evaluable	16 (64%)	23 (46%)	48 (48%)
Completed not Evaluable	9 (36%)	13 (57%)	22 (46%)
Discontinued Patients	25 (50%)	27 (54%)	52 (52%)
Discontinued Evaluable	11 (44%)	21 (78%)	32 (62%)
Discontinued Unevaluable	14 (56%)	6 (22%)	20 (38%)

DEMOGRAPHICS

The demographic data of the evaluable patients and of the unevaluable patients were similar to those of the all treated patients and were similar in the two treatment groups.

The demographic information of all the treated patients are shown in table 3.1 from volume 33, page 34 of the NDA.

CONCOMITANT MEDICATIONS

All 100 treated patients reported the use of concomitant medications. Opiate and opioids were used in 98% of patients. Other diagnostic agents, other analgesics and antibiotics (cephalosporins) were used in more than 90% of patients. Other medications included tranquilizers and anti-histaminics. The use of concomitant drugs was equally distributed between the two treatment groups with the exception of anti-histaminics which were more frequent in the placebo group.

Twenty of the patients prematurely discontinued from the study because of failure were treated with other antithrombotic drugs such as heparin or warfarin.

CONCURRENT ILLNESSES AND MEDICAL HISTORY

All 100 treated patients had other presenting condition or disease. The most frequent were diseases of the musculoskeletal system and connective tissue, diseases of the circulatory system,

endocrine, nutritional, metabolic, immune systems and neoplasms. The incidence of the conditions was similar in the two treatment groups. There was no increased incidence of DVT predisposing conditions in any group.

Table 3.1
Demographic Information (All Treated Patients)
(Appendix B.3.2)

<u>Characteristic</u>	<u>Treatment Group</u>		<u>Overall</u>
	<u>Enoxaparin</u>	<u>Placebo</u>	
	<u>n (%)</u>	<u>n (%)</u>	<u>n (%)</u>
All Treated Patients	50 (100%)	50 (100%)	100 (100%)
Sex:			
Male	26 (52%)	19 (38%)	45 (45%)
Female	24 (48%)	31 (62%)	55 (55%)
Age (yrs):			
N	50	50	100
Mean years	66.8	67.4	67.1
STD	9.6	8.9	9.2
Range	41-84	44-82	41-84
Weight (kg):			
N	50	50	100
Mean	73.8	72.4	73.1
STD	12.4	13.9	13.1
Range	40-100	46-102	40-102
Height (cm):			
N	50	50	100
Mean	167.3	166.7	167.0
STD	10.8	10.8	10.7
Range	140-191	140-185	140-191

MEDICAL AND SURGICAL HISTORY

The overall incidence of positive medical/surgical history was 100%. Diseases of the musculoskeletal system were the cause of surgery in 97% of patients. There was no difference between the treatment groups or among evaluable patients.

PRIMARY DIAGNOSIS AND SURGERY DATA

Osteoarthritis was the primary diagnosis in 83% of patients and its incidence was similar in all groups.

Eighty-eight percent (88%) of patients received blood during surgery. The mean number of units given during surgery or in the recovery room was 2.9 units.

There were no differences between the all treated and the evaluable patients populations, between the evaluable and unevaluable patient population, or between treatment groups for evaluable and unevaluable patients regarding primary diagnosis, surgery, and transfusion data.

The primary diagnoses, surgery data, and transfusion data are summarized in table 6.1.

EFFICACY RESULTS

CLINICAL OVERVIEW OF EFFICACY RESULTS: There was a statistically significant difference in rate of DVT in the enoxaparin treated patients compared to the placebo group in both the all treated population and evaluable patients population. In the all treated population, the incidence of DVT was 10% in the enoxaparin group and 46% in the placebo group. The incidence of proximal DVT was 2% in the enoxaparin group compared to 22% in the placebo group. Similar results were seen in the evaluable patient population. Two patients experienced pulmonary embolization, one in the placebo and one in the enoxaparin group. The placebo patient had study treatment discontinued and was removed from the study on post-operative day 4 for "adverse events". The patient developed DVT and PE on post-operative day 13. Venography and angiogram not done, ventilation/perfusion lung scan was positive. The enoxaparin patient was discontinued from the study of post-operative day 10 due to discharge from the hospital after venography which was negative. On post-operative day 15, bilateral PE were diagnosed by lung scan.

Table 6.1
Summary of Primary Diagnosis and Transfusion Data
(All Treated Patients)
(Appendix B.6.2)

<u>Diagnosis and Transfusion Data</u>	<u>Treatment Group</u>		<u>Overall</u>	
	<u>Enoxaparin</u> n (%)	<u>Placebo</u> n (%)	<u>n</u>	<u>(%)</u>
All Treated Patients	50	50	100	
Primary Diagnosis:				
Osteoarthritis	41 (82%)	42 (84%)	83	(83%)
Rheumatoid Arthritis	7 (14%)	2 (4%)	9	(9%)
Arthritis	1 (2%)	3 (6%)	4	(4%)
Avascular Necrosis	1 (2%)	2 (4%)	3	(3%)
Bone Metastases	0	1 (2%)	1	(1%)
Duration of Surgery:				
N	50 (100%)	50 (100%)	100	(100%)
Mean (minutes)	129.8	123.6	126.7	
STD	26.7	23.9	25.4	
Range	80-220	70-180	70-220	
Total Units of All Blood Transfused at Surgery ^a				
Patients Transfused	45 (90%)	43 (86%)	88	(88%)
Mean	3.1	2.8	2.9	
STD	1.8	1.4	1.6	
Range	1-8	1-9	1-9	
Blood Loss > 1 Liter				
Number of Patients	36 (72%)	28 (56%)	64	(64%)

^a Blood transfused in operating and recovery rooms only.

CROSS TABULATION OF DVT FINDINGS BETWEEN CONTRAST MEDIA
VENOGRAPHY AND OTHER VASCULAR EXAMINATION METHODS

The DVT findings determined by the other two methods of vascular assessment used in the study: the ¹²⁵I-fibrinogen scan performed

daily and the IPG performed on days 5, 7, 9, 11 and 13, were independently compared to those found by VG in the same patients. The results of cross tabulation of the ¹²⁵I-Fibrinogen scan findings versus the venography findings are shown in table 7.1. The results of cross tabulation of negative fibrinogen scan with positive VG differed between treatment groups. In the enoxaparin group, 13% of the patients with negative fibrinogen scan had positive VG. In the placebo group, 20% of patients with negative fibrinogen scan had positive VG, but 95% of patients with positive fibrinogen scan had positive VG findings.

The results of cross tabulation of the IPG scans with the venography findings are shown in table 7.2:

Table 7.2
Cross Tabulation of Impedance Plethysmography Findings with Corresponding Venography Findings
(Appendix B.7.1)

<u>IPG Findings</u>		<u>Corresponding Venography Findings</u>			<u>Findings In Agreement</u>	
<u>Finding</u>	<u>n</u>	<u>Finding</u>	<u>n</u>	<u>(%)^a</u>	<u>Finding</u>	<u>n</u>
Negative	52	Negative	35	(67%)	Negative	35
		Positive	17	(33%)		
Positive	4	Negative	2	(50%)	Positive	2
		Positive	2	(50%)		
Total	56	56				37
Overall Agreement						(66%)

^a Percent of patients with impedance plethysmography findings.

The results of cross tabulation of negative IPG findings with positive VG findings differed between the treatment groups. Fourteen percent (14%) of the enoxaparin patients with negative

IPG had positive VG and 0% who had positive IPG had positive VG. In the placebo group, 57% who had negative IPG had positive VG and 67% who had positive IPG had positive VG.

DVT FINDINGS

Treatment outcome was assessed by DVT findings from VG in 67% of all patients (67/100) and by other vascular or clinical assessment in 33% (33/100) of patients. No differences among the treatment groups were observed for the distribution of all patients with or without VG findings.

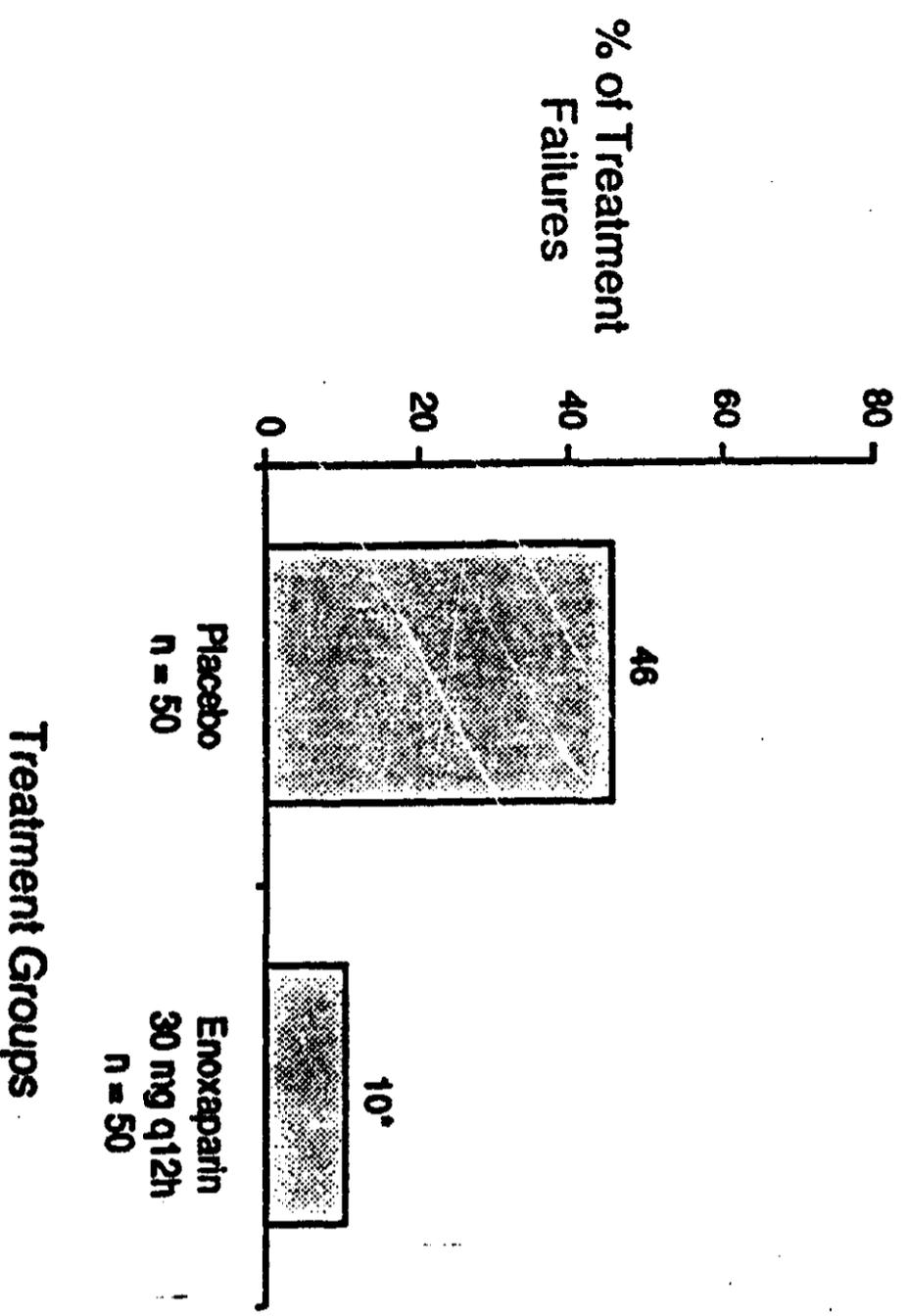
ANALYSIS OF INCIDENCE OF DVT

ALL RANDOMIZED PATIENTS EFFICACY ANALYSIS: All randomized patients were treated, therefore this group is analyzed in the all treated group.

ALL TREATED PATIENTS EFFICACY ANALYSIS: When all patients with positive vascular data or clinical evidence of DVT (groups 3 and 4) were combined with the patients with positive venogram (groups 1), 28 patients had evidence of DVT following surgery (table 8.1). The incidence of DVT was 10% in the enoxaparin group (5/50) and 46% in the placebo group (23/50). The difference was statistically significant ($p=0.0002$). The odds ratio was 8.34 with a 95% CI that supported the difference (fig. 1A and 1B). The incidence of proximal DVT was 2% in the enoxaparin group (1/50), and 22% in the placebo group (11/50).

The results in the all treated patient population are summarized in table 8.1 and 8.2.

Figure 1A
Statistical Result of DVT Findings by Treatment Group
Percent of Treatment Failures
All Treated Patients
ENO884



* Statistically significantly favored over the placebo group at the 5% level

Figure 1B
Statistical Result of DVT Findings by Treatment Group
Confidence Intervals for Odds Ratio of Treatment Failures
All Treated Patients
ENO884

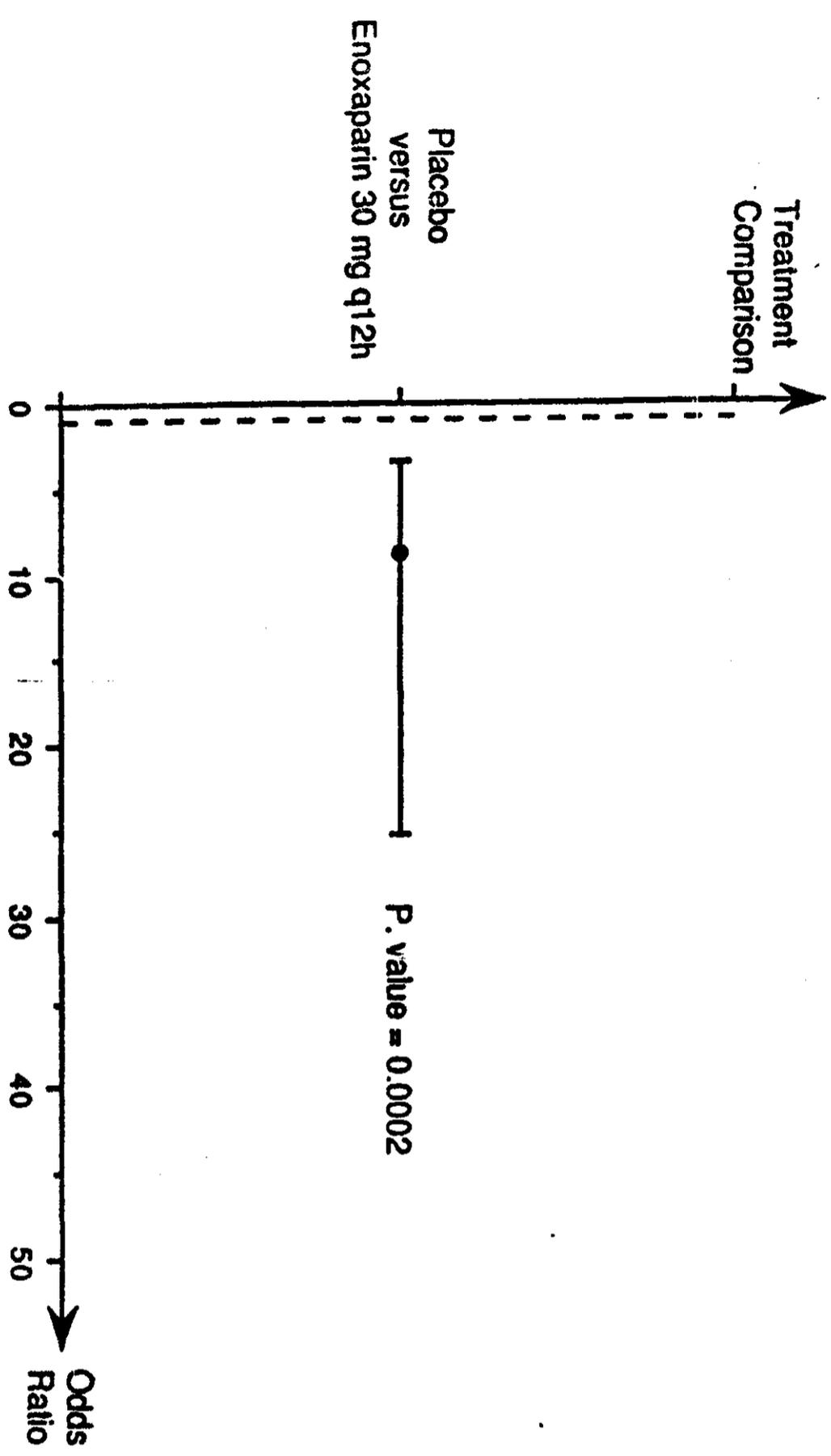


Table 8.1
Summary of the Distribution of DVT Findings
by Treatment Group for All Treated Patients
(Appendix B.8.1)

Venography	Treatment Group		Overall n (%)
	Enoxaparin n (%)	Placebo n (%)	
All Treated Patients	50	50	100
Treatment Outcome Groups:			
Patients with Definitive Venography Results:	33 (66%)	34 (68%)	67 (67%)
(1) Positive	5	21	26
(2) Negative	28	13	41
Patients without Definitive Venography Results:	17 (34%)	16 (32%)	33 (33%)
Clinical Evidence of DVT:			
(3) Positive; Other Vascular Methods	0	1	1
(4) Other Positive Clinical Data	0	1	1
(5) No Positive Clinical Evidence	17	14	31

* Patient 303 discharged with negative findings; returned on day 27 with clinical signs of DVT.

Table 8.2
Summary of Statistical Results of DVT Findings
By Treatment Group for All Treated Patients
(Appendix B.9.1)

Patients Treated	Treatment Group		Overall n (%)
	Enoxaparin n (%)	Placebo n (%)	
All Treated Patients	50 (100%)	50 (100%)	100 (100%)
Treatment Failures	5 (10%)	23 (46%)	28 (28%)
Proximal DVT	1 (2%)	11 (22%)	12 (12%)
Distal DVT	4 (8%)	10 (20%)	14 (14%)
Other Vascular Methods	0	2 (4%)	2 (2%)

Between-Group Comparison of Treatment Failures

Treatment Comparison	Odds Ratio ^a	p-value	95% Confidence Interval for Odds Ratio
Placebo: 30 mg q12h	0.34	0.0002*	(2.72, 25.56)

^a Estimated from a logistic regression model with treatment and center effects.

* Statistically significant at the 5% level.

EVALUABLE PATIENTS EFFICACY ANALYSIS: Twenty-three (23) of the 58 evaluable patients (40%) had VG confirmed DVT. The incidence of DVT was 15% (4/27 patients) in the enoxaparin group, and 61% (19/31) in the placebo group. The difference was statistically significant (p= 0009).

The incidence of proximal DVT was 4% (1/27) in the enoxaparin group, and 29% (9/31) in the placebo group.

One of the distal DVTs in the enoxaparin group was reclassified as proximal DVT by the sponsor on subsequent analysis. One distal DVT in a placebo patient was reclassified by the sponsor as both proximal and distal DVT.

The results in the evaluable patient population are shown in the following table:

<u>Patients</u>	<u>Treatment Group</u>		
	<u>Enoxaparin</u>	<u>Placebo</u>	<u>Overall</u>
	n (%)	n (%)	n (%)
Patients Evaluable	27 (100%)	31 (100%)	58 (100%)
Treatment Failures	4 (15%)	19 (61%)	23 (40%)
Proximal DVT	1 (4%)	9 (29%)	10 (17%)
Distal DVT	3 (11%)	10 (32%)	13 (17%)

Between-groups comparison of treatment failures

<u>Treatment Comparison</u>	<u>Odds Ratio</u>	<u>p-value</u>	<u>95% CI for Odds Ratio</u>
Placebo/ Enoxaparin	10.18	0.0009	(2.57-40.25)

The odds ratio was estimated from a logistic regression model with treatment and center effects.

SUBSET EFFICACY ANALYSIS FOR ALL TREATED PATIENTS AND FOR EVALUABLE PATIENTS: DEMOGRAPHIC SUBSETS: The distribution of treatment failure in the all treated patients and evaluable patients groups was similar among males (29%) and females, and among patients under and over 65 years of age. The results were also similar within treatment groups.

SAFETY RESULTS

CLINICAL OVERVIEW OF SAFETY RESULTS: Enoxaparin appeared to be well tolerated at the dose of 30 mg.q12h sc. The overall safety profile, including the incidence of severe bleeding, was similar to placebo.

The incidence of adverse reactions was 48% in the enoxaparin group and 58% in the placebo group. The incidence of discontinuation due to adverse events was not higher in the enoxaparin group compared to placebo. No differences in laboratory tests were noted between treatment groups except for the increase in SGPT in the enoxaparin group.

NUMBER OF PATIENTS EVALUATED AND DURATION OF EXPOSURE: All patients who received at least one dose of study medication were included in the safety assessment.

STUDY DRUG ADMINISTRATION: The mean duration of treatment for all patients was 11.2 days \pm 4.0 days (range 1-14 days) and it was similar for both treatment groups. The mean number of doses of study medications for all patients was 21.8 \pm 8.1 doses (range 1-28 doses).

PATIENTS WITH EPISODES OF BLEEDING DURING THE STUDY: Four episodes of bleeding, three major and one minor, were reported in the entire study population, resulting in an incidence of bleeding of 4% in both treatment groups. The incidence of major bleeding was 2% (1/50) in the enoxaparin group and 4% (2/50) in the placebo group. The bleeding episodes are summarized in table

<u>Patients</u>	<u>Treatment Group</u>		<u>Overall</u>
	<u>Enoxaparin</u>	<u>Placebo</u>	
	<u>n (%)</u>	<u>n (%)</u>	<u>n (%)</u>
All Treated Patients	50 (100%)	50 (100%)	100 (100%)
Major & Minor Bleeding	2 (4%)	2 (4%)	4 (4%)
Major Bleeding	1 (2%)	2 (4%)	3 (3%)
Minor Bleeding	1 (2%)	0	1 (1%)
No Bleeding	48 (95%)	48 (96%)	96 (96%)

Between-groups comparison of treatment failures

<u>Treatment Comparison</u>	<u>Odds Ratio</u>	<u>p-value</u>	<u>95% CI for Odds Ratio</u>
<u>Major or Minor Bleeding Episodes</u> Placebo/ Enoxaparin	1.01	0.9898	(0.14-7.51)
<u>Minor Bleeding Episodes:</u> Placebo/ Enoxaparin	2.01	0.5733	(0.18-23.01)

The odds ratio was estimated from a logistic regression model with treatment and center effects.

The single episode of major bleeding in the enoxaparin group occurred on day 2 and consisted of hematemesis.

The two episodes of major bleeding in the placebo group occurred on day 1 and were represented by wound bleeding and hematemesis.

POSTSURGICAL BLOOD TRANSFUSIONS: Fifty-two (52) of the 100 treated patients received at least one unit of blood. Twenty-eight percent (28%) of the patients received one or two units; 24% of the enoxaparin group (12/50) and 32% of the placebo group (16/50).

Twenty-four percent (24%) of the patients received more than two units of blood: the incidence was higher in the enoxaparin group, 14/50 or 28%, than in the placebo group, 10/50 or 20%.

The mean number of units of blood transfused post-surgery was 3.3 in the enoxaparin and 2.8 in the placebo groups.

The data on post-surgical transfusion requirement are summarized in the following table:

<u>Units Transfused</u>	<u>Treatment Group</u>		
	<u>Enoxaparin</u> n=50	<u>Placebo</u> n=50	<u>Overall</u> n=100
0 Units	24 (48%)	24 (48%)	48 (48%)
1-2 Units	12 (24%)	16 (32%)	28 (28%)
> 2 Units	14 (28%)	10 (20%)	24 (24%)
<u>Patients Transfused</u>			
N	26 (52%)	26 (52%)	52 (52%)
Mean (Units)	3.3	2.8	3.0
STD	2.3	1.5	2.0
Range	1-10	1-7	1-10

ADVERSE EVENTS: Adverse events included all untoward events observed by the investigator or reported by the patient throughout the study period. All adverse events were mapped to the COSTART dictionary.

ALL ADVERSE EVENTS: Overall, 76% of patients, equally distributed in the two treatment groups, reported at least one adverse event. Most of the adverse events reported by the patients were of mild or moderate severity. However, 13/50 patients (26%) in the enoxaparin group and 15/50 (30%) in the placebo group reported at least one event which was regarded by the investigator as severe in nature.

All adverse events by body system are summarized in table 12.1.

Table 12.1
Summary of Adverse Events by Body System, All Adverse Events
(Appendix B.13)

<u>Body System</u> Totals*	<u>-----All Adverse Events-----</u> <u>Treatment Group</u>		<u>p-value^a</u>
	<u>Enoxaparin</u> (n = 50)	<u>Placebo</u> (n = 50)	
Overall	37 (74%)	39 (78%)	0.815
Body As A Whole	14 (28%)	15 (30%)	1.000
Digestive	13 (26%)	14 (28%)	1.000
Cardiovascular	11 (22%)	11 (22%)	1.000
Hemic/Lymphatic	6 (12%)	11 (22%)	0.287
Metabolic and Nutritional	11 (22%)	5 (10%)	0.171
Nervous	4 (8%)	7 (14%)	0.525
Urogenital	5 (10%)	4 (8%)	1.000
Skin and Appendages	1 (2%)	7 (14%)	0.059
Musculoskeletal	2 (4%)	1 (2%)	1.000
Respiratory	1 (2%)	1 (2%)	1.000
Injection Site Reactions	1 (2%)	1 (2%)	1.000

^a p-values computed for enoxaparin versus placebo.
* Percentages based on number of patients in each treatment group.

ANALYSIS OF ADVERSE EVENTS EXCLUDING THOSE NOT RELATED TO STUDY MEDICATION: Overall, 53% of patients had adverse events which were considered to be related study medication. No significant difference in incidence rate was noted in the two treatment groups. All adverse events by body system with an incidence of 5% or higher are summarized in table 12.2. All study drug-related adverse events by body system reported with an incidence of 5% or higher are summarized in table 12.4.

Table 12.2
Summary of Adverse Events with an Incidence of $\geq 5\%$ in a Treatment Group
(All Adverse Events)
(Appendix B.13)

Body System COSTART Term Totals*	-----All Adverse Events----- Treatment Group		
	Enoxaparin (n = 50)	Placebo (n = 50)	p-value ^a
Overall	37 (74%)	39 (78%)	0.815
BODY AS A WHOLE			
Pain	7 (14%)	7 (14%)	1.000
Fever	5 (10%)	3 (6%)	0.715
Infection	0	3 (6%)	0.242
Abdominal Pain	0	3 (6%)	0.242
DIGESTIVE SYSTEM			
Nausea	4 (8%)	5 (10%)	1.000
Vomiting	3 (6%)	3 (6%)	1.000
Nausea and Vomiting	5 (10%)	0	0.056
Diarrhea	1 (2%)	4 (8%)	0.362
CARDIOVASCULAR SYSTEM			
Thrombosis	2 (4%)	6 (12%)	0.269
Hemorrhage	4 (8%)	3 (6%)	1.000
HEMIC & LYMPHATIC SYSTEM			
Hypochromic Anemia	4 (8%)	8 (16%)	0.357
METABOLIC AND NUTRITIONAL SYSTEM			
Edema	10 (20%)	4 (8%)	0.148
NERVOUS SYSTEM			
Hallucinations	0	3 (6%)	0.242
UROGENITAL SYSTEM			
Anuria	3 (6%)	2 (4%)	1.000
SKIN AND APPENDAGES			
Rash	0	4 (8%)	0.117

^a p-values computed for enoxaparin versus placebo.
* Percentages based on number of patients in each treatment group.

Table 12.4
Summary of Adverse Events with an Incidence of $\geq 5\%$ in a Treatment Group
-Excluding Those Events Unrelated to Study Medication-
(Appendix B.14)

Body System COSTART Term Totals*	-----Adverse Events----- Treatment Group		
	Enoxaparin (n = 50)	Placebo (n = 50)	p-value ^a
Overall	24 (48%)	29 (58%)	0.423
BODY AS A WHOLE			
Pain	1 (2%)	4 (8%)	0.362
HEMIC & LYMPHATIC SYSTEM			
Hypochromic Anemia	3 (6%)	8 (16%)	0.200
CARDIOVASCULAR SYSTEM			
Thrombosis	2 (4%)	5 (10%)	0.436
DIGESTIVE SYSTEM			
Diarrhea	1 (2%)	3 (6%)	0.617
METABOLIC AND NUTRITIONAL SYSTEM			
Edema	5 (10%)	2 (4%)	0.436
NERVOUS SYSTEM			
Hallucinations	0	3 (6%)	0.242
SKIN AND APPENDAGES			
Rash	0	4 (8%)	0.117

^a p-values computed for enoxaparin versus placebo.
* Percentages based on number of patients in each treatment group.

PATIENTS WHO DIED DURING THE STUDY: One patient in the placebo group died on day 11, 8 days after discontinuation of study medication and while on heparin therapy for DVT developed on postoperative day 7. The cause of death was bilateral adrenal hemorrhage.

PATIENTS PREMATURELY DISCONTINUED FROM THE STUDY DUE TO ADVERSE EVENTS: Overall, six patients were prematurely discontinued from the study because of adverse events: 2 in the enoxaparin and 4 in the placebo groups. One placebo patient experienced nausea, vomiting and hematemesis, and the second developed hypochromic anemia. The adverse events in these patients were considered possibly related to study medication.

One enoxaparin patient developed thrombosis on day 13 of study, one patient developed edema, the third patient experienced

hematemesis and the fourth had dizziness and hallucinations which were considered possibly related to study medication.

Four patients experienced severe adverse events. One death occurred in the placebo group; the patient died on post-operative day 11 from bilateral adrenal medullary hemorrhage while receiving heparin therapy for proximal DVT diagnosed on post-operative day 7. One life-threatening event represented by PE occurred in a placebo patient. Two life-threatening events were reported in the two enoxaparin patients: one developed PE and the second developed an anteroseptal MI with CHF.

CLINICAL LABORATORY EVALUATIONS: Post-operative increase in platelet counts, as well as elevations of SGOT, SGPT, AP and LDH serum levels were observed in both treatment groups. The elevation of SGPT was more pronounced in the enoxaparin group. The shifts from the normal range for the laboratory parameters were similar in the two groups except that the increase from baseline in platelets counts and SGOT were more frequent in the enoxaparin group, and the decrease in calcium level was more frequent in the placebo group.

The summary of patients with possibly clinically significant values of selected laboratory tests is shown in table 16.

Table 16
Summary of the On-Study Incidence of Patients with Clinically Significant Values for Selected Laboratory Parameters
(Appendix B.19)

Parameter Value	Treatment Group			Overall n (%)
	Enoxaparin n (%)	Placebo n (%)	p-value ^a	
All Treated Patients	50 (100%)	50 (100%)		100 (100%)
Platelets: Thrombocytopenia ^b				
Mild	2 (4%)	4 (8%)	0.678	5 (6%)
Moderate	1 (2%)	1 (2%)	1.000	2 (2%)
Platelets: Thrombocytosis ^c				
Mild	15 (30%)	9 (18%)	0.241	24 (24%)
Moderate	11 (22%)	9 (18%)	0.803	20 (20%)
Hemoglobin:				
< 8 gm/dL	3 (6%)	1 (2%)	0.617	4 (4%)
Dec ≥ 2 gm/dL	10 (20%)	6 (12%)	0.414	16 (16%)
SGOT:				
3-6x Normal	1 (2%)	0	1.000	1 (1%)
> 6x Normal	1 (2%)	0	1.000	1 (1%)
SGPT:				
3-6x Normal	2 (4%)	0	0.495	2 (2%)
Alk-Phosphatase:				
> 2x Normal	0	2 (4%)	0.495	2 (2%)
Creatinine:				
≥ 2 mg/dL	2 (4%)	0	0.495	2 (2%)
BUN:				
≥ 30 mg/dL	3 (6%)	0	0.242	3 (3%)

^a p-values from two-tailed Fisher's Exact Test comparison

The markedly abnormal laboratory values encountered throughout the course of the trial are summarized in Table 17.

Table 17
Listing of Patients with Selected Markedly
Abnormal Values for Laboratory Values by Treatment Group
(Appendices D.10.1, D.10.2, D.11.1 and D.11.2)

Treatment Group	Patient Number	Baseline Value	Significant Value (Day)	Final Value (Day)	Comments
Hemoglobin < 7 g/dL					
Enoxaparin	313	11.9	6.5 (POD-2)	12.5 (EOS)	D/Cd; occult bleed on Day 2
Platelets \leq 100,000/mm ³					
Enoxaparin	330	185,000	91,000 (POD-2)	527,000 (EOS)	
Placebo	321	118,000	87,000 (POD-1) 89,000 (POD-2) 100,000 (POD-3)	293,000 (EOS)	
BUN \geq 30 mg/dL					
Enoxaparin	113	30.8	---	22.1 (EOS)	
	125	31.7	---	16.2 (EOS)	
	134	37.3	---	19.3 (EOS)	
	139	20.4	43.4 (EOS)	42.4 (EOS)	*baseline only
	195	39.8	---	---	
	216	40.9	---	29.1 (EOS)	
	304	30.5	30.5 (EOS)	30.5 (EOS)	
	313	26.3	39.8 (EOS)	39.8 (EOS)	
Placebo	206	42.3	---	19.6 (EOS)	
	303	38.4	---	12.6 (EOS)	
Creatinine \geq 2 mg/dL					
Enoxaparin	134	2.1	---	1.6 (EOS)	*baseline only
	195	2.1	---	---	
	216	2.0	2.1 (EOS)	2.1 (EOS)	
	304	2.0	2.0 (EOS)	2.0 (EOS)	
	329	4.1	---	0.8 (EOS)	
SGOT > 6 x ULM IU/L					
Enoxaparin	211	22.0	396 (POD-3)	395 (POD-3)	

POD = Post-operative Day; EOS=End of study; D/Cd = Discontinued from study.

NON-LABORATORY EVALUATION

VITAL SIGNS: There were no changes from baseline of vital signs and no differences between treatment groups.

SUMMARY AND CONCLUSIONS: In this study, the effectiveness of enoxaparin 30 mg q12h sc for the prophylaxis of DVT in patients undergoing elective total hip replacement was compared to placebo.

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One hundred patients were enrolled in the study: 50 on enoxaparin and 50 on placebo. All received at least one dose of study medication and all were included in the "all treated patients analysis" or "intent to treat" analysis.

The endpoint of the study was treatment failure or development of DVT. An initial surveillance for DVT was made with daily ¹²⁵I-Fibrinogen scans and serial IPG. Abnormal results of these tests would be confirmed by venogram. Because the rate of DVT detected by the screening non-invasive vascular tests in the first 24 patients was unexpectedly low, venograms were made mandatory for the remainder of the study. Fifty-eight (58) patients (27 or 54% enoxaparin and 31 or 62% placebo patients) had interpretable bilateral venography and constituted the evaluable patients group.

The original protocol included evaluation of Pulmonary Embolism (PE) with baseline and end-of-study lung scans. No data have been submitted on lung scans, therefore, this assessment was not performed.

The incidence of DVT among the all treated patients was 10% (5/50) in the enoxaparin group and 46% (23/50) in the placebo group. The difference was statistically significant ($p=0.0002$). The incidence of DVT among the evaluable patients was 15% (4/27) in the enoxaparin group and 61% (19/31) in the placebo group. The difference was statistically significant ($p=0.0009$).

Proximal DVT was detected in one enoxaparin patient and in 11 placebo patients ($p=0.0020$). DVT occurred on the side of the hip replacement in 14 patients and in the contralateral side in 8. Two patients had bilateral DVT and one patient had both proximal and distal bilateral DVT.

¹²⁵I-fibrinogen scans and IPG were also used to assess the occurrence of DVT. A total of 67 patients had definite VG finding and ¹²⁵I-fibrinogen scans and a total of 56 patients had definite VG findings and IPG scans. The results of these two non-invasive tests were compared to the VG results obtained in the same patients.

Cross tabulation of ¹²⁵I-fibrinogen scans with VG findings indicates an overall agreement of 78%. It must be noted, however, that 16% (6/38) of negative fibrinogen scan had positive VG findings and that 31% (9/29) of positive fibrinogen scans had negative VG. The results of cross tabulation of negative fibrinogen scan findings with positive VG findings differed between treatment groups. In the enoxaparin group, 13% (3/23) of patients who had negative fibrinogen scan had positive VG and

only 20% (2/10) who had positive fibrinogen scans had positive VG. In the placebo group, 20% (3/15) of patients who had negative fibrinogen scan had positive VG, but 95% (18/19) who had positive fibrinogen scan had positive VG findings. The sensitivity of the ¹²⁵I-fibrinogen for detecting DVT was 76%; the specificity was 82%; the positive predictive value was only 68.9% and the negative predictive value was 84.2%.

Cross tabulation of the IPG scans with the venography findings showed an overall agreement of 66%. However, 33% (17/52) of patients with negative IPG had positive VG findings and 2 of the 4 positive IPG had negative VG and 2 had positive VG. The results of cross tabulation of negative IPG findings with positive VG findings differed between the treatment groups. Fourteen percent (14%, 4/29) of the enoxaparin patients with negative IPG had positive VG and the only patient with positive IPG had negative VG. In the placebo group, 57% (13/23) of patients with negative IPG had positive VG and 67% (2/3) of patients with positive IPG had positive VG. The sensitivity of IPG to detect DVT was only 10.5%; the specificity was 94%. The positive predictive value was 50% and the negative predictive value was 67.3%. The two non-invasive tests were unsatisfactory for surveillance detection of DVT due to lack of both sensitivity and specificity. Among a total of 67 evaluable patients, only two patients, both in the placebo group, had their outcome defined by these tests.

The study was performed in three centers. The number of patients enrolled by each center were 42, 33, and 25; all three centers had sufficient enrollment so that no pooling of data was necessary. The results were homogeneous across centers. In each of the three centers the incidence rate of treatment failure (positive DVT) was uniformly higher in the placebo group than in the enoxaparin group.

The study protocol included assessment of incidence of pulmonary embolism with preoperative and end-of-study lung scans. This assessment was not performed during the clinical trial. The number of subjects enrolled and evaluable may not have been adequate for the analysis of incidence of PE even if ventilation perfusion scans had been used for detection.

Enoxaparin appeared to be well tolerated. The incidence of bleeding complication was similar in the two treatment groups: the incidence of major bleeding was 2% in the enoxaparin group compared to 4% in the placebo group. The blood transfusion

requirements were similar in the two groups: the mean number of RBC units transfused in the enoxaparin patients was 3.3 compared to 2.8 units in the placebo patients.

Although more than 50% of the patients in both treatment groups experienced adverse events considered to be related to study medication, no particular association was noted with enoxaparin. The only laboratory abnormality of possible clinical significance associated to the administration of enoxaparin was represented by elevation of SGOT which in one patient was greater than 6 x baseline value.

Fifty-two patients (52%) were prematurely discontinued from the study. In addition to 19 failures and 16 improvements, the reasons for discontinuation were: 6 adverse reactions (4 of which were serious), 4 lost to follow up, 3 intercurrent illnesses, 1 medication error, 3 other causes.

The four serious adverse events included one death, one acute MI with CHF and two pulmonary embolisms. The death occurred in the placebo group; this patient was terminated from the study on day 3 because of excessive bleeding from operative site, he was subsequently found to have proximal DVT by venography on day 7, was treated with heparin and died on day 11 of bilateral adrenal hemorrhage. Acute MI and CHF occurred in one enoxaparin patient. The two episodes of pulmonary embolism occurred in one enoxaparin and one placebo patients. In both cases, the patients had been discontinued from the study. The enoxaparin patient had been discontinued from the study and discharged on post-operative day after negative VG, but on day 15 she experienced bilateral PE. The placebo patient was discontinued from the study on day 4 because of adverse reaction with negative ¹²⁵I-fibrinogen scan. On day 13 PE was diagnosed by lung scan. IPG was negative, VG was not performed.

Discrepancies in the assignment of patients to the discontinuation categories was noted. For example, patient 115 on placebo was discontinued for "treatment emergent signs and symptoms", the case summary, however, indicates that she was a treatment failure with documented DVT. Patient 218 on placebo was discontinued for "other" reasons while the summary indicate that the patient should have been classified as improved since he was discharged on day 14 with negative venogram. In fact, most of the discontinuations for "improvement" were early discharges due to uncomplicated postoperative course. Patient 141 was listed under the discontinuations for "improvement" on day 12 after having received aspirin on day 9 and 10 in violation of the protocol. The outcome group assignments were, however, correct.

A change in protocol design was introduced while the study was ongoing; mandatory bilateral VG, to be performed on day 14 or prior to discharge, was added to the surveillance of DVT by fibrinogen scan and IPG. In view of the fact that the study was double-blind, that the change affected both placebo and active treatment groups, and that the rate of venography was similar in both groups, the results of the study have not been biased by the interim change.

The results of this study indicate that enoxaparin provided effective and safe antithrombotic prophylaxis in patients undergoing elective hip surgery. The efficacy results in the treated group were highly significant when analyzed either by intent to treat or in the evaluable patients.

The results of this study were published by A.G.G. Turpie et al.: A Randomized Controlled Trial of a Low-Molecular-Weight Heparin (Enoxaparin) to Prevent Deep-Vein Thrombosis in Patients Undergoing Elective Hip Surgery (N. Engl J Med 1986; 315-925-9).

STUDY PK 523

TITLE: A randomized double-blind trial comparing enoxaparin low molecular weight heparin and fixed dose calcium heparin in patients undergoing elective hip surgery.

NDA volumes: 35, 36, 2.16

This study was conducted at five centers in Canada.

<u>Investigators</u>	<u>Study Centers</u>	<u>Patients Treated</u>
J. Hirsh, M.D.	Hamilton Gen. H., Hamilton	108
M. Levine, M.D.	Henderson Gen. H., Hamilton	154
P. J. Powers, M.D.	St. Joseph's H., Hamilton	181
J. Leclerc, M.D.	Montreal Gen. H., Montreal	168
J. Neemeh, M.D.	L'Hotel-Dieu de Montreal, Montreal	54

OBJECTIVE OF THE STUDY: The objective of this study was to compare the safety and efficacy of enoxaparin, 30 mg q12h sc, with that of calcium heparin, 7500 IU q12h sc, in the post-operative prophylaxis of venous thromboembolism in patients undergoing elective hip surgery.

STUDY DESIGN: This study was conducted as a phase III double-blind, active-controlled, parallel-group, multicenter trial comparing the efficacy of enoxaparin with calcium heparin in the prevention of DVT in patients undergoing elective hip replacement.

Except for being active controlled, the study design was similar to that of protocol ENO-0884. Hospitalized patients fulfilling the eligibility criteria for the study, were randomly assigned to receive either enoxaparin 30 mg q12h sc or calcium heparin 7500 IU q12h sc; the treatment was started 12-24 hours after surgery and was continued for up to 14 days.

STUDY POPULATION: Males and females, 40 years and older, eligible for elective hip surgery, who had given written informed consent, were eligible for the study.

Exclusion criteria were: presence of underlying bleeding disorder; allergy to iodine, heparin or contrast dye; pregnancy; need for aspirin or other antiplatelet therapy during hospitalization; severe hepatic disease; acute or chronic renal failure, thrombocytopenia, history of MI or stroke within 6 months.

CONCOMITANT MEDICATIONS: Aspirin and other NSAID were not allowed during the study. All concomitant medications were recorded.

DISCONTINUATION FROM THE STUDY: Patients were discontinued from the study and considered drop-outs for non-compliance with the protocol (errors in dosage or schedule of treatment, omission of Lugol's solution administration, surgery not performed). Permanent early termination of study medication was due to consent withdrawal, adverse events or intercurrent illness. - Patients whose medication was temporarily discontinued because of bleeding and patient with DVT diagnosed at study completion were not categorized as prematurely discontinued.

All discontinued cases were reviewed by the sponsor to determine the event that most directly resulted in early study termination.

EFFICACY PROCEDURES: The primary efficacy assessment was bilateral venography (VG) performed between day 10 and 14 of study, or earlier if clinically indicated. Additional efficacy assessment included daily ¹²⁵I-Fibrinogen leg scans and IPG performed on day 5, 7, 9, 11 and 13, as well as clinical evidence of DVT. A lung scan was performed if there was clinical evidence of PE, and, if necessary, a pulmonary angiogram was performed to confirm the diagnosis of PE. The case report forms of patients who had no IPG, no ¹²⁵I-fibrinogen scans and no venography performed were reviewed by the sponsor for clinical signs or symptoms suggestive of DVT or for diagnosis of PE and administration of anti-thrombotic therapy.

SAFETY PROCEDURES: Laboratory tests included complete CBC, coagulation tests, serum biochemistry, urinalysis, and anti_Xa activity measurements. The results of the APTT were reported to the treating clinician only if the value exceeded 85 seconds and reduction of study medication dosage may have been necessary.

Bleeding episodes were recorded for severity, site, clinical events associated with the bleeding, concomitant laboratory tests, time of onset, etc.

STUDY FLOW SCHEMATIC: The phases of the study procedures are summarized in table 1 reproduced from the NDA, vol 35.

Table 1
Study Flow Schematic-Overview

Evaluation/Procedures	Prior to Surgery ¹	Randomized Interval														End of Study ⁵
		Calendar/Treatment Day ¹														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Personal Data Inventory	X															
Physical Examination	X															
Vital Signs, Wt., Ht.	X															
Written Informed Consent	X															
Laboratory Tests:																
Hematology																
Hemoglobin	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematocrit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
R.B.C.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Platelet	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
W.B.C.	X															
Coagulation																
PT ²	X															
APTT ³	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-factor Xa Activity ³	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Chemistry	X															
Routine Urinalysis	X															
Bleeding Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Experience Evaluation		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
¹²⁵ I-Fibrinogen Leg Scan		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Impedance Plethysmography (IPG)																
Venography ⁴																
Long Scan ⁶																
Pulmonary Angiography ⁷																

¹Day 1 was the first post-operative day.
²Performed for screening purposes only.
³Samples collected six hours after morning injection.
⁴Venography was performed on all patients between days 10 and 14, at the time of premature study discontinuation, or earlier if clinically indicated.
⁵End of study refers to day 14 or the day of premature discontinuation from study.
⁶Long scan performed on patients suspected of having pulmonary embolism.
⁷Pulmonary angiography was performed to confirm diagnosis of pulmonary embolism.

ADVERSE EVENTS: These were defined as untoward events observed by the investigator or reported by the patient. Adverse events were recorded for severity and relationship to study medication.

CLINICAL MONITORING: The study was approved by the IRB and signed informed consents were obtained.

The study was monitored by the sponsor. In addition to reviewing the CRF, the sponsor reviewed portions of the patients' hospital records as well.

BLINDING: Study medications were supplied in prefilled identical syringes containing 30 mg/0.3 ml of enoxaparin or 7500 IU/0.3 ml of calcium heparin. Each patient was supplied with a supply of 30 syringes labeled only with the randomization number, the study number and the investigator's name. Individual sealed envelopes containing the identity of the study medication were provided for each patient to permit unblinding in case of an emergency.

STATISTICAL METHODS

SAMPLE SIZE

Initially, a sample size of 400 patients was determined based on an estimated rate of thrombosis of 10% in the enoxaparin group and of 20% in the heparin group. Based on these rates of DVT, a statistically significant difference with a two-tailed test, at a significance level of 0.05 and with a power of 80% could be demonstrated with 195 patients in each group.

During the course of the study the sample size was progressively increased: first to 520 patients to reduce the chance of Type II error, later on to 650 because it appeared that bilateral VG was likely to be performed only on 80% of patients. Lastly, the sample size was increased to 700 patients in order to replace 40 observed patients who would be excluded from the evaluable efficacy analysis having received NSAID or anticoagulants.

RANDOMIZATION AND PATIENTS ASSIGNMENT

The randomization schedule was generated by the sponsor. Patients were randomized in a 1:1 ratio in blocks of 4 to receive either enoxaparin or heparin. Eligible patients were randomly assigned to the next available randomized number from a schedule that was stratified for center, for previous history of venous thromboembolic disease (TED) and for the use of surgical cement. Each center was assigned a set of 5 digit numbers, the first three digits would indicate the treatment center, the fourth indicated the history of TED and the fifth the use of cement.

EFFICACY EVALUATION

DEFINITION OF EFFICACY OUTCOME: Efficacy was assessed by the incidence rate of DVT. Evidence of DVT was obtained from bilateral VG, IPG, ¹²⁵I-fibrinogen leg scan and other clinical evidence of DVT. A positive VG was defined by a positive finding in either the operative or non-operative limb or both limbs. A negative VG was defined as a negative bilateral VG. An inadequate VG was one in which the diagnosis of DVT could not be made nor excluded. A unilateral negative VG was classified as inadequate.

The diagnosis of DVT by venogram had first priority for the assessment of efficacy. Diagnosis of DVT by either a positive ¹²⁵I-fibrinogen scan or IPG had second priority. Clinical

evidence of DVT was defined as either a positive result of fibrinogen scan or IPG or other clinical evidence such as PE or administration of anticoagulant therapy for DVT.

All treated patients who had received any study medication and had had at least one clinical evaluation were classified into one of the following outcome groups:

Outcome Group	Venogram	-----Clinical Evidence-----	
		¹²⁵ I-Fibrinogen or IPG	Other Clinical Evidence of DVT
1	+	All	All
2	-	All	All
3	In/ND	+	All
4	In/ND	-, In/ND	+
5	In/ND	-, In/ND	Not +

"In/ND" indicates that the VG was inadequate or not done.

"All" indicated all situations (+, -, In/ND).

- Group 1 included patients with positive VG regardless of the results of other tests.

- Group 2 included patients who had negative VG regardless of the results of other tests.

- Group 3 and 4 included patients in whom a VG was not done or it was inadequate and who had a DVT confirmed by IPG, fibrinogen scan or who had other clinical evidence of DVT.

- Group 5 included patients in whom all diagnostic tests were either not done or inadequate and had no other clinical evidence of DVT.

STUDY POPULATIONS

The study population included in the efficacy analysis was represented by:

1. all randomized patients: these included all randomized patients regardless of whether they had efficacy data.
2. all treated patients with efficacy data; these included all treated patients with at least one post-treatment efficacy evaluation.
3. evaluatable patients: these included the patients from the second group for whom none of the following occurred during the study:
 - administration of disallowed concomitant therapy.
 - insufficient therapy, i.e., less than 3 day treatment
 - no definitive VG was obtained at the end of study.

4. unevaluable patients: this include all patients in each treatment group who were the complement of evaluable patients with respect to the all treated population. In this study all randomized patients were treated, therefore, there were no unevaluable patients.

EFFICACY ANALYSES

INTENT-TO-TREAT ANALYSES was performed on ALL TREATED PATIENTS WITH EFFICACY DATA. The efficacy endpoints (incidence of DVT or treatment failure) for this patient population was defined as follows:

Groups 1, 3, 4 (positive)
Groups 1, 3, 4 (positive + Groups 2, 5 (negative))

The incidence of DVT was also summarized within the subsets of type of surgery (primary hip replacement or revision), type of anesthesia (regional/epidural or inhalation/IV), use of surgical cement, sex, age, previous history of DVT or PE.

ALL RANDOMIZED PATIENTS

This group was essentially identical to the "all treated" group as only 4 of the 669 randomized patients were not treated.

EVALUABLE PATIENTS EFFICACY ANALYSIS

All evaluable patients had definitive VG, thus, the efficacy endpoint (treatment failure) was defined as:

Group 1 (positive)
Group 1 (positive) + Group 2 (negative)

Group 3 (noninvasive vascular evidence of DVT) and 4 (clinical evidence of DVT) were not considered in the evaluation of efficacy for the evaluable patients.

Within the population of evaluable patients, the incidence of DVT was also summarized for the subsets of type of surgery, type of anesthesia, use of surgical cement, use of GCS, sex, age and previous history of DVT or PE.

SAFETY EVALUATION

PATIENT POPULATION: All patients who received at least one dose of study medication were included in the safety evaluation.

SAFETY ANALYSES; The primary safety endpoints determined for each of the treatment groups were:

- Incidence of death, premature discontinuation from treatment, adverse events (according to severity and relationship to study medication).
- incidence of major or minor bleeding episodes.
- the mean number of total units of blood transfused post-surgery (aside from operative and recovery room units) and the incidence of 0, 1-2, and more than 2 units of blood transfused post-surgery.
- the incidence of abnormal values of clinical concern for selected laboratory tests, including:

Platelets:

Decrease: Thrombocytopenia-

mild: equal or greater than $1 \times 10^5/\text{mm}^3$ and less than the investigator's lower limit of normal

moderate: equal or greater than $2 \times 10^4/\text{mm}^3$ and lower than $1 \times 10^5/\text{mm}^3$

severe: lower than $2 \times 10^4/\text{mm}^3$

Increase: Thrombocytosis-

mild: greater than the investigator's upper limit of normal and lower than $6 \times 10^5/\text{mm}^3$

moderate: higher than $6 \times 10^5/\text{mm}^3$ and lower than $1 \times 10^6/\text{mm}^3$

severe: higher than $1 \times 10^6/\text{mm}^3$

Hemoglobin: Values lower than 8 gm/dL or a decrease equal or greater than 2 gm/dL from baseline.

SGOT and SGPT: 3- to 6-fold increase and more than 6-fold higher than the investigator's upper limit of normal.

Total Bilirubin: Values greater than 2 mg/dL.

Alkaline Phosphatase: Any value greater than 2-fold higher than the investigator's upper limits of normal.

Creatinine: Any value greater than 2 mg/dL.

BUN: Any value greater than 30 mg/dL.

- The mean changes from baseline for hematology (post-surgery, first day of study drug) laboratory tests at post-op day 1 through 14 and end of study and follow-up and for serum chemistry (pre-surgery) laboratory tests at end of study.
- Shifts in the percentage of patients with hematology and chemistry laboratory values outside the normal range at the end of the study relative to baseline.

-the mean change from pre-surgery baseline for systolic and diastolic blood pressure and pulse rate at end of study.

STATISTICAL ANALYSIS

Demographic and Baseline Characteristics: The two treatment groups were compared at baseline using descriptive statistics for categorical variables (sex) and other demographic variables (age, weight), medical and surgical histories, and transfusions. Each variable was summarized for all treated and all evaluable patients. The randomized and unevaluable patients were summarized for demographic, surgery and transfusion data.

Efficacy Analyses: The endpoint was represented by development of DVT (treatment failure). The incidence of DVT was analyzed for both all treated patients with efficacy data and for the evaluable patients.

Justification for pooling across centers was investigated using a two-way logistic regression model with factors of treatment group, center and treatment-by center interaction. The results were also summarized by investigator to provide a heuristic assessment of the presence of interaction.

A two-way logistic regression model including factors for treatment group and center with no interaction term was used to compare the two treatment groups. The treatment comparison between the two treatment groups was based on a 5% significance level. All tests were two-sided. An approximate 95% confidence interval for the odds ratio of treatment failure in placebo versus enoxaparin was computed. The odds of a treatment failure are defined as estimated incidence rate of treatment failure/estimated incidence rate of treatment success. The incidence rate of treatment failure by treatment group was summarized in patients subpopulations defined by the demographic characteristics, type of surgery (primary or revision), use of surgical cement and type of anesthesia.

Adverse Events: The COSTART dictionary was used to classify the adverse events. Events for a particular COSTART occurring more than once were counted only once. Repeated reporting of the same adverse event in a patient was reported only as the most severe. Each type of event occurring within a body system was counted. Adverse events incidence rates (all events excluding those unrelated to study medication) were summarized by treatment group. The adverse events were summarized for each body system and overall. Overall indices reflected the number of patients reporting any adverse event.

Fisher's exact test was performed for the statistical comparison of the enoxaparin and the placebo groups for total adverse events in each body system, for each event with an incidence of 5% or higher, for all adverse reactions, and for each event with an incidence of 5% or higher for all adverse events excluding those unrelated to study medication. These analyses were requested at a pre-NDA meeting with the FDA in March 1991.

Bleeding Assessment

The overall incidence of major bleeding, minor bleeding, absence of bleeding and the percentage of patients who experienced any major or minor bleeding during the study period was determined for each treatment group. A two-way logistic regression model with factors for treatment group and center was used.

Laboratory Data

Baseline values for hemoglobin, hematocrit, RBC, platelets and APTT were defined as postoperative, first day of treatment values. Baseline values for all other parameters were the presurgical values. Mean changes from baseline were determined on Day 14 or at the end of the study for all laboratory parameters, except CBC and coagulation which were measured daily and whose changes were assessed daily and at the end of study.

The mean changes from pooled parameters across investigators were summarized for the two treatment groups using descriptive statistics. No formal statistical analyses were performed for these laboratory data.

Fisher's exact test was performed for the statistical comparison between the two groups of the selected laboratory values of clinical concern. Shift tables were generated that summarize the distribution (below, within, above normal or unknown categories) of baseline and end of study hematology and chemistry values.

Vital Signs

The mean changes from baseline for systolic and diastolic pressure were summarized for the two treatment groups. No formal statistical test of hypothesis was performed.

PROTOCOL ADDENDUM: The protocol was amended on 8-24, 1989 to increase the sample size from 400 to 700 patients

RESULTS

PATIENTS DISPOSITION/ACCOUNTABILITY

A total of 669 patients were randomized in this study: 335 to enoxaparin treatment and 334 to heparin treatment. Four of the 669 patients (two enoxaparin and two heparin) did not receive study medication: one patient withdrew consent, one had delayed primary hemostasis and two had GI bleeding. Of the remaining 665 patients, 333 received enoxaparin and 332 received heparin. A total of 81% (540/665) of all treated patients completed the study. Nineteen percent (19%, 125/665) of all treated patients were prematurely discontinued from the study: 16% (72/332) in the enoxaparin group and 22% (72/332) in the heparin group. The most common cause for discontinuation was occurrence of DVT.

All patients who received study medication had at least one on study evaluation and were included in the all treated patients efficacy analysis.

A total of 73% (486/665) of all treated patients had definitive VG analysis. Seventy-one percent (71%, 236/333) of the enoxaparin group and 75% (250/332) of the heparin group were evaluable. One hundred twenty-five (125) patients were discontinued. Development of DVT was the most frequent cause of discontinuation.

All patients who received at least one dose of study medication were included in the safety evaluation.

The patients disposition and accountability are summarized in the following table:

<u>Patient Disposition</u>	<u>Treatment Group</u>		<u>Total</u> n (%)
	<u>Enoxaparin</u> n (%)	<u>Heparin</u> n (%)	
Patients Randomized	335	334	669
Patients Not Treated	2	2	4
Patients Treated	333 (100%)	332 (100%)	665 (100%)
1. Completed	280 (84%)	260 (78%)	540 (81%)
a. Evaluable	236 (71%)	250 (75%)	486 (73%)
b. Not Evaluable	97 (29%)	82 (25%)	179 (27%)
VG not done	34 (10%)	38 (11%)	72 (11%)
VG Inadequate	40 (12%)	27 (8%)	67 (10%)
Medications	17 (5%)	15 (5%)	32 (5%)
Insuff. therapy	6 (2%)	2 (<1%)	8 (1%)
2. Discontinued	53 (16%)	72 (22%)	125 (19%)
DVT	38 (11%)	45 (14%)	83 (12%)
Adverse Events	7 (2%)	9 (3%)	16 (2%)
Consent withdrawn	5 (2%)	7 (2%)	12 (2%)
Bleeding Events	3 (<1%)	6 (2%)	9 (1%)
Intercur. Illness	0	5 (2%)	5 (<1%)
Death	0	0	0

DEMOGRAPHICS

The two treatment groups of all randomized patients, treated patients and evaluable patients were similar with respect to demographic characteristics. In the all treated patients group, the male/female ratio was 54/46, the average age was 66.5, the average body weight 74.1 kg and the average height 166.0 cm.

CONCOMITANT MEDICATIONS.

All study patients received concomitant medications: 96% of patients received opiates and opioids, 93% received other analgesics, 91% received cephalosporins, 82% received tranquilizers, 52% received systemic antihistaminics, 47% received laxatives and 43% received hematinics.

The two treatment groups were similar for the frequency of use of aspirin and NSAID.

CONCOMITANT ILLNESSES AND MEDICAL/SURGICAL HISTORIES

Sixty percent (60%) of all treated patients had other presenting condition or disease involving any organ or system.

The incidence rate of these conditions among patients in the two treatment groups was similar.

One hundred percent (100%) of the patients in the study had other medical or surgical history. The most frequently reported were diseases of the musculoskeletal system and connective tissue (88%), diseases of the nervous system (59%), diseases of the circulatory system (37%) and diseases of the GI tract (27%). The most frequent surgical histories were previous surgical operations on the musculoskeletal system (44%), on the GI system (34%) and GYN. system (88/360 females, 24%). The incidence of any of the medical or surgical histories was similar in the two treatment groups. The incidence of conditions which could predispose to DVT was similar in the two treatment groups.

PRIMARY DIAGNOSIS AND SURGERY DATA

The primary diagnosis, the type of surgery performed, type of anaesthesia, use of surgical cement, duration of surgery or blood loss and transfusion requirement during surgery were similar in the two groups of patients treated with enoxaparin or heparin. Osteoarthritis was the primary diagnosis in 78% of patients. Seventy-seven percent (77%) of all patients had first total hip replacement, and 22% of patients had revision of a previously performed hip replacement.

General anesthesia was used in 97% of patients and epidural anesthesia in 3%. Surgical cement was used in 39% of all surgeries performed.

The mean number of units of blood transfused during the operation and in the recovery room was 2.7 units. The average intraoperative blood loss was 1139 ml. The mean duration of surgery was 2.8 hours.

There were no differences between the all treated and the evaluable patients or between the two treatment groups for any of these variables.

EFFICACY RESULTS

CLINICAL OVERVIEW OF EFFICACY RESULTS

The incidence of DVT diagnosed by any method of vascular assessment (VG, ¹²⁵I-Fibrinogen scan, IPG) was similar in the enoxaparin group (17%) and the heparin group (19%).

Among evaluable patients, the incidence of DVT was 18% in the enoxaparin group and 23% in the heparin group. This numerical difference was not statistically significant.

The incidence of DVT among demographic and surgical subpopulation in the two treatment groups reflected that found in the overall population of patients.

DVT FINDINGS

Treatment outcome was assessed by DVT findings from VG results in 79% of patients and by other vascular examination or clinical assessment in the remaining 21% of patients. The percentage of patients with or without definitive VG was similar in both treatment groups.

ANALYSIS OF INCIDENCE OF DVT

ALL RANDOMIZED and ALL TREATED PATIENTS EFFICACY ANALYSIS

The number of randomized but not treated patients represented <1% of the randomized population. This proportion of patients was too small to influence the intent-to-treat analysis.

One hundred-twenty (120) of 665 patients (18%) had positive evidence of DVT. The incidence of DVT was 17% (57/333 patients) in the enoxaparin group and 19% (63/332 patients) in the heparin group ($p=0.5317$).

In each of the treatment groups, the incidence of DVT in distal sites was higher than in proximal sites.

EVALUABLE PATIENTS EFFICACY ANALYSIS

One hundred one of the 486 evaluable patients (21%) had VG confirmed DVT. The incidence of venography-confirmed DVT was 18% among the enoxaparin treated patients and 23% among the heparin treated patients. The difference was not statistically significant ($p=0.1611$).

The majority of the DVTs in both treatment groups involved the distal veins. The incidence of DVT in the operated limb was similar to that in the non-operated limb; 42% and 40% respectively; 19 patients developed bilateral DVT.

The distributions of DVT findings for All Treated Patients and for Evaluable Patients groups are shown in the following table:

	<u>Treatment Group</u>		<u>Overall</u> (n=665)
	<u>Enoxaparin</u> (n=333)	<u>Heparin</u> (n=332)	
<u>All Treated Patients</u>			
Treatment Outcome Group:			
Patients with definitive Venography:			
(1) Positive	259 (78%)	267 (80%)	526 (79%)
(2) Negative	50	61	111
Patients without definitive venography:			
Clinical Evidence of DVT			
(3) Positive noninvasive tests	209	206	415
(4) Other Positive Clinical Data	74 (22%)	65 (20%)	139 (21%)
(5) No positive Clinical Evidence	7	2	9
All Treatment Failures	57 (17%)	63 (19%)	120 (18%)
Proximal DVT	16 (5%)	18 (5%)	34 (5%)
Distal DVT	41 (12%)	45 (14%)	86 (13%)
<u>Evaluable Patients</u>	236 (100%)	250 (100%)	486 (100%)
Treatment Failures	43 (18%)	58 (23%)	101 (21%)
Proximal DVT	10 (4%)	17 (7%)	27 (6%)
Distal DVT	33 (14%)	41 (16%)	74 (15%)
Operated limb	17	25	
Non-operated limb	18	22	
Bilateral DVT	8	11	

Between-Group Comparison of the incidence of treatment failure (DVT) was calculated for the All Treated Patients and Evaluable patients. The following results were obtained:

All Treated Patients:

<u>Treatment Comparison:</u>	<u>Odds Ratio</u>	<u>p-value</u>	<u>95% CI for Odds Ratio</u>
Heparin/Enoxaparin	1.14	0.5317	(0.76, 1.69)

VALUABLE Patients:

<u>Treatment Comparison:</u>	<u>Odds Ratio</u>	<u>p-value</u>	<u>95% CI for Odds Ratio</u>
Heparin/Enoxaparin	1.38	0.1611	(0.88, 2.15)

These data are summarized graphically in Fig. 1A and 1B.

Figure 1A
Statistical Result of DVT Findings by Treatment Group
Percent of Treatment Failures
All Treated Patients
PK 523

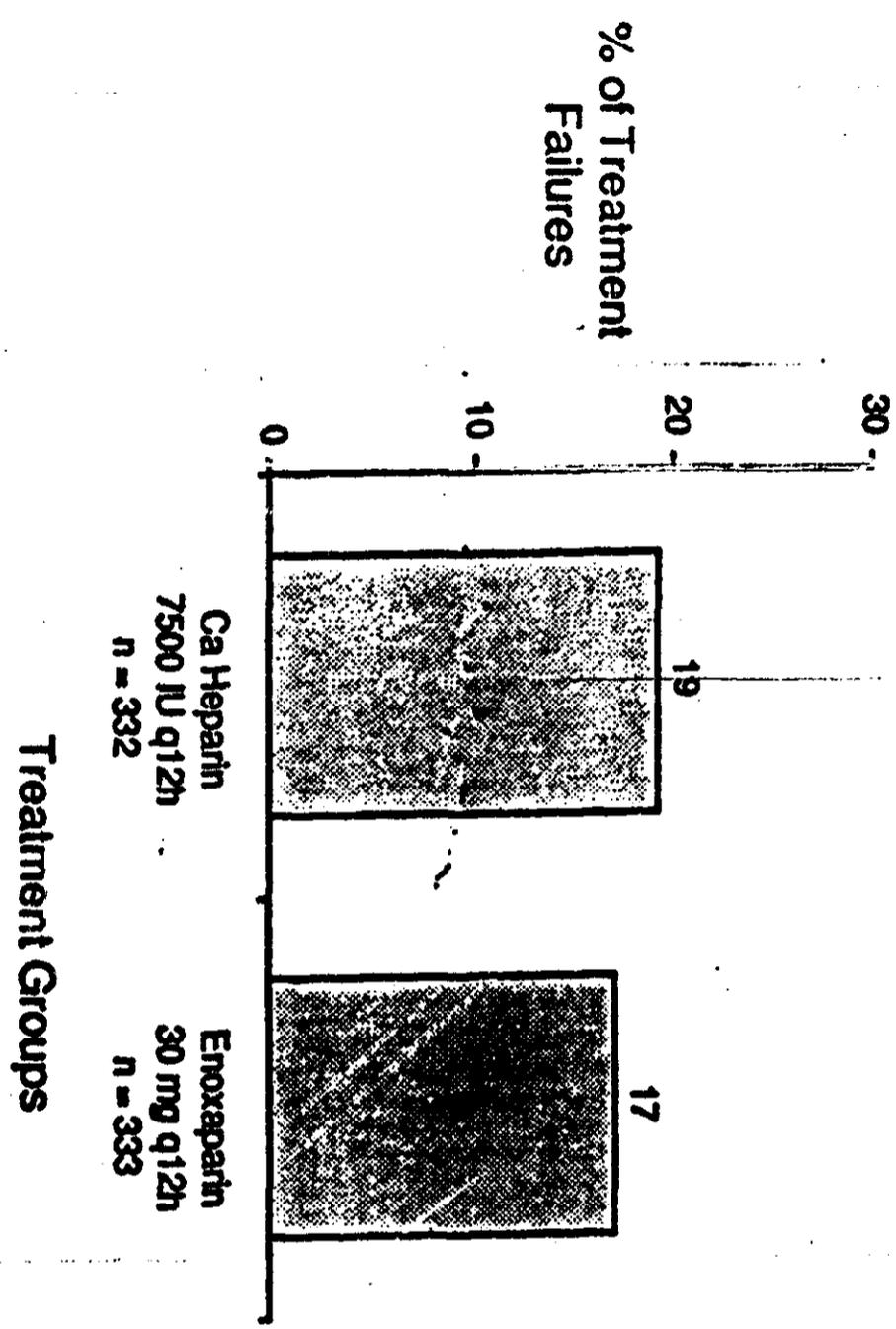
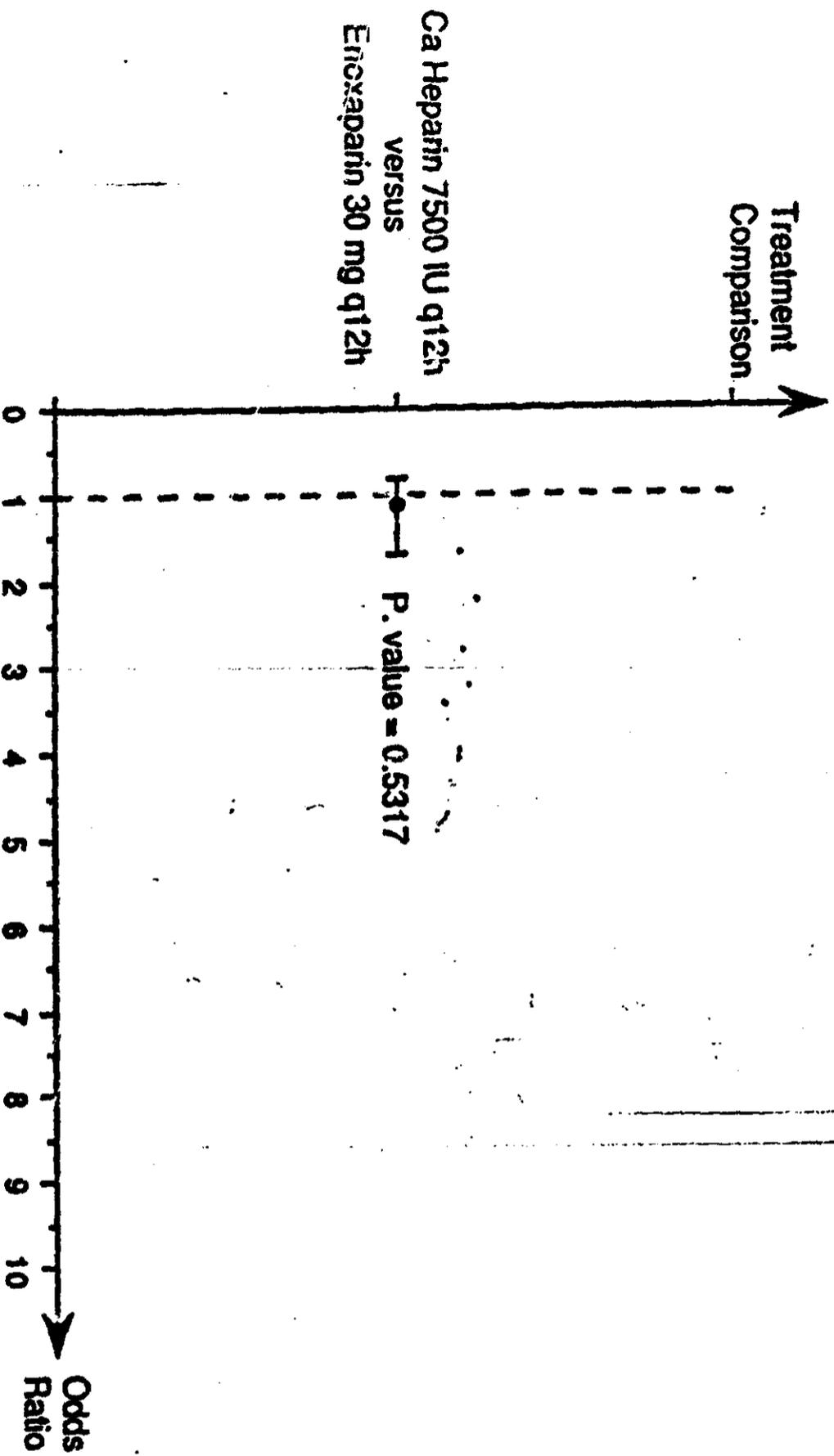


Figure 1B
Statistical Result of DVT Findings by Treatment Group
Confidence Intervals for Odds Ratio of Treatment Failures
All Treated Patients
PK 523



Because of the large number of patients treated in this study and the substantial sample sizes obtained in all five participating centers, analysis of the data from each individual center was possible. The distribution of treatment outcome by center are shown in the following table:

<u>Center</u>	<u>All Treated</u>		<u>Evaluable</u>	
	<u>Enoxaparin</u>	<u>Heparin</u>	<u>Enoxaparin</u>	<u>Heparin</u>
Hamilton	13.0% 7/54	13.0% 7/54	14.7% 5/34	20.6% 7/34
Montreal	12.9% 11/85	20.5% 17/83	14.8% 8/54	27.6% 16/58
St. Joseph	14.3% 13/91	20.0% 18/90	8.8% 6/68	21.1% 16/76
Henderson	26.0% 20/77	23.4% 18/77	32.1% 18/56	28.1% 16-57
Hotel-Dieu	23.1% 6/26	10.7% 3/28	25.0% 6/24	12.0% 3/25

The efficacy results in the evaluable patient population from three centers favored enoxaparin. The difference between the two treatment groups was not, however, statistically significant. One center favored heparin over enoxaparin, but the difference was not statistically significant.

The p-values for center by treatment interaction which had been preselected at a level of 0.15, were 0.46 and 0.147 for the all treated and evaluable patients respectively. The marginally significant interaction, due primarily to one center, was considered by the sponsor to have minimal impact on the conclusion that the two treatments were not significantly different. These data will be discussed with the Biostatistics Reviewer.

SUBSET EFFICACY ANALYSIS FOR ALL TREATED PATIENTS

Among all treated patients and within each of the treatment groups, the incidence rate was similar in males and females, slightly lower in patients under 65 years of age compared to older patients, higher in patients with positive history of venous thromboembolic disease. Among the patients with a positive history of thromboembolic disease, the incidence of DVT was lower in the enoxaparin treated group.

Among surgical subpopulations of all treated patients, the incidence of DVT was similar with regard to type of surgery and

use of surgical cement. A slight difference was found for patients receiving epidural anesthesia compared to general anesthesia; the difference was not meaningful due to the small number of patients.

SUBSET EFFICACY ANALYSIS FOR EVALUABLE PATIENTS

The overall incidence of DVT and the incidence of DVT within each treatment group showed no difference for gender or age. In the enoxaparin group the incidence of DVT was similar in patients with or without previous history of thromboembolic disease (TED). In the heparin group, the incidence of DVT was higher in the patients with previous history of TED and it was higher than in the enoxaparin patients with history of previous TED.

The data from the evaluable patients population are summarized in the following table:

<u>Demographic Parameter</u>	<u>Treatment Group</u>		<u>Overall</u>
	<u>Enoxaparin</u>	<u>Heparin</u>	
Gender:			
Male	21% (22/106)	22% (27/125)	21% (49/231)
Female	16% (21/130)	25% (31/125)	20% (52/255)
Age:			
< 65 yrs	14% (13/90)	19% (17/90)	17% (30/180)
> 65 yrs	21% (30/146)	26% (41/160)	32% (71/306)
<u>Previous History of DVT:</u>			
Positive History	20 (4/20)	48% (11/23)	35% (15/43)
Negative History	18% (39/216)	21% (47/227)	19% (86/443)
<u>Previous History of PE:</u>			
Positive History	17% (1/6)	50% (3.6)	33% (12/4)
Negative History	18% (42/230)	23% (55/244)	20% (97/474)
<u>Previous History of DVT or PE:</u>			
Positive History	18% (4/22)	42% (11/26)	31% (12/48)
Negative History	18% (39/214)	21% (47/224)	20% (86/438)
<u>Previous History of DVT and PE:</u>			
Positive History	25% (1/4)	100% (3/3)	57% (4/7)
Negative History	18% (42/232)	22% (55/247)	20% (97/479)

None of the surgical variables (type of surgery, anesthesia, use of cements) was found to affect the overall efficacy outcome and the incidence of DVT within each treatment group.

SAFETY RESULTS

CLINICAL OVERVIEW OF SAFETY RESULTS

Enoxaparin and heparin appeared comparable for incidence of adverse events (30% and 36% respectively). The incidence of

overall bleeding was less in the enoxaparin group. The rate of discontinuation due to adverse events was similar in both treatment groups.

Study medication was discontinued on post-operative day 11 in one patient in the heparin group because of development of symptoms of PE. The patient had positive V/Q lung scan, negative bilateral venogram and positive pulmonary angiogram.

NUMBER OF PATIENTS EVALUATED AND DURATION OF EXPOSURE

All patients who received at least one dose of study medication (n=665) were entered in the safety evaluation.

STUDY DRUG ADMINISTRATION

The mean duration of treatment for all patients was 10.8 ± 3.13 days (range: 1-15 days) and it was similar for both treatment groups.

The mean number of doses of study medication taken by all patient and by each treatment group patients was 20.5 ± 6.37 (range: 1-29 doses).

PATIENTS WITH EPISODES OF BLEEDING DURING THE STUDY

Major or minor bleeding occurred in 48 patients (7%). The incidence of major or minor bleeding episodes was 5% for the enoxaparin group and 9% for the heparin group. The difference was statistically significant ($p=0.0375$).

The overall incidence of major bleeding was 5% (30/665) and included 3% (11/333) in the enoxaparin group and 6% (19/332) in the heparin group. This difference was not statistically significant.

The data are summarized in the following table:

<u>Bleeding</u>	<u>Treatment Group</u>		<u>Overall</u> n (%)
	<u>Enoxaparin</u> n (%)	<u>Heparin</u> n (%)	
All patients Treated	333 (100%)	332 (100%)	665 (100%)
Major or Minor	17 (5%)	31 (9%)	48 (7%)
Major	11 (3%)	19 (6%)	30 (5%)
Minor	6 (2%)	12 (4%)	18 (3%)
None	316 (95%)	301 (91%)	617 (93%)

Between-Group Comparison of the incidence of patients with bleeding episodes:

<u>Comparison</u>	<u>Odds Ratio</u>	<u>p-value</u>	<u>95% CI for Odds Ratio</u>
<u>Major or Minor bleeds</u>			
Heparin/Enoxaparin:	1.92	0.0375	(1.04, 3.56)
<u>Major Bleeds</u>			
Heparin/Enoxaparin	1.79	0.1349	(0.83, 3.85)

In the heparin group, the episodes of major bleeding were represented by GI bleeding in three patients and by bleeding at operative site in 11 patients. In the enoxaparin group, one of the 11 patients with major bleeding experienced GI bleeding and all 11 experienced major bleeding at the operative site.

POST SURGICAL BLOOD TRANSFUSION

A total of 48% of all treated patients received transfusion of one or more units of blood from day 1 post-surgery through the end of study. The proportion of patients who required transfusion were similar in the two treatment groups. The transfusion data are summarized in the following table:

<u>Units Transfused</u>	<u>Treatment Group</u>		<u>Overall</u>
	<u>Enoxaparin</u>	<u>Heparin</u>	
	(n=333)	(n=332)	(n=665)
0 Units	177 (53%)	170 (51%)	347 (52%)
1-2 Units	121 (36%)	118 (36%)	239 (36%)
> 2 Units	35 (11%)	44 (13%)	79 (12%)
Mean (Units)	2.4 ± 1.91	2.3 ± 1.41	2.3 ± 1.67
Range	1-20	1-9	1-20

PATIENTS DISCONTINUED DUE TO BLEEDING EPISODES

Three patients in the enoxaparin group and six patients in the heparin group had study medication discontinued due to major bleeding

ADVERSE EVENTS

Adverse events, defined as untoward events either observed by the investigator or reported by the patient, were mapped and displayed by COSTART terms.

ADVERSE EVENT RATES--ALL ADVERSE EVENTS

Overall, 92% of patients (613/665), similarly distributed in the two treatment groups, reported at least one adverse event.

The most common adverse events affected the body as a whole and were reported by 50% of enoxaparin patients (187/333) and by 65% of the heparin patients (216/332). The difference between the two groups was statistically significant ($p=0.021$).

The most common complaints within were fever, pain, chest pain and abdominal pain. Local pain occurred less frequently with the administration of enoxaparin.

Next in frequency were events affecting the GI tract which occurred equally in both treatment groups (37% and 41%). Hematemesis was the most frequent event affecting the digestive system and it occurred less frequently in the enoxaparin group ($p=0.004$).

The incidence rates of other adverse events affecting other body systems were similar in the two treatment groups.

The incidence of all the adverse events are summarized in table 12.1 and the incidence of those regarded as related to study medication are summarized in table 12.3.

Overall, 33% of all patients (30% of the enoxaparin and 36% of the heparin patients) experienced adverse events which were regarded by the investigator as related to the study medication. The most frequent adverse events were reported for the metabolic and nutritional system (peripheral edema, edema and hypokalemia), for the hemic-lymphatic system (ecchymosis, anemia) and for the cardiovascular system (hemorrhage, hypotension, postural hypotension). The incidence of these events was similar for the two treatment groups except for the body as a whole and the hemic-lymphatic system which show a lower incidence of anemia in the enoxaparin group.

PATIENTS DISCONTINUED DUE TO AN ADVERSE EVENT

Sixteen (16) patients were discontinued from study because of adverse event, 7 in the enoxaparin and 9 in the heparin group. The listing of the patients, the adverse event and of their severity and attribution are summarized in table 13

Table 12.1
Summary of Adverse Events by Body System
(All Adverse Events)
(Appendix B.12)

Body System	Treatment Group		p-value ^a
	Enoxaparin (N=333)	Calcium Heparin (N=332)	
Totals^b			
Overall	307(92%)	306(92%)	1.000
Body as a Whole	187(56%)	216(65%)	0.021*
Digestive	123(37%)	135(41%)	0.340
Metabolic and Nutritional	108(32%)	99(30%)	0.503
Cardiovascular	91(27%)	105(32%)	0.235
Nervous	70(21%)	72(22%)	0.850
Urogenital	75(23%)	69(21%)	0.638
Hemic and Lymphatic	52(16%)	68(20%)	0.108
Skin and Appendages	61(18%)	59(18%)	0.920
Respiratory	40(12%)	41(12%)	0.906
Injection Site Reaction	17(5%)	20(6%)	0.617
Musculoskeletal	13(4%)	13(4%)	1.000
Special Senses	3(<1%)	3(<1%)	1.000

a Two sided p-values.
b Percents are based on number of patients in each treatment group. Patients are counted only once for an event in each body system and once in the overall total.
* Indicates p<0.05.

Table 12.3
Summary of Adverse Events by Body System
-Excluding those Not Study Drug Related-
(Appendix B.13)

Body System	Treatment Group		p-value ^a
	Enoxaparin (N=333)	Calcium Heparin (N=332)	
Totals^b			
Overall	101(30%)	121(36%)	0.100
Metabolic and Nutritional	37(11%)	40(12%)	0.718
Hemic and Lymphatic	27(8%)	46(14%)	0.019*
Cardiovascular	34(10%)	35(11%)	1.000
Body as a Whole	22(7%)	38(11%)	0.031*
Digestive	20(6%)	27(8%)	0.294
Nervous	14(4%)	21(6%)	0.230
Urogenital	7(2%)	9(3%)	0.625
Skin and Appendages	5(2%)	9(3%)	0.296
Respiratory	6(2%)	8(2%)	0.603
Injection Site Reactions	2(<1%)	6(2%)	0.177
Musculoskeletal	1(<1%)	2(<1%)	0.624
Special Senses	2(<1%)	0	0.499

a Two sided p-values.
b Percents are based on number of patients in each treatment group. Patients are counted only once for an event in each body system and once in the overall total.
* Indicates p<0.05

Table 12
Listing of Patients Discontinued Due to an Adverse Event
(Appendix C. 18)

Patient Number	Study Day Discontinued	Adverse Event	Severity	Relationship to Study Medication
Enoxaparin:				
30080	7	Gout	Severe	None
30103	9	Thrombocytopenia	Severe	Possible
30048	11	Edema	Severe	Possible
20136	2	Electrocardiogram abnormal	Severe	None
	2	Sweating	Severe	None
	2	Tachycardia	Severe	None
31008	2	Melena	Moderate	Possible
40157	2	Hypoxia	Severe	Possible
30124	10	Dyspnea	Severe	Possible
Calcium Heparin:				
20014	3	Hypochromic anemia (Hb decreased)	Severe	Definite
	3	Hemoptysis	Severe	Possible
30060	8	Thrombocytopenia	Severe	Definite
40105	10	Chest pain	Severe	Possible
30137 ^a	11	Lung disorder	Severe	Probable
	12	Embolus Pulmonary ^b	Severe	Definite
40120	11	Pain	Severe	Possible
	11	Edema	Moderate	Possible
40183	11	Thrombocytopenia	Severe	Probable
60030 ^b	11	Thrombocytopenia	Severe	Definite
	12	Headache ^c	Moderate	Possible
60108	13	Hematuria	Moderate	Possible
30029	10	Injection site reaction	Severe	Definite

^a Patient was discontinued on post-operative day 11 and the citing of embolus pulmonary occurred after the patient was discontinued.

^b Patient was discontinued on post-operative day 11 and the citing of headache occurred after the patient was discontinued.

PATIENTS WITH SERIOUS ADVERSE EVENTS

The occurrence of serious adverse events (life-threatening or resulting in death, prolonged hospitalization, rehospitalization, permanent disability, etc.) was assessed retrospectively from the review of the CRF. No deaths occurred during the study period. Nine patients were considered to have experienced serious adverse events including 4 patients reporting 14 events in the enoxaparin group and 5 patients reporting 11 events in the heparin group. The listing of the patients with serious adverse events is shown in table 14.

Table 14
Listing of Patients With Serious Adverse Events*
(Appendices D.14 and D.18)

<u>Patient Number (Center)</u>	<u>Relationship to Study Drug</u>	<u>Serious Adverse Event</u>
<u>Life Threatening Events</u>		
<u>Enoxaparin</u>		
30124 (Henderson General Hospital)	Possible None None None	Dyspnea Atrial Fibrillation Atrioventricular Block Arrhythmia
31008 (Henderson General Hospital)	Possible Possible Possible	Melena Hypotension Arrhythmia
40157 (St. Joseph's Hospital)	Possible None Remote	Hypoxia Hydrourterer Hypokalemia
<u>Calcium Heparin</u>		
30060 (Henderson General Hospital)	Definite	Thrombocytopenia
30137 (Henderson General Hospital)	Probable Possible Definite	Lung Disorder Pleural Effusion Embolus Pulmonary
40104 (St. Joseph's Hospital)	Probable	Hematemesis
40183 (St. Joseph's Hospital)	Probable	Thrombocytopenia
60108 (Montreal General Hospital)	Possible None None Possible None	Hematuria Lung Disorder Urinary Retention Hematemesis Syncope
<u>Prolonged Hospitalizations</u>		
<u>Enoxaparin</u>		
90001 (Henderson General Hospital)	None None None Remote	Hemorrhage Hypochromic Anemia Lung Disorder Intestinal Perforation

* Deaths or life-threatening events; events which required prolonged hospitalization, rehospitalization, or caused permanent disability; any cancer, congenital anomaly or drug overdose.

Two cases of pulmonary embolism occurred in the heparin group: one was diagnosed by lung scan on day 9 in a patient who had been diagnosed with proximal DVT on day 7 and the second was diagnosed on day 11 by pulmonary angiogram.

CLINICAL LABORATORY EVALUATION

No unanticipated results on laboratory tests were reported during the study. In both treatment groups, elevations of platelet counts, SGOT, SGPT, LDH, and AP occurred post-operatively. The increase in SGOT and SGPT was slightly lower in the enoxaparin group.

MEAN VALUES FOR LABORATORY PARAMETERS

The baseline for CBC and coagulation tests was represented by the first data obtained post-operatively. The baseline for the other laboratory parameters was represented by their preoperative values.

Similar mean changes were observed in the two treatment groups at the end of study for hemoglobin, hematocrit, WBC, LDH, AP. The elevation of transaminases was slightly lower in the enoxaparin group.

INCIDENCE OF "POSSIBLY CLINICALLY SIGNIFICANT" VALUES FOR SELECTED LABORATORY PARAMETERS

Abnormal values of possible clinical significance occurred in both treatment groups for platelet counts, hemoglobin, SGOT, SGPT, AP, BUN and creatinine.

Levels of hemoglobin below 8 gm/dL were observed in 12% of patients, 11% in the enoxaparin group and 13% in the heparin group. A decrease in hemoglobin of greater than 2 gm/dL was reported in 24% of patients: 22% in the enoxaparin group and 25% in the heparin group.

Twenty-seven percent (27%) of the enoxaparin and 27% of the heparin patients experienced thrombocytopenia which was classified as mild in most cases and severe in one heparin patient.

Mild thrombocytosis occurred in 69% of the enoxaparin and in 65% of the heparin patients; moderate thrombocytosis occurred in 29% of the enoxaparin and 27% of the heparin patients. Severe thrombocytosis occurred in less than 1% in either treatment group.

Two percent (2%) and 3% of all patients had SGOT and SGPT elevations from 3 to 6 times normal values, elevations of SGOT and AGPT above six times normal occurred only in 1% of all patients. The incidence rates of the elevated serum transaminases were similar in both groups. Elevations of AP occurred at similar rates in the two groups (5% and 8%). Four percent (4%) of all patients had clinically significant elevation of BUN, and less than 1% had creatinine values of clinical significance. The data are summarized in table 16.

Table 16
Summary of the On-Study Incidence of Patients with Clinically Significant Values for Selected Laboratory Parameters
(Appendix B.18)

	Treatment Group		P-value ^a	Overall n(N)
	Enoxaparin n(N)	Calcium heparin n(N)		
All Treated Patients	333(100%)	332(100%)		665(100%)
Hemoglobin:				
< 8 gm/dL	38(11%)	43(13%)	0.636	80(12%)
> 2 gm/dL drop	74(22%)	84(25%)	0.363	158(24%)
Platelets: Thrombocytopenia ^b				
mild	82(25%)	75(23%)	0.524	158(24%)
moderate	8(2%) ^d	12(4%)	0.376	20(3%)
severe	0	1(<1%)	0.499	1(<1%)
Platelets: Thrombocytosis ^c				
mild	231(69%)	216(65%)	0.268	447(67%)
moderate	97(29%)	88(27%)	0.489	185(28%)
severe	2(<1%)	3(<1%)	0.686	5(<1%)
SGOT/AST:				
3-6x Up-Norm	8(2%)	10(3%)	0.203	18(3%)
>6x Up-Norm	0	1(<1%)	0.499	1(<1%)
SGPT/ALT:				
3-6x Up-Norm	9(3%)	13(4%)	0.397	22(3%)
>6x Up-Norm	3(<1%)	8(2%)	0.505	8(1%)
Bilirubin:				
>2 mg/dL	1(<1%)	0	1.000	1(<1%)
Alkaline Phosphatase:				
>2x Up-Norm	16(5%)	28(8%)	0.063	44(7%)
Creatinine:				
≥2 mg/dL	3(<1%)	3(<1%)	1.000	6(<1%)
BUN:				
≥30 mg/dL	10(3%)	17(5%)	0.176	27(4%)

^a P-values from two tailed Fisher's Exact Test comparison vs the heparin dose group.
^b Platelets, thrombocytopenia:
Mild, $100,000/mm^3 \leq x < \text{lower limit of normal}$;
Moderate, $20,000/mm^3 \leq x < 100,000/mm^3$;
Severe, $x < 20,000/mm^3$;
^c Platelets, thrombocytosis:
Mild, upper limit of normal $< x < 600,000/mm^3$;
Moderate, $600,000/mm^3 \leq x < 1,000,000/mm^3$;
Severe, $x \geq 1,000,000/mm^3$;
Up-Norm, upper limit of investigator's normal range.
^d A data entry error was made for the end of study platelet count for patient number 70026 in the enoxaparin treatment group. The erroneous value of $30,000/mm^3$ remains in the database and is included in the total number of patients for whom moderate thrombocytopenia was reported. The correct value from the case report form is $300,000/mm^3$.

PATIENTS WITH MARKEDLY ABNORMAL LABORATORY VALUES

The number of patients in each treatment group exhibiting markedly abnormal laboratory values, as defined in the following table, were:

<u>Laboratory Parameter</u>	<u>Treatment Group</u>	
	<u>Enoxaparin</u>	<u>Heparin</u>
	n	n
Hemoglobin < 7 gm/dL	6	9
Platelets = or < 100.000/ mmc	8	13
Platelets = or > 1.000.000/mmc	2	3
Bilirubin > 2 mg/dL	2	1
Alkaline Phosphatase > 300 IU/L	8	13
SGOT/AST > 6x upper limit of normal	0	1
SGPT/ALT > 6x upper limit of normal	3	5
BUN = or > 30 mg/dL	23	30
Creatinine = or > 2 mg/dL	6	7

Most of the abnormalities were attributable to major surgery. The effect of heparin on transaminases and on platelets had been described, the effect of enoxaparin on transaminases had been observed previously; no unexpected abnormalities were encountered.

Eight (8) patients in the enoxaparin group had platelet counts below 100.000/mm³; the lowest count being 64.000/mm³ on day 11 of study. Thirteen patients in the heparin group had platelet counts below 100/mm³; in three of them the lowest counts were 18.000, 28.000 and 34.000/mm³ at day 9, 8 and end of study respectively. The platelet counts had stabilized or improved by the end of study in all thrombocytopenic patients.

NON-LABORATORY EVALUATION-VITAL SIGNS

No clinically significant changes in mean values for systolic and diastolic blood pressure or pulse rate were observed during the studies. The mean changes from baseline were similar for both treatment groups.

SUMMARY AND CONCLUSIONS

A total of 669 patients were included in this study: 335 were randomized to enoxaparin (333 treated: 236 evaluable) and 334 to heparin (332 treated: 250 evaluable).

The results of the study were published by M.N.Levine et al: Prevention of DVT after elective hip surgery. - A randomized trial comparing LMWH with UH. Ann.Int. Med. 1991; 114:545-551.

Three investigators from 3 Canadian centers had participated in a previous study, study ENO 884, a pivotal efficacy study for the present NDA. Although these two studies are different in design (ENO 884 assesses the effect of enoxaparin compared to placebo and PK 523 compares enoxaparin to heparin), they fail to fulfill the requirement of independence.

Prophylaxis with low-dose heparin is an approved regimen for the prevention of DVT and PE following high risk general surgery. Although effective in orthopedic surgery, similar prophylaxis with low-dose heparin is not approved for this indication, nor it is widely accepted because of the concern about excessive perioperative bleeding caused by the anticoagulant therapy. Moreover, the post-operative administration of heparin in the attempt to reduce perioperative bleeding has not been investigated. Thus, in study PK 523, enoxaparin was compared to a non-approved, untested regimen of prophylaxis of DVT in elective orthopedic surgery with sc heparin 7500 U q12h. Protocol PK 523 was initially designed based on: 1) the hypothesis that the incidence of DVT would be 20% in the heparin group and that it would be reduced to 10% in the enoxaparin, and 2) that this hypothesis could be demonstrated by entering 195 patients in each group ($\alpha=0.05$, two-tailed, and $\beta=0.20$). In the course of the study, in order to avoid Type II error, the sample size had to be increased to 520 to have a power of 90% for true rates of DVT of 20% and 10%. Further increase of sample size become necessary to maintain the 90% power because of inadequacy of non-invasive vascular tests, rate of VG of 80% and patients exclusions.

The results of the study failed to show superiority of enoxaparin compared to heparin or the anticipated reduction of post-operative DVT. In four of the five centers participating in the study, enoxaparin was as effective as heparin in preventing DVT in patients undergoing elective hip replacement surgery. In one center, heparin appeared to be superior to enoxaparin, however, the difference was not statistically significant and the center had the smallest number of patients. There is no evidence that the enrollment of patients in this center was prematurely discontinued.

The overall results of the study show that both enoxaparin and heparin regimens effectively reduce the risk of DVT and, particularly, the risk associated with proximal deep veins thrombosis, given the reported incidence of DVT in the range of 40%-60% in patients undergoing elective hip replacement in the absence of surveillance or without prophylactic antithrombotic therapy.

Pulmonary embolization occurred in two patients treated with heparin and in none of the patients receiving enoxaparin, however, the total number of patients is not large enough to permit statistical conclusions.

Enoxaparin appeared to have some safety advantages over heparin with statistically significantly less overall bleeding. The incidence of major and minor bleeding was 5% in the enoxaparin group and 9% in the heparin group ($p=0.0375$). Study treatment had to be discontinued due to excessive bleeding in 6 patients on heparin compared to 3 on enoxaparin. However, the incidence of severe bleeding and the transfusion requirements were similar in the two treatment groups.

Skin rash was reported in 9% of patients in the enoxaparin group compared to 5% in the heparin group ($p=0.021$). The significance of this finding is unclear, as no skin rash was reported in the enoxaparin group in study ENO 884 and equal incidence of about 7% was reported for each of the three groups (heparin 5000U q8h, enoxaparin 30 mg q12h and enoxaparin 40 mg QD) in study PK 525. Severe thrombocytopenia occurred only in the heparin-treated group. At present, it is unclear whether the low molecular weight heparins are less immunogenic, thus, less likely to stimulate the production of heparin antibodies and/or less likely to cross-reacting with preformed heparin antibodies. It is possible, however, that the lower incidence of heparin-induced thrombocytopenia associated with enoxaparin administration is due mainly to the limited exposure to this new compound compared to wide-spread use of unfractionated heparin. Whether this difference will persist after repeated administration of enoxaparin remains to be seen.

STUDY NUMBER: PK525

TITLE

Multiple-dose, open-label clinical trial of the safety and efficacy of Enoxaparin versus Heparin for the prevention of post-operative DVT following total hip replacement surgery.

INVESTIGATORS:

The study was performed by 32 investigators in the US. The investigators that enrolled more than 10 patients are listed below:

NDA VOLUMES: 43-45; 2.17

<u>INVESTIGATOR</u>	<u>STUDY CENTERS</u>	<u>PATIENTS TREATED</u>
R.J. Davis, M.D.	Baptist Med.Ctr. Columbia SC	72
H.C. Kwaan, M.D.	Northwestern Mem. H. Chicago IL	24
W.D. Haire, M.D.	Univ. Nebraska, Omaha, NE	11
L.P. Brady, M.D.	Florida H. Orlando, FL	52
A.J. Comerota, M.D.	Temple U. H., Philadelphia, PA.	26
R.W. Geckler, M.D.	Mercy Med.Ctr. Baltimore, MD	60
W.J. Howard, M.D.	Washington H.Ct. Washington, DC	12
J.H. Joist, M.D.	St.Mary's Health Ctr, St Louis, MS	11
T. Young, M.D.	Medical Col. Georgia, Augusta, GA	23
J.D. Blaha, M.D.	W.Virginia Univ. Morgantown, WV	25
T. Whitsett, M.D.	V.A. Med. Ctr. Oklahoma City, OK	17
C. Colwell, M.D.	Scripps Clin/Res. Fnd., La Jolla, CA	32
N.Economides, M.D.	Baptist Mem. H. Memphis, TN	46
A.Trobridge, M.D.	Scott & White Clinic, Temple, TX	61
W. Davison, M.D.	White River Junct. V.A.M.C., VT	14
L. Aledort, M.D.	Mt.Sinai Hospital, New York, NY	15
R. Gustilo, M.D.	Metrop.M.Sinai M.Ctr. Minneapolis, MN	26
J. Finley, M.D.	Lincoln Gen. H., Ruston, LA	12
R.Zimmerman, M.D.	Emanuel H.& Health Ctr; Portland, OR	11

IDENTITY OF TEST MATERIAL

Enoxaparin, 30 mg: lots CB 3419, CB 3645, CB 4372
Enoxaparin, 40 mg: Lots CB 3425, CB 3868, CB 3974
Tubex[®]R Heparin, 5000 U (Wyeth-Ayerst): 4880239, 4890441, 490047

STUDY OBJECTIVE

The objective of the study was to compare the efficacy and safety of enoxaparin administered subcutaneously for up to 7 days at doses of 40 mg once daily or 30 mg q12h (total daily dose 60 mg)

to that of unfractionated heparin 500 U sc q8h (total daily dose 15,000 U) for the prevention of DVT in patients undergoing elective hip replacement.

STUDY DESIGN

This study was randomized, open-label, parallel-group, multicenter. The patients were randomized to receive either enoxaparin at the dose of 40 mg once daily, enoxaparin at the dose of 30 mg q12h, or heparin at the dose of 5000 U q8h for a period of up to 7 days starting within the first 24 hours after surgery.

The primary efficacy assessment for DVT was bilateral VG at day 7, or earlier if clinically indicated. Additional efficacy assessment was performed with non-invasive vascular procedures represented by IPG, Doppler sonography or ultrasonography obtained at day 4 and 7 or earlier if necessary, and by evaluation of clinical signs or symptoms of DVT.

Safety evaluation was obtained daily during treatment, at the end or discontinuation of the treatment and within 14 days after discontinuation of study treatment.

SELECTION OF STUDY POPULATION

ELIGIBILITY CRITERIA

Male and female patients, 40 years of age or older, scheduled for elective hip replacement (placement of prosthetic device in the intramedullary space of femur, with or without reconstruction of acetabulum), with negative noninvasive vascular examination for DVT within 14 days prior to surgery and consenting to the study were eligible for the study.

EXCLUSION CRITERIA

Female patients of child-bearing potentials, patients with presurgical diagnosis of DVT by noninvasive techniques, history of surgery of the ipsilateral hip within the preceding year, history of DVT, bleeding disorder, heparin-induced thrombocytopenia, surgery to eyes, spinal cord, or CNS within three months, active PUD, hypertension, uncontrolled asthma, allergy to heparin, allergy to fish, porcine products, sulfites, iodine or contrast medias, regular use of ASA or other NSAID for four days before surgery, current drugs or alcohol abuse, treatment with investigational drugs during the previous 4 weeks,

any disease or medication that may interfere with the effect of enoxaparin, clinically significant abnormalities of physical examination, chest X-ray, ECG or laboratory tests were not eligible for the study.

CONCOMITANT MEDICATIONS

Patients requiring medications that may interfere with the kinetic, action or efficacy of enoxaparin were discontinued from the study. The concomitant use of heparin was allowed only for maintenance of patency of intravenous lines.

All medications allowed, including blood transfusions, administered from 7 days before initiation of the study and through the study period up to the follow-up evaluation were recorded in the patient's CRF with date, dosage, indication, etc.

REASONS FOR DISCONTINUATION OF PATIENTS FROM THE STUDY

Patients were discontinued from the study at their request, at the decision of the investigator and sponsor, if they required medications that interfered with the evaluation of enoxaparin (ASA, NSAID, dextran, warfarin and pneumatic compression devices), or if they experienced adverse experiences or treatment failure (development of DVT during treatment). The reason for withdrawal and any efficacy data obtained were recorded in the CRF.

DOSING SCHEDULE

Patients were assigned to one of the three regimens according to a sponsor-supplied randomization code. Two doses of enoxaparin were studied: 40 mg QD and 30 mg q12h; the heparin dosage was 5,000 IU q8h. No dosage adjustments were allowed. All doses were administered by subcutaneous injection in the abdominal area. The first dose of study medication was given within 24 hours from surgery, provided that hemostasis had been achieved. Treatment was continued for 7 days unless the patient was discharged earlier or discontinued from the study.

EVALUATION AND SCHEDULING

The study procedures and study schedule are outlined in table 1

TABLE 1
STUDY SCHEMATIC - OVERVIEW

Evaluation/Procedure	Prior to Surgery	Upon Admission	Paraldehyde Interval Calendar/Treatment Day							End of Study	Follow Up	
			1	2	3	4	5	6	7			
Informed Consent	X											
Complete Medical History	X										X	X
Complete Physical Examination	X										X	X
12-Lead ECG	X											
Chest X-Ray	X											
Interim History		X										
Brief Physical Examination		X										
Biochemistry and Urinalysis	X										X	X
Hematology and Coagulation	X										X	X
SGOT, SGPT, and Total Bilirubin	X										X	X
Noninvasive Vascular Examination	X										X	X
Vital Signs	X										X	X
Anti-Xa, Anti-IIa, and Fibrinolytic-A Levels	X										X	X
Assessment of Operative Sites											X	X
Bleeding Assessment											X	X
Adverse Experience Evaluation											X	X
Dosing											X	X
Bilateral Venography											X	X
Concomitant Medications											X	X

1 Up to 14 days prior to surgery.
 2 If complete history and physical examination were performed more than 48 hours prior to surgery.
 3 Day 1 was the first dosing day; the next calendar day was Day 2.
 4 Only if results of chest X-ray done within the preceding six months were not available.
 5 Immediately prior to first dose of study drug on a dosing day.
 6 Data were collected from patients enrolled after March 1990 and are located in the CRFs and CRF tabulations.
 7 Several techniques were permitted, but each center was to select one technique to be used for all patients.
 8 At designated centers only; plasma samples to be obtained 3 hours after first daily dose.
 9 Within 24 hours of last dose of study medication.

EFFICACY PROCEDURES

EVALUATION FOR DEEP VEIN THROMBOSIS BY VENOGRAM

Venography (VG) represented the primary assessment of DVT. VG were to be performed within 24 hours from last dose of study medication.

VG were read at the study site by two qualified physicians. In case of disagreement in the reading of the VG, this would be sent to a study-blinded independent panel specialized in the diagnosis of DVT. The panel was headed by Jack Hish, M.D. in Hamilton, Ontario. Dr. Hirsh had participated in studies ENO 884 and PK 523 as investigator. Dr. Hirsh's role in the present study was, however, limited to heading the independent panel who blindly interpreted the venogram films in cases of disagreement between the two radiologists at the study site.

The results of the venograms were recorded separately for the operated and the unoperated limbs as "positive" if DVT was present in either limb, "negative" if no DVT was present in either limb, "inadequate" if technically inadequate, if a positive diagnosis could not be excluded, or if only a unilateral negative VG was available. Positive VG were classified as proximal or distal.

NONINVASIVE VASCULAR EVALUATION FOR DVT

The noninvasive assessment of DVT was performed at each site using their method of choice: B-mode and duplex ultrasonography, impedance and strain gauge pletismography, Doppler sonography. The tests were performed according to standard procedure in use at each site and the same method was to be used for all patients at each site. Noninvasive tests were performed at day 4 and at the end of the study, or earlier if clinically indicated.

CLINICAL EVALUATION

Evaluation of clinical signs and symptoms of DVT was performed blindly by the sponsor at the end of the study from review of CRFs. Adverse events, contra-active medications were reviewed to corroborate the diagnosis of DVT.

SAFETY PROCEDURES

LABORATORY TESTS

The routine laboratory tests were performed at each study site according to standard procedures. Special coagulation tests (anti-Xa, anti-IIa, FPA) were performed at designated centers. The following tests were performed:

Hematology: Complete CBC with WBC differential and platelet count.

Coagulation: PT and APTT. At selected centers, daily measurements of anti-Xa, anti-IIa activity and FPA levels were obtained.

Serum Biochemistry: SMA 24

Urinalysis: including microscopic examination.

NONLABORATORY PROCEDURES

BLEEDING ASSESSMENT

The site and source of bleeding were identified. Any clinical events associated with the bleeding and any actions taken as result of bleeding were reported. Bleeding was identified as operative, nonoperative or unknown.

Bleeding was classified as minor or major. Major bleeding was overt and resulted in death or serious or life-threatening clinical events, or it was retroperitoneal, intracranial or gastrointestinal and was associated with the postoperative transfusion of more than 2 units of blood or with a drop in hemoglobin of more than 2 gm/dL.

Operative site wound hematomas were graded and recorded as: absent, grade 0 (no unusual hematoma), grade I (hemorrhagic wound), grade II (swollen wound with delayed removal of stitches), grade III (partial dehiscence of the wound or wound drainage), grade IV (requiring surgery). However, no formal analysis of surgical wound hematomas was performed. A blinded retrospective reassessment of the bleeding was made by the sponsor at the end of the study using a standardized set of criteria.

The combination of clinical data and quantitative assessment of blood loss were used to classify the bleeding into major or minor categories. The definition of major bleeding was modified to

exclude transfusion of autologous blood and to increase the minimum transfusion requirement to three units.

The time to bleeding was the first postoperative day when the bleeding was reported or the drop in hemoglobin occurred or the transfusion of more than 2 units was required.

Wound drainage was classified as significant when it exceeded 1000 mL throughout the study.

VITAL SIGNS

Vital signs included blood pressure, pulse rate, respiratory rate and temperature.

ADVERSE EVENTS

Adverse events were defined as untoward events either observed by the investigator or reported by the patient during the study period. All events were recorded with date of onset and cessation, frequency, duration, severity (mild, moderate, severe) action taken (change of dose, discontinuation of medication, use of contr-active treatment) and investigator's assessment of relationship to study medication (probably related, possibly related or unrelated).

CLINICAL MONITORING PROCEDURES

Approval by the IRB and Informed consent were obtained. The study was monitored on a regular basis by the sponsor or by the contract research organization, The Hardardt Group, Clinical Development Associates, P.O. Box 867, Bernardsville, NJ 07924, The ICF and the CRF were compared with the patient's medical record for completeness and accuracy. A safety audit of a subset of CRF and a completeness audit of all CRF were performed by: Bio-Pharm Clinical Services, Inc. Four Valley Square, 512 Township Line Road, Blue Bell, PA 19422.

PACKAGING AND LABELING PROCEDURES

Study medication was supplied in prefilled syringes containing either Enoxaparin 30 mg/0.4 ml (lots CB 3419, CB 3645, CB4372), Enoxaparin 40 mg/0.4 ml (lots CB 3425, CB3868, CB 3974), or heparin 5000 U/0.5 ml (Tubex Heparin, Wyeth-Ayerst, lots 4880239, 4890441, 490047).

The Enoxaparin 30 mg contained 4.6 mg of mannitol to maintain isotonicity, both enoxaparin preparations contained 0.6 mg of

sodium metabisulfite and the heparin preparation contained not more than 5 mg of benzyl alcohol as preservative.

Prepackaged patient kits containing 10 syringes for the Enoxaparin 40 mg qd group, 20 syringes for the Enoxaparin 30 mg bid group and 30 Wyeth Tubex syringes for the Heparin 5000 IU q8h group.

Instructions specified that the entire content of the syringe were to be injected sc in the abdominal area.

STATISTICAL METHODS

PLANNED SAMPLE SIZE AND HOW IT WAS DETERMINED

The sample size was determined from the anticipated incidence of DVT of 12.5% in patients treated with either 40 mg qd or 30 mg bid and of 25% in patients treated with a total daily dose of heparin of 15000 IU. Assuming that 80% of the enrolled patients were evaluable for efficacy, it was determined that approximately 195 patients would be required for each treatment group in order to achieve 80% power using a two-tailed test at a significance level of 0.05 for comparing the treatment groups.

RANDOMIZATION AND PATIENT ASSIGNMENT

Patients were assigned to treatment groups in a 1:1:1 ratio in blocks of 9, using a computerized randomization schedule supplied by the sponsor. Eligible patients were assigned the next number in a sequential ascending fashion from the open-label randomization schedule of 36 patients maintained at each investigator's site. Treatment numbers were assigned either presurgery or postsurgery.

EFFICACY EVALUATION

Definition of efficacy outcome: Efficacy was assessed by the incidence rate of DVT. The diagnosis of DVT by venogram had absolute priority. A "positive" VG was defined by a positive finding in either the operation or non-operative limb or both limbs. A "negative" VG was defined as a negative bilateral VG. An "inadequate" VG was one in which the diagnosis of DVT could not be made nor excluded. A unilateral negative VG was classified as inadequate.

Diagnosis of DVT by either a positive result of the ¹²⁵I-fibrinogen scan or IPG had second priority. Clinical evidence of DVT was defined as either a positive result of fibrinogen scan or

IPG or other clinical evidence such as PE or administration of anticoagulant therapy for DVT.

All treated patients who had received any study medication and had had at least one clinical evaluation were classified into one of the following outcome groups:

Outcome Group	-----Clinical Evidence of DVT-----		
	Venogram	Other Vascular Procedures <u>¹²⁵I-Fibrinogen or IPG</u>	Other Clinical Findings
1	+	All	All
2	-	All	All
3	IN/ND	+	All
4	IN/ND	-, IN/ND	+
5	IN/ND	-, IN/ND	Not +

"IN/ND" indicates that the venogram was inadequate or not done.

"All" indicates all situations (+, -, IN/ND)

- Group 1 included patients with positive VG (unilateral or bilateral), regardless of the results of the other evaluations.

- Group 2 included patients with negative bilateral VG, regardless of the results of the other evaluations.

- Groups 3 and 4 included patients with inadequate VG, without bilateral VG in whom the diagnosis of DVT was made by noninvasive tests or other clinical evidence.

- Group 5 included patients in whom VG was inadequate or not done, noninvasive vascular tests were negative, inadequate or not done and in whom there was no clinical evidence of DVT.

Patients in Groups 1, 3 and 4 were classified as treatment failure; patients in Groups 4 and 5 as non failures.

STUDY POPULATION

The efficacy analysis for ALL RANDOMIZED PATIENTS included all patients who were randomized and received medication, all randomized patients who never received medication and had no efficacy evaluation and all randomized patients who received treatment but had no efficacy data.

The efficacy analysis for ALL TREATED PATIENTS WITH EFFICACY DATA included all treated patients with at least one post-treatment efficacy evaluation.

The efficacy evaluation for all EVALUABLE PATIENTS included all patients who received study medication, had at least one post-treatment evaluation and for whom none of the following conditions occurred during the study:

- Presurgical noninvasive vascular examination positive was for DVT.
- Patients had undergone surgery of ipsilateral hip or knee within one month before hip surgery.
- Patients underwent surgery for other than hip replacement or revision, e.g. underwent surgery for hip fracture.
- Patients had received more than 1500 U/day of heparin within four days prior to or during administration of study medication.
- Patients received more than one dose of Warfarin within 4 days prior to study or during study drug administration.
- Patients received the first dose of study medication later than 24 hours after surgery
- Patients received insufficient therapy (less than 75% of dose or less than 4 days of therapy)
- VG was not performed or bilateral VG not definitive or definitive VG not performed within 4 days or less after final dose of study medication.

UNEVALUABLE PATIENTS in each treatment group included the complement of the evaluable patients with respect to the all treated patient population.

EFFICACY ANALYSES

INTENT- TO-TREAT ANALYSES/ALL TREATED PATIENTS WITH EFFICACY DATA

For this patient population, the efficacy endpoints (incidence of treatment failure) was defined as follows:

Groups 1, 3, 4 (positive)
Groups 1, 3, 4 (positive + Groups 2, 5 (negative))

For this patient population, the incidence of DVT was also summarized within the subsets of type of surgery (primary hip replacement or revision), type of anesthesia (regional/epidural or inhalation/IV), use of surgical cement, use of graduated compression stockings (GCS), sex, age and race.

ALL RANDOMIZED PATIENTS

Only three patients from 610 randomized patients never received treatment. The impact of this small number on the all treated group with efficacy data was negligible.

EVALUABLE PATIENTS EFFICACY ANALYSIS

All evaluable patients had definitive VG, thus, the efficacy endpoint (treatment failure) was defined as:

Group 1 (positive) + Group 2 (negative) + Group 3 (noninvasive vascular evidence of DVT) and 4 (clinical evidence of DVT) were not considered in the evaluation of efficacy for the evaluable patients.

Within the population of evaluable patients, the incidence of DVT was also summarized for the subsets of type of surgery, type of anesthesia, use of surgical cement, use of GCS, sex, age and race.

SAFETY EVALUATION

PATIENT POPULATION: All patients who received at least one dose of study medication were included in the safety evaluation.

SAFETY ANALYSES: The primary safety endpoints determined for each of the treatment groups were:

- Incidence of death, premature discontinuation from treatment, adverse events (according to severity and relationship to study medication)
- incidence of patients with major or minor bleeding episodes and day of onset of total units of blood transfused on study (aside from operative and recovery room units) and the incidence of 0, 1-2, and more than 2 units of blood transfused on study.
- the incidence of abnormal values of clinical concern for selected laboratory tests from day 1 through the end of the study, including:

Platelets: Thrombocytopenia -
mild: equal or greater than $1 \times 10^5/\text{mm}^3$ and less than the investigator's lower limit of normal;
moderate: $1 \times 10^5/\text{mm}^3$; greater than $2 \times 10^4/\text{mm}^3$ and lower than $2 \times 10^4/\text{mm}^3$
severe: lower than $2 \times 10^4/\text{mm}^3$

Platelets: Thrombocytosis -
mild: greater than the investigator's upper limit of normal and lower than $6 \times 10^5/\text{mm}^3$;
moderate: higher than $6 \times 10^5/\text{mm}^3$ and lower than $1 \times 10^6/\text{mm}^3$;
severe: higher than $1 \times 10^6/\text{mm}^3$

Hemoglobin: Values lower than 8 gm/dL or a decrease equal or greater than 2 gm/dL from baseline.
SGOT and SGPT: 3- to 6-fold increase and more than 6-fold higher than the investigator's upper limit of normal.

Total Bilirubin: Values greater than 2 mg/dL.

Alkaline Phosphatase: Any value greater than 2-fold higher than the investigator's upper limits of normal.

Creatinine: Any value greater than 2 mg/dL.

BUN: Any value greater than 30 mg/dL.

- The mean changes from baseline for hematology (post-surgery, pre-study drug) laboratory tests at day 4, day 7, end of study and follow-up and for serum chemistry (pre-surgery) laboratory tests at end of study and follow-up.
- Shifts in the percentage of patients with hematology and chemistry laboratory values outside the normal range at the end of the study relative to baseline.
- The mean change from pre-surgery baseline for systolic and diastolic blood pressure and pulse rate and temperature at day 4, day 7, end of study and follow-up.

PHARMACOKINETIC ANALYSES

FIBRINOPEPTIDE-A, ANTI-Xa AND ANTI-IIa ACTIVITY

The assay of Fibrinopeptide A was found to be unreliable and the analysis of the data was not performed. The failure was attributed to inadequate collection and processing of specimens. Plasma levels of anti-IIa and anti-Xa activity were obtained at selected centers.

STATISTICAL ANALYSIS

Statistical analyses were obtained from SAS Version 5.18.²².

Demographic and Baseline Characteristics

The three treatment groups were compared at baseline for categorical variables (gender) and other demographic variables (age, weight, BP, medical and surgical histories, transfusions) using descriptive statistics. Each variable was summarized for all treated and all evaluable patients. All randomized patients and all unevaluable patients were summarized for demographic, surgical and transfusion data.

Efficacy Analyses

The endpoint was represented by development of DVT (treatment failure). The incidence of DVT was analyzed for both all treated patients with efficacy data and for the evaluable patients.. Justification for pooling across centers was investigated using a two-way logistic regression model with factors of treatment group, center, and treatment-by-center interaction. The results of the DVT findings were also summarized by investigator to provide a qualitative assessment of the presence of interactions. A two-way logistic regression model including factors for treatment group and center was used to compare the treatments. These analyses were carried out using the SAS procedure CATMOD, the CONTRAST statement was used to compare the treatment groups pairwise. Since it was expected that the two enoxaparin doses would be superior to heparin, the pairwise comparison of the two enoxaparin doses to the heparin dose were considered to be the primary treatment comparison.

A Bonferroni-adjusted significance level of 2.5% was used for each of the primary treatment comparisons (all p-values multiplied by 2). Statistical significance corresponded to p-value equal or lower than 5%, after adjustment for these comparisons. Comparison between the two enoxaparin doses was based on a 5% significance level. All tests were two-sided. Approximate 95% confidence intervals for the odds ratio of treatment failure between each pair of treatment groups were computed. The odds of a treatment failure are defined as estimated incidence rate of treatment failure/estimated incidence rate of treatment success.

The incidence rate of treatment failure by treatment group was summarized in patients subpopulations by demographic characteristics, type of surgery, type of anesthesia, use of surgical cement, use of graduated compression stockings (GCS).

Adverse Events

The COSTART dictionary was used to classify the adverse events. Events for a particular COSTART occurring more than once were counted only once. Repeated reporting of the same adverse event in a patient was reported only as the most severe. Each type of event occurring within a body system was counted.

Adverse events incidence rates (all events excluding those unrelated to study medication) were summarized by treatment group. The adverse events were summarized for each body system and overall. Overall indices reflected the number of patients reporting any adverse event.

Fisher's exact two-sided test was performed for the statistical comparison of the heparin group with the two enoxaparin groups for total adverse events in each body system, for each event with an incidence of 5% or higher in a treatment group for all adverse events, and for each event with an incidence of 2% or higher in a treatment group for all adverse events excluding those unrelated to study medication.

These analyses were not initially planned; they were included in the statistical evaluation of the study following a pre-NDA meeting with the FDA in March 1991. The p-values of these analyses are useful only to flag certain events and do not identify statistical significance.

Bleeding Assessment

The overall incidence rates of patients with major or minor bleeding at operative, non-operative or unknown sites during the study period were summarized for each treatment group. Treatment comparisons were based on the overall incidence rates of patients with major bleeding and of patients with major or minor bleeding. A logistic regression model with factors for center and treatment effect was used.

Laboratory Data

Mean changes from baseline for hematology parameters were determined on Day 4, day 7, end of study and follow-up, and at the end of the study and at follow-up for all serum chemistry laboratory parameters. The mean changes from pooled parameters across investigators were summarized for the three treatment groups using descriptive statistics. No formal statistical analyses were performed for these laboratory data.

Fisher's exact test was performed for the statistical comparison between the heparin group and the two enoxaparin groups for selected laboratory values of clinical concern.

Shift tables were generated that summarize the distribution (below, within, above normal range) of baseline and end of study hematology and chemistry values.

Vital Signs

The mean changes from baseline for vital signs combined across investigators on day 4, day 7, at end of study and at follow-up were summarized for the three treatment groups. No formal statistical test of hypothesis was performed.

PROTOCOL AMENDMENTS

The protocol was amended on four separate occasions (6/15/1988; 11/15/1988; 6/15/89; 3/9/1990).

The protocol, as summarized, includes all the amendments.

PROTOCOL VARIATIONS

Patients with the following protocol deviations were included in the study and considered evaluable for efficacy because the variations were not believed to have sufficient impact on the outcome of the DVT analysis;

- patients 37 years of age or older (protocol age=40)
- any type of hip replacement was accepted for eligibility.
- presurgical exclusion of DVT by any noninvasive vascular examination was permitted, patients with positive results were, however, excluded.
- surgery on the ipsilateral hip within three months was permitted.
- use of NSAID was permitted during the four days before surgery and concomitant with study medication throughout the study.
- Two or more doses of warfarin were required to exclude a patient from evaluability.
- infrequent administration of up to 1500 U of heparin throughout the study was permitted.

RESULTS

PATIENT DISPOSITION/ACCOUNTABILITY

Six hundred ten (610) patients were randomized to one of three treatments: 205 to enoxaparin 40 mg qd, 195 to enoxaparin 30 mg q12h and 210 to heparin 5000 U q8h. Only three patients among the 610 (two enoxaparin 40 mg qd and one heparin 5000 U q8h) were randomized but received no study medication. One patient had intercurrent illness and did not have surgery, one patient experienced bleeding during surgery and one patient received a contraindicated medication.

The disposition of the 607 randomized and treated patients is shown in the following table.

<u>Disposition</u>	<u>Heparin</u>		<u>Enoxaparin</u>		<u>Total</u>
	<u>5000 U q8h</u>	<u>40 mg OD</u>	<u>30 mg q12h</u>		
	n (%)	n (%)	n (%)	n (%)	
<u>Patients Randomized:</u>	210	205	195	610	
<u>Patients Treated:</u>	209(100%)	203(100%)	195(100%)	607(100%)	
<u>Completed Patients:</u>	150(72%)	144(71%)	137(70%)	431(71%)	
<u>Evaluable</u>	138(92%)	130(90%)	131(96%)	399(93%)	
<u>Not Evaluable</u>	12(8%)	14(10%)	6(4%)	32(7%)	
<u>Discontinued Patients:</u>	59(28%)	59(29%)	58(30%)	176(29%)	
<u>Evaluable</u>	4(7%)	6(10%)	5(9%)	15(9%)	
<u>Not Evaluable</u>	55(93%)	53(90%)	53(91%)	161(91%)	
<u>Reason for discontinuation:</u>					
<u>Protocol violation</u>	37(18%)	47(23%)	42(22%)	126(21%)	
<u>Adverse Event</u>	12(6%)	5(2%)	7(4%)	24(4%)	
<u>Lost to follow-up</u>	3(1%)	2(<1%)	3(<1%)	8(1%)	
<u>Treatment Failure</u>	0	0	1(<1%)	1(<1%)	
<u>Death</u>	1(<1%)	0	0	1(<1%)	
<u>Other</u>	6(2%)	5(2%)	5(2%)	16(3%)	
<u>Patients Evaluated for Efficacy:</u>					
<u>All randomized</u>	210	205	195	610	
<u>All treated</u>	207(98%)	203(100%)	194(100%)	604(100%)	
<u>Evaluable</u>	142(68%)	136(67%)	136(70%)	414(68%)	
<u>Not Evaluable</u>	67(32%)	67(33%)	59(30%)	193(32%)	
<u>Reasons for Exclusion:</u>					
<u>Inadeq. or No VG</u>	61(29%)	61(30%)	56(29%)	178(29%)	
<u>Insuffic. Therapy</u>	5(2%)	2(<1%)	3(2%)	10(2%)	
<u>Inapprop. Surgery</u>	1(<1%)	3(1%)	0	4(<1%)	
<u>Concomit. Heparin</u>	0	1(<1%)	0	1(<1%)	

DEMOGRAPHICS

In the all three patient populations (randomized, all treated and evaluable patients), the three treatment groups were comparable with respect to patient demographic characteristics.

CONCOMITANT MEDICATIONS

All 607 treated patients received concomitant medications. The most frequently used drugs included opiates and opioids (94%), cephalosporins (91%), laxatives (77%), analgesics and antipyretics, including ASA and NSAID (74%), hematinics (49%), hypnotics and sedatives (46%).

The three treatment groups were comparable for the incidence of use of each of these drugs.

CONCURRENT ILLNESS AND MEDICAL/SURGICAL HISTORIES

473 of the 607 treated patients had other presenting conditions or illnesses. The incidence rates were similar in all three treatment groups.

All of the 607 treated patients had other medical, surgical or orthopedic histories. The data for the all treated patient population are shown in table 5.2.

Table 5.2
Summary of Frequent (>10% Overall) Medical
and Surgical Histories^a
(All Treated Patients)
(Appendices B.4.1 and B.6.2)

Prior History	Heparin		Enoxaparin		Overall
	5000 U q6h n (%)	40 mg QD n (%)	30 mg q12h n (%)	n (%)	
All Treated Patients	209(100%)	203(100%)	195(100%)	607(100%)	
Patients with Positive ^b Medical/Orthopedic/ Surgical History	209(100%)	203(100%)	195(100%)	607(100%)	
Medical History:					
Injury/ Poisoning	32(15%)	29(14%)	33(17%)	94(15%)	
Diseases of the Digestive System	28(13%)	25(12%)	31(16%)	84(14%)	
Diseases of the Circulatory System	24(11%)	18(9%)	24(12%)	66(11%)	
Orthopedic History ^c	209(100%)	203(100%)	195(100%)	607(100%)	
Surgical History:					
Musculoskeletal System	110(53%)	114(56%)	99(51%)	323(53%)	
Digestive System	62(30%)	62(31%)	75(38%)	199(33%)	
Integumentary System	28(13%)	30(15%)	28(14%)	86(14%)	
Gender Related Surgical History ^d :					
All Treated Females	108	104	97	309	
Female Genital Organs	61(56%)	61(59%)	52(54%)	174(56%)	
All Treated Males	101	99	98	298	
Male Genital Organs	16(16%)	12(12%)	14(14%)	42(14%)	

- ^a Patients may have multiple conditions; but each patient was counted only once in the total of patients with a positive history.
- ^b The Medical and Surgical History counts in Appendix B.4.1 do not include orthopedic history as specified in their primary diagnosis.
- ^c Details of orthopedic history can be found in Table 6.1 listed as their primary diagnosis.
- ^d Percents are based on gender-specific column totals (Appendix B.3.2).

PRIMARY DIAGNOSIS AND SURGICAL DATA: The three treatment groups were similar for the incidence of primary diagnosis and surgical data (type of surgery, type of anesthesia, use of surgical cement, duration of surgery, use of GCS, blood loss and transfusion requirement during surgery).

The data for the all treated patient population are shown in table 6.1. The all treated population and the evaluable population were comparable with respect to the primary diagnosis and surgical parameters.

Table 6.1
Summary of Surgery and Transfusion Data
(All Treated Patients)
(Appendix B.6.2)

Surgical Data	Heparin		Enoxaparin		Overall
	5000 U q8h n(%)	40 mg QD n(%)	30 mg q12h n(%)	n(%)	
All Treated Patients:	209(100%)	203(100%)	195(100%)	607(100%)	
Primary Diagnosis:					
Osteoarthritis	154 (74%)	157 (77%)	153 (78%)	464 (76%)	
Avascular Necrosis	26 (12%)	20 (10%)	18 (9%)	64 (11%)	
Rheumatoid Arthritis	9 (4%)	12 (6%)	7 (4%)	28 (5%)	
Hip Fracture/Trauma	10 (5%)	6 (3%)	4 (2%)	20 (3%)	
Congenital Dysplasia	8 (4%)	2 (<1%)	4 (2%)	14 (2%)	
Ankylosing Spondylitis	0	1 (<1%)	0	1 (<1%)	
Osteomyelitis	0	0	1 (<1%)	1 (<1%)	
Psoriatic Arthritis	0	0	1 (<1%)	1 (<1%)	
Chondrolysis	0	1 (<1%)	0	1 (<1%)	
Other	2 (<1%)	4 (2%)	7 (4%)	13 (2%)	
Type of Surgery:					
Primary	181 (87%)	169 (83%)	168 (86%)	518 (85%)	
Total	178 (85%)	166 (82%)	166 (85%)	510 (84%)	
Hemi	1 (<1%)	3 (1%)	1 (<1%)	5 (<1%)	
Not Specified	2 (<1%)	0	1 (<1%)	3 (<1%)	
Revision	28 (13%)	30 (15%)	25 (13%)	83 (14%)	
Total	27 (13%)	28 (14%)	23 (12%)	78 (13%)	
Hemi	0	1 (<1%)	2 (1%)	3 (<1%)	
Not Specified	1 (<1%)	1 (<1%)	0	2 (<1%)	
Unknown	0	4 (2%)	2 (1%)	6 (<1%)	
Type of Anesthesia:					
Regional/epidural ^a	60 (29%)	64 (32%)	56 (29%)	180 (30%)	
Inhalation/IV	125 (60%)	114 (56%)	120 (62%)	359 (59%)	
Not Specified	24 (11%)	25 (12%)	19 (10%)	68 (11%)	

^a These patients may have received IV or inhalation anesthesia as a supplement to the anesthesia listed.

(continued next page)

Table 6.1 (continued)
Summary of Surgery and Transfusion Data (All Treated Patients)
(Appendix B.6.2)

<u>Surgical Data</u>	<u>Heparin</u>		<u>Enoxaparin</u>		<u>Overall</u>
	<u>5000 U q8h</u>		<u>40 mg QD</u>	<u>30 mg q12h</u>	
	n (%)		n (%)	n (%)	n (%)
All Treated Patients:	209(100%)		203(100%)	195(100%)	607(100%)
Use of GCS:					
Yes	67 (32%)		69 (34%)	70 (36%)	206 (34%)
No	118 (56%)		109 (54%)	104 (53%)	331 (55%)
Unknown	24 (11%)		25 (12%)	21 (11%)	70 (12%)
Use of Surgical Cement:					
Yes	60 (29%)		55 (27%)	45 (23%)	160 (26%)
No	149 (71%)		146 (72%)	149 (76%)	444 (73%)
Unknown	0		2 (<1%)	1 (<1%)	3 (<1%)
Type of Blood Transfused ^b :					
Autologous	88 (42%)		89 (44%)	89 (46%)	266 (44%)
Salvage	44 (21%)		52 (26%)	45 (23%)	141 (23%)
Unspecified	24 (11%)		19 (9%)	20 (10%)	63 (10%)
Units of All Blood Transfused ^c :					
Patients Transfused	117 (56%)		108 (53%)	112 (57%)	337 (56%)
Mean Units	1.9		1.9	2.0	1.9
STD	0.95		0.99	1.02	0.98
Range	1-6		1-7	1-7	1-7
Blood Loss (mL):					
N	207 (99%)		202(100%)	195(100%)	604(100%)
Mean	797.4		820.5	792.2	803.5
STD	477.53		587.72	525.20	530.97
Range	100-3500		0-3000	100-4000	0-4000
Duration of Surgery (hrs):					
N	208(100%)		203(100%)	193 (99%)	604(100%)
Mean	2.7		2.6	2.5	2.6
STD	1.27		1.38	1.08	1.25
Range	0.7-9.3		0.5-9.7	0.7-6.3	0.5-9.7

^b Some patients received blood not specified as autologous or salvage (e.g., nonautologous blood); some patients received a combination of autologous, salvage, and/or other blood.

^c Mean, STD, and range include only those patients who received blood transfusions in the operating room and/or recovery room.

EFFICACY RESULTS

CROSS TABULATION OF DVT FINDINGS FROM CONTRAST MEDIA VENOGRAPHY (VG) AND NON-INVASIVE VASCULAR EXAMINATION

411 of the 607 treated patients had both definitive VG and non-invasive vascular examination findings. Cross tabulation of the findings from VG and non-invasive vascular examination are shown in the following table:

<u>Noninvasive Findings</u>		<u>Venography Findings</u>		<u>Findings in Agreement</u>	
	n		n(%)		n
Negative	387	Negative	339(88%)	Negative	339
Positive	24	Positive	48(12%)	Positive	7
-----		-----		-----	
Total	411		411		346

Overall Agreement = 84%
Diagnostic Sensitivity of Noninvasive tests (True positive x100 / True positive + False positive) = 12.7%
Diagnostic Specificity of Noninvasive tests (True negative 100 / True negative + False positive) = 95.2%
Positive Predictive Value (True positive x100 / True positive + False positive) = 29.1%
Negative Predictive Value (True negative x100 / True negative + False negative) = 87.5%

The finding of positive VG in patients with negative non-invasive vascular examination was 20/134 (15%) in the heparin group; 5/122 (4%) in the enoxaparin 30 mg q12h and 23/131 (18%) in the enoxaparin 40 mg qd. The finding of positive VG in patients with positive non-invasive vascular examination was 0/8 (0%) in the heparin group, 3/11 (27%) in the enoxaparin 30 mg q12h group and 4/5 (80%) in the enoxaparin 40 mg qd.

DVT FINDINGS

Three of the 607 treated patients had no efficacy data. Treatment outcome was assessed from VG results in 71% of all treated patients with efficacy data (429/604) and from clinical evidence of DVT in 29% of patients with efficacy data (175/604). The distribution of the DVT findings in the various types of all treated patients is summarized in the following table:

<u>Venography</u>	<u>Heparin</u>	<u>Enoxaparin</u>		<u>Overall</u>
	<u>5000Uq8h</u>	<u>40mgQD</u>	<u>30mgq12h</u>	
All Treated Patients:	209	203	195	607
Patients with Efficacy Data:	207 (100%)	203 (100%)	194 (100%)	604 (100%)
Patients with definitive VG results:	148 (71%)	142 (70%)	139 (72%)	429 (71%)
(1) Positive	21	28	8	57
(2) Negative	127	114	131	372
Patients without definitive VG results:	59 (29%)	61 (30%)	55 (28%)	175 (29%)
Clinical evidence of DVT				
(3) Positive non-invasive Data	3	2	1	6
(4) Other positive Clinical Data	0	0	0	0
(5) No positive clinical Evidence	56	59	54	169

ANALYSIS OF INCIDENCE OF DVT

ALL RANDOMIZED PATIENTS EFFICACY ANALYSIS

The total number of patients who were randomized but not treated (n=3) and of those with no efficacy data (n=3) was too small to influence the outcome of their respective treatment groups in an intent-to-treat analysis.

ALL TREATED PATIENTS (WITH EFFICACY DATA) EFFICACY ANALYSIS

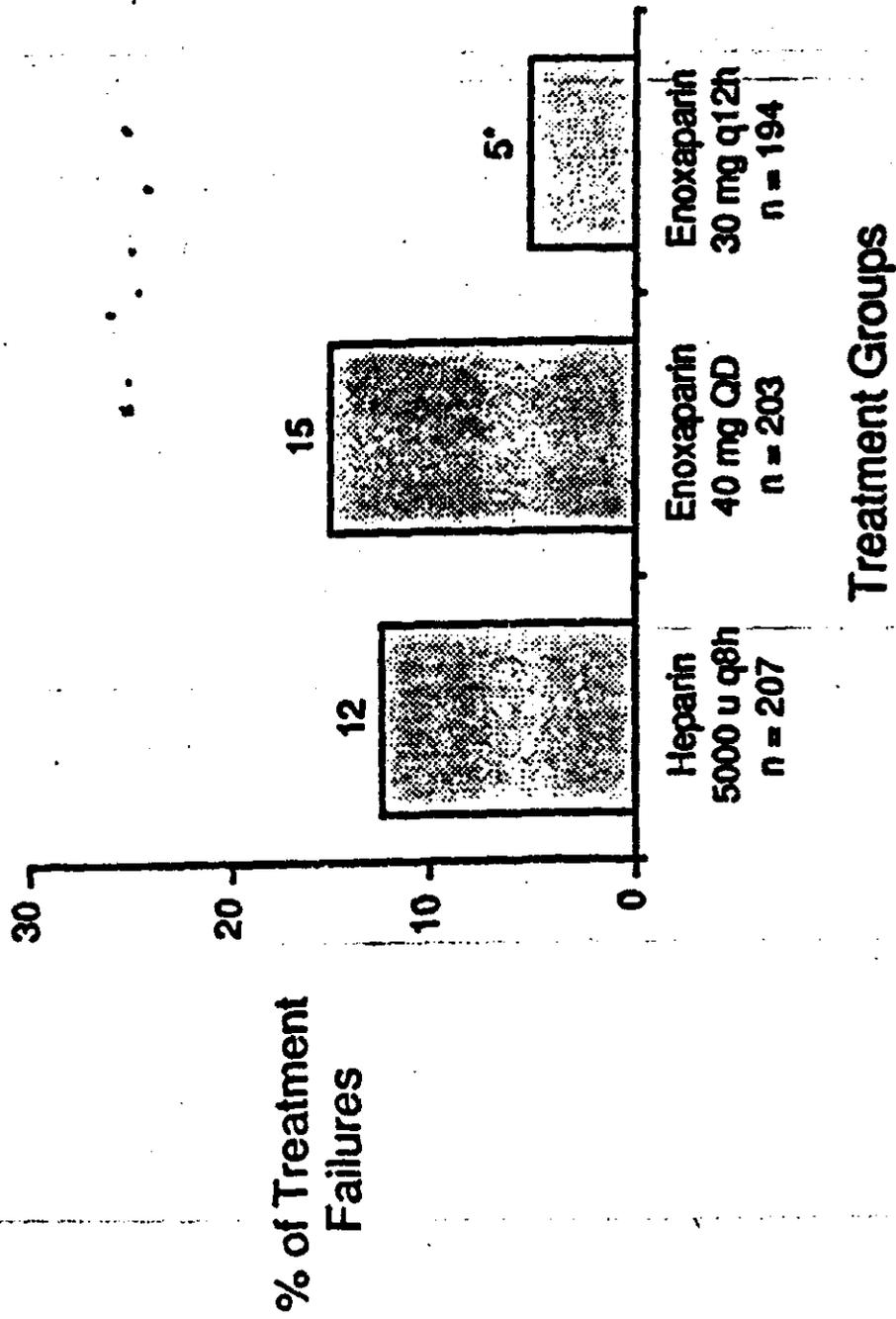
Positive evidence of DVT, determined by either VG or non-invasive vascular examination and other clinical findings, was found in 10% of all treated patients following surgery (outcome groups 1, 3, 4). The incidence of DVT was 15% among patients treated with enoxaparin 40 mg qd; 5% among patients treated with enoxaparin 30 mg q12h, and 12% among patients treated with heparin 5000 U q8h. The summary of the statistical analysis of these results by treatment group for the All Treated Patients is shown in the following table:

<u>Patients Treated</u>	<u>Heparin</u>	<u>Enoxaparin</u>		<u>Overall</u>
	<u>5000Uq8h</u>	<u>40mgQD</u>	<u>30mgq12h</u>	
	n (%)	n (%)	n (%)	n (%)
All Treated Patients	207(100%)	203(100%)	194(100%)	604(100%)
Treatment Failures	24(12%)	30(15%)	9(5%)	63(10%)
Proximal DVT	10(5%)	8(4%)	4(2%)	22(10%)
Distal DVT	11(5%)	20(10%)	4(2%)	35(6%)
Noninvasive Data	3(1%)	2(<1%)	1(<1%)	6(<1%)
Between-Group Comparison of the incidence of treatment failures:				
<u>Treatment Comparison</u>	<u>Odds Ratio</u>	<u>p-value</u>	<u>95% CI for Odds Ratio</u>	
Heparin / Enoxaparin 40 mg QD	0.60	0.2366	(0.29, 1.25)	
Heparin / Enoxaparin 30 mg q12h	2.94	0.0278	(1.10, 7.84)	
Enoxaparin 40 mg QD/ Enoxaparin 30 mg q12h	4.89	0.0002	(2.11, 11.34)	

EVALUABLE PATIENTS EFFICACY ANALYSIS

Fifty-seven (57) of the 414 evaluable patients (14%) had VG confirmed DVT. The incidence of DVT was 21% (28/136) in the enoxaparin 40 mg/qd group; it was 6% (8/136) in the enoxaparin 30 mg/q12h, and 15% (21/142) in the heparin group. The difference between the two enoxaparin groups was statistically significant (p-value=0,0003). The differences between either enoxaparin groups and heparin group were not statistically significant. The summary of statistical results of DVT findings by treatment group for the Evaluable Patients in shown in the following table and in Fig 1A and-1B:.

Figure 1A
Statistical Result of DVT Findings by Treatment Group
Percent of Treated Patients
PK 525



* Statistically significantly favored over the Enoxaparin 40 mg QD and Heparin 5000 u q8h groups at the 5% level

Figure 1B
Statistical Result of DVT Findings by Treatment Group
Confidence Intervals for Odds Ratio of Treatment Failures
All Treated Patients
PK 525

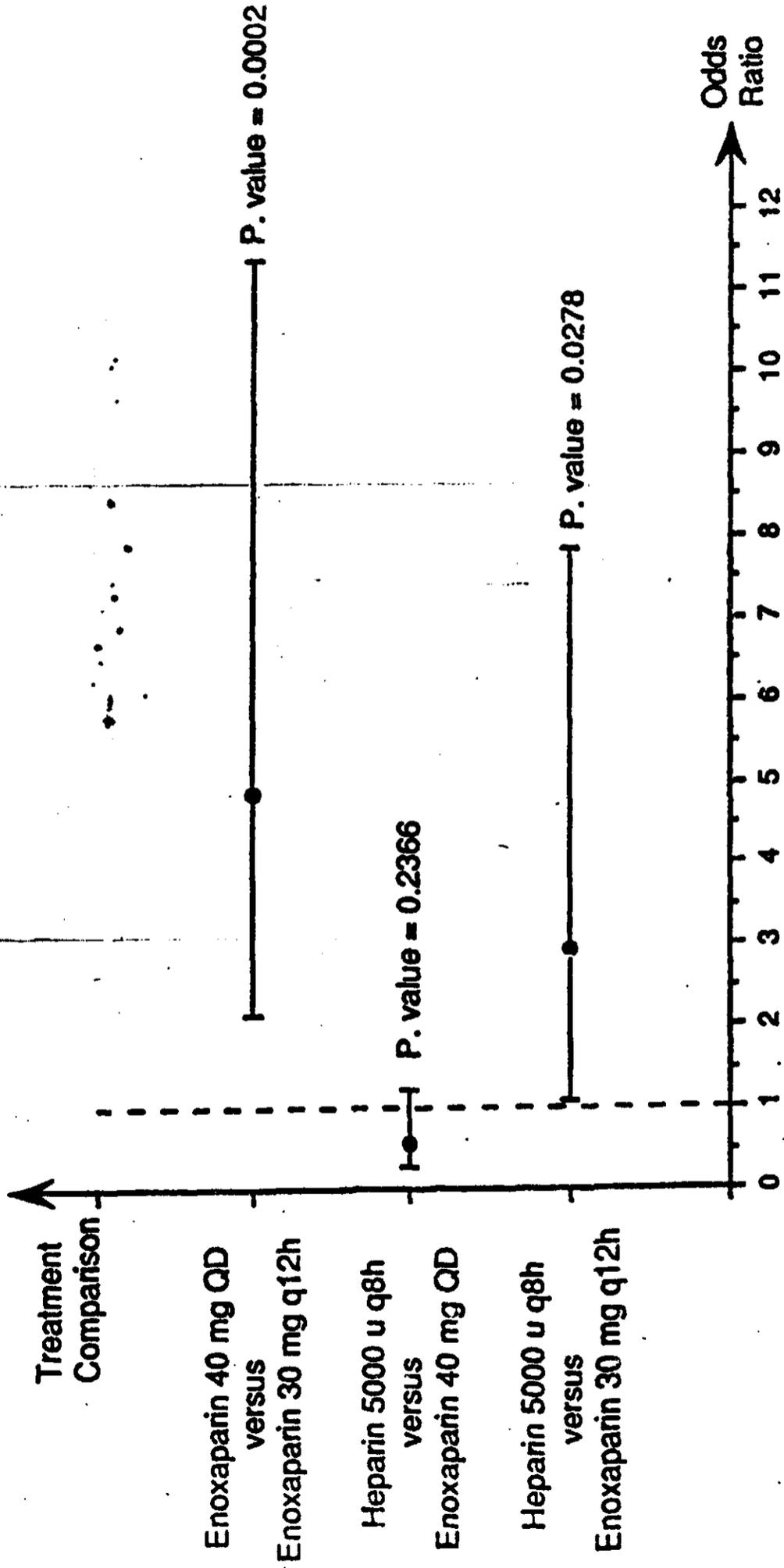
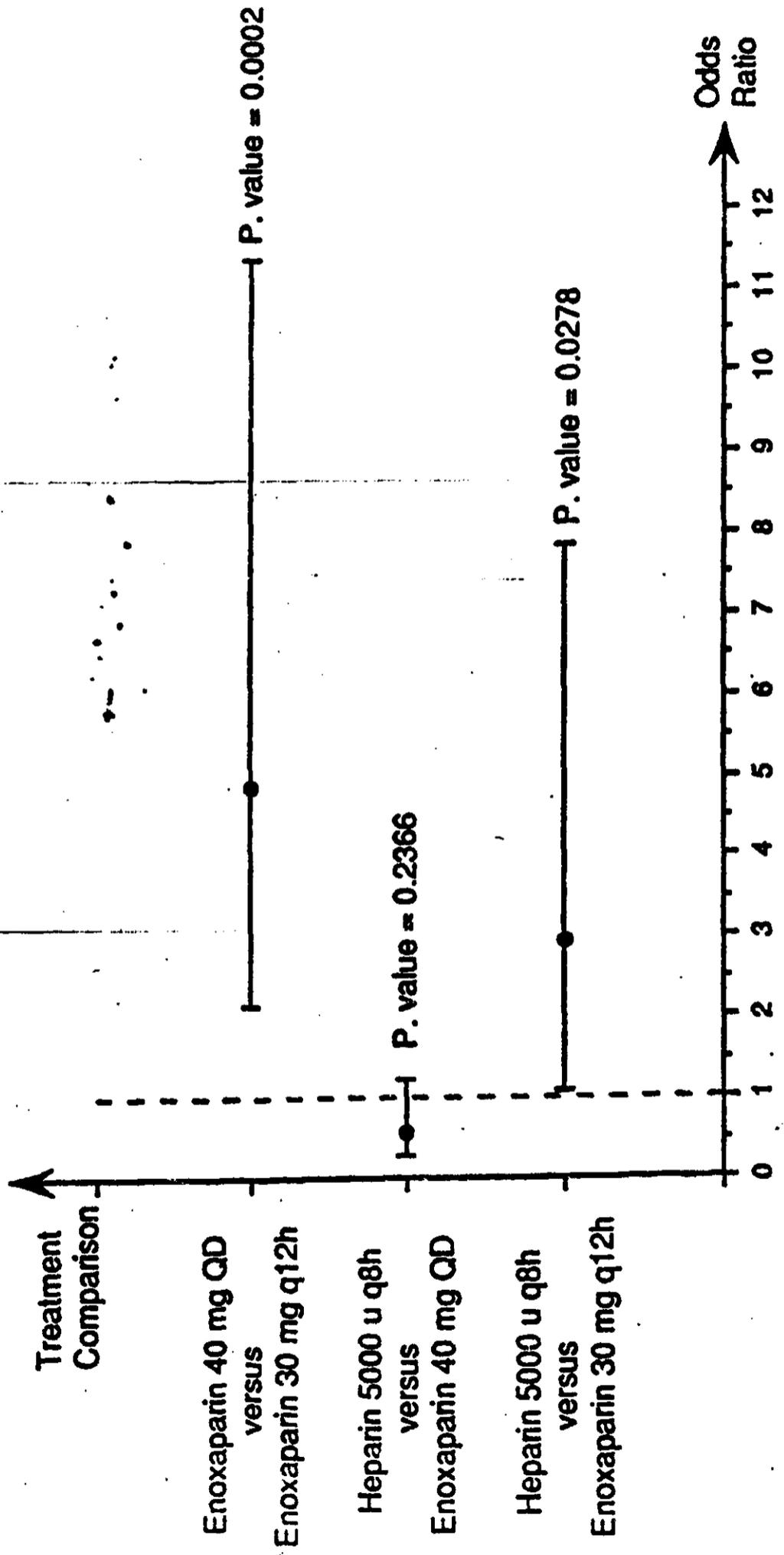


Figure 1B
Statistical Result of DVT Findings by Treatment Group
Confidence Intervals for Odds Ratio of Treatment Failures
All Treated Patients
PK 525



<u>Patients Treated</u>	<u>Heparin</u>	<u>Enoxaparin</u>		<u>Overall</u>
	<u>5000Uq8h</u>	<u>40mgQD</u>	<u>30mgq12h</u>	
	n (%)	n (%)	n (%)	n (%)
Evaluable Patients	142(100%)	136(100%)	136(100%)	414(100%)
Treatment Failures	21(15%)	28(21%)	8(6%)	57(14%)
Proximal DVT	10(7%)	8(6%)	4(3%)	22(5%)
Distal DVT	11(8%)	20(15%)	4(3%)	35(8%)

Between-Group Comparison of the incidence of treatment failures:

<u>Treatment Comparison</u>	<u>Odds Ratio</u>	<u>p-value</u>	<u>95% CI for Odds Ratio</u>
Heparin / Enoxaparin 40 mg QD	0.46	0.0636	(0.20, 1.03)
Heparin / Enoxaparin 30 mg q12h	2.55	0.1030	(0.87, 7.48)
Enoxaparin 40 mg QD/ Enoxaparin 30 mg q12h	5.56	0.0003	(2.21, 14.00)

The time to VG was similar for all groups with all three mean values of 6 day.

The incidence rate of proximal and distal DVT was similar in the heparin and enoxaparin 30 mg/q12h; in the enoxaparin 40 mg/qd group the incidence of proximal DVT was lower (6%) than that of distal DVT (15%).

The majority of patients who failed therapy had DVT in the operative side. In the enoxaparin 30 mg/q12h, 5 out of 8 had DVT in the operated limb; in the enoxaparin 40 mg/qd, 14 out of 28 had DVT in the operated limb, 7 had DVT in the controlateral limb and 7 patients had bilateral DVT. Of the 21 evaluable patients in the heparin group with DVT, 11 had DVT in the operative limb, six had DVT in the unoperated limb, and 4 had bilateral DVT.

SUBSET EFFICACY ANALYSIS FOR ALL TREATED PATIENTS WITH EFFICACY DATA

DEMOGRAPHIC SUBSETS OF ALL TREATED PATIENTS WITH EFFICACY DATA

Among all treated patients and within the three treatment groups, the incidence of DVT was similar between men and women, in patients younger than 65 years of age or older, and among caucasian and blacks.

SURGICAL SUBSETS OF ALL TREATED PATIENTS WITH EFFICACY DATA

The incidence of DVT was comparable among all patients with regard to type of surgery, type of anesthesia, use of surgical cement and use of GCS.

SUBSET EFFICACY ANALYSIS FOR ALL EVALUABLE PATIENTS

DEMOGRAPHIC SUBSETS OF EVALUABLE PATIENTS

The overall incidence of DVT and the incidence of DVT within each treatment group were similar for sex, age and race. In all subsets, the incidence of DVT remained lower in the enoxaparin 30 mg/q12h.

SURGICAL SUBSETS OF ALL EVALUABLE PATIENTS

The incidence of DVT was comparable among all patients with regard to type of surgery and anesthesia, use of cement and of GCS as shown in the following table:

<u>Surgical Subsets</u>	<u>Heparin</u>	<u>Enoxaparin</u>		<u>Overall</u>
	<u>5000Uq8h</u>	<u>40mgQD</u>	<u>30mgq12h</u>	
<u>Type of Surgery:</u>				
Primary	16% (20/125)	19% (22/113)	7% (8/116)	14% (50/354)
Revision	6% (1/17)	30% (6/20)	0% (0/19)	13% (7/56)
<u>Anesthesia:</u>				
Region./Epidur.	10% (4/39)	19% (8/42)	0% (0/33)	11% (12/114)
Inhalation/IV	16% (14/85)	24% (18/76)	8% (7/89)	16% (39/250)
Unspecified	17% (3/18)	11% (2/18)	7% (1/14)	12% (6/50)
<u>Surgical Cement:</u>				
Yes	23% (8/35)	25% (09/36)	0% (0/34)	16% (17/105)
No	12% (13/107)	18% (18/99)	8% (8/102)	13% (39/308)
<u>GCS:</u>				
Yes	17% (08/47)	23% (12/53)	10% (5/50)	17% (25/150)
No	13% (10/77)	22% (14/65)	3% (2/71)	12% (26/213)
Unknown	17% (3/18)	11% (2/18)	7% (1/15)	12% (6/51)

For all subsets, the incidence rates of DVT were lower in the enoxaparin 30 mg q12h than in the other two treatment groups.

SAFETY RESULTS

NUMBER OF PATIENTS EVALUATED AND DURATION OF EXPOSURE

All patients who received at least one dose of study medication were entered in the safety analysis.

STUDY DRUG ADMINISTRATION

The mean duration of treatment for all patients was 6,7 days ± 1.21 days (range 1-12 days, which was similar to the mean values for each treatment group.

N20-164

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The mean number of doses of study medication in each treatment group reflected the dosing regimen for that group.

PATIENTS WITH EPISODES OF BLEEDING DURING THE STUDY

Most major bleeding episodes occurred at the operative site in all three treatment groups. The overall incidence of major bleeding at the operative site was two percent: 3% in the heparin group, 3% in the enoxaparin 30 mg/q12h and <1% in the enoxaparin 40 mg/qd group.

Two episodes of major bleeding at extraoperative sites and 8 at unknown sites occurred among all patients.

PATIENTS WITH EPISODES OF MAJOR BLEEDING

Major bleeding occurred in 24 patients. Major bleeding occurred on the operative day or on the 1 postoperative day in 14/24 patients, on postoperative day 2 in six patients and on postoperative day in 3 patients.

The mean weight (71.0 kg) for the patients with bleeding was slightly lower than that of all treated patients (78.4 kg). Ten additional patients experienced clinically significant wound drainage: three enoxaparin 40 mg/qd patients, three enoxaparin 30 mg/q12h patients and four heparin patients.

The comparison of the incidence of major and minor bleeding and of the site of bleeding among the treatment groups are summarized in tables 10.1 and 10.2.

Table 10.1
Summary of Patients with Episodes of Bleeding
(Appendix B.12.1)

Bleeding	Heparin	Enoxaparin		Overall
	5000 U q8h n (%)	40 mg QD n (%)	30 mg q12h n (%)	
All Treated Patients	209(100%)	203(100%)	195(100%)	607(100%)
Major or Minor	25 (12%)	21(10%)	24(12%)	70(12%)
Major	13(6%)	3(1%)	8(4%)	24(4%)
Minor	12(6%)	18(9%)	16(8%)	46(8%)
None	184(88%)	182(90%)	171(88%)	537(88%)

Between-Group comparison of the Incidence of Patients with Bleeding Episodes:

Comparison	Odds Ratio ^a	p-value	95% Confidence Interval for Odds Ratio
Major or Minor Bleeding Episodes:			
Heparin: Enoxaparin 40 mg QD ^b	1.16	>0.50	(0.56, 2.42)
Heparin: Enoxaparin 30 mg q12h ^b	0.93	>0.50	(0.46, 1.89)
Enoxaparin 40 mg QD: 30 mg q12h	0.80	0.486	(0.42, 1.51)
Major Bleeding Episodes:			
Heparin: Enoxaparin 40 mg QD ^b	4.51	0.0432*	(1.04, 19.57)
Heparin: Enoxaparin 30 mg q12h ^b	1.59	>0.50	(0.55, 4.57)
Enoxaparin 40 mg QD: 30 mg q12h	0.35	0.1312	(0.09, 1.37)

^a Estimated from a logistic regression model with treatment and center effects.
^b Two-sided p-values and confidence intervals are Bonferroni-adjusted (multiplied by 2).
* Statistically significant at the 5% level.

Table 10.2
Summary of Patients with Episodes of Bleeding by Site
(Appendix B.12.2)

Bleeding	Heparin	Enoxaparin		Overall
	5000 U q8h n (%)	40 mg QD n (%)	30 mg q12h n (%)	
All Treated Patients	209(100%)	203(100%)	195(100%)	607(100%)
Major	13(6%)	3(1%)	8(4%)	24(4%)
Wound	7(3%)	1(<1%)	6(3%)	14(2%)
Extra-operative	2(<1%)	0	0	2(<1%)
Unknown Site	4(2%)	2(<1%)	2(1%)	8(1%)
Minor	12(6%)	18(9%)	16(8%)	46(8%)
Wound	4(2%)	8(4%)	7(4%)	19(3%)
Extra-operative	6(3%)	8(4%)	4(2%)	18(3%)
Unknown Site	2(<1%)	2(<1%)	5(3%)	9(1%)
None	184(88%)	182(90%)	171(88%)	537(88%)

POST-SURGICAL, NON-AUTOLOGOUS BLOOD TRANSFUSION

Sixty-nine percent (69%) of all treated patients received at least one unit of blood transfusion from post-surgery to end of study. The proportion of patients who were transfused was similar among the three treatment groups. The transfusion requirements are summarized in the following table.

<u>Units Transfused</u>	<u>Treatment Group</u>			<u>Overall</u>
	<u>Heparin</u>	<u>Enoxaparin</u>		
	<u>5000 U q8h</u>	<u>40 mg OD</u>	<u>30 mg q12h</u>	
	(n=209)	(n=203)	(n=195)	(n=607)
0 Units	118 (56%)	132 (65%)	116 (59%)	366 (60%)
1-2 Units	69 (33%)	56 (28%)	57 (29%)	182 (30%)
> 2 Units	22 (11%)	15 (7%)	22 (11%)	59 (10%)
<u>Patients Transfused</u>				
N	91 (44%)	71 (35%)	79 (41%)	241 (40%)
Mean (units)	2.5	2.3	2.5	2.4
S.D.	2.18	1.53	1.75	1.86
Range	1-18	1-10	1-11	1-18

ADVERSE EVENTS

Adverse events were defined as any untoward event observed by the investigator or reported by the patient between the start of surgery and the final evaluation. All adverse events were mapped to the COSTART dictionary.

ADVERSE EVENT RATES

ALL ADVERSE EVENTS

Overall, 524 of 607 patients (86%) who received study medication reported at least one adverse event. The overall incidence of patients reporting adverse events was higher in the enoxaparin 30 mg/q12h group (91%) than in the enoxaparin 40 mg/qd group (84%), (p-value=0,035).

The most frequently reported adverse events affected the body as a whole and included fever, pain, headache.

Next most common were events affecting the GI system: nausea, constipation, vomiting and dyspepsia.

The adverse events are summarized in table 12.1

Table 12.1
Summary of Adverse Events By Body System
(All Adverse Events)
(Appendix B.13)

Body System Totals ^b	All Adverse Events				
	Heparin 5000 U q8h (n=205)	Enoxiparin		30 mg q12h (n=195)	p-value ^a
		40 mg QD (n=203)	p-value ^a		
Overall	176(84%)	171(84%)	1.001	178(91%)	0.035*
Body as a Whole	120(57%)	111(55%)	0.620	123(63%)	0.264
Cardiovascular	42(20%)	34(17%)	0.446	40(21%)	1.000
Digestive	93(44%)	89(44%)	0.921	83(43%)	0.763
Endocrine	1(<1%)	0(0%)	1.000	0(0%)	1.000
Hemic/Lymphatic	26(13%)	26(13%)	0.883	27(14%)	1.000
Injection Site Reaction	12(6%)	7(3%)	0.349	10(5%)	0.829
Metabolic and Nutritional	23(11%)	30(15%)	0.303	22(11%)	1.000
Musculoskeletal	13(6%)	13(6%)	1.000	3(2%)	0.020*
Nervous	42(20%)	40(20%)	1.000	48(25%)	0.284
Respiratory	23(11%)	15(7%)	0.235	15(8%)	0.307
Skin and Appendages	42(20%)	44(22%)	0.717	27(14%)	0.112
Special Senses	5(2%)	2(<1%)	0.449	3(2%)	0.725
Urogenital	42(20%)	38(19%)	0.803	32(16%)	0.369

^a P-value from two tailed Fisher's Exact test comparison versus Heparin.
^b Percents are based on number of patients in each treatment group.
^{*} Indicates p<0.05.

ANALYSIS OF ADVERSE EVENTS EXCLUDING THOSE NOT RELATED TO STUDY MEDICATION

Overall, 26% of all patients had adverse events that were regarded as related to study medication. The most common events were reported for the cardiovascular system (hemorrhage). The most common events associated with the GI system were nausea and constipation.

The treatment groups were similar for overall incidence of adverse events except for skin and appendages which were higher in the heparin group and were represented by skin rashes and pruritus.

The majority of adverse reactions regarded as related to study medication were of mild or moderate severity. One percent of patients in the enoxaparin 40 mg/qd group, 2% of patients in the enoxaparin 30 mg/q12h group and 3% of the patients in the heparin group experienced at least one adverse event which was reported by the investigator as severe.

The adverse events regarded as related to study medication are summarized in table 12.3.

Table 12.3
Summary of Adverse Events By Body System
-Excluding Those Not Study Drug Related-
(Appendix B.14)

Body System	Adverse Events Excluding Those Not Study Drug Related				
	Heparin 5000 U q8h (n=209)	40 mg QD (n=203)	p-value ^a	30 mg q12h (n=195)	p-value ^a
Totals ^b					
Overall	58(28%)	46(23%)	0.257	52(27%)	0.824
Body as a Whole	8(4%)	9(4%)	0.808	12(6%)	0.360
Cardiovascular	13(6%)	12(6%)	1.000	14(7%)	0.842
Digestive	13(6%)	10(5%)	0.669	10(5%)	0.673
Hemic/Lymphatic	11(5%)	7(3%)	0.472	8(4%)	0.644
Injection Site Reaction	9(4%)	4(2%)	0.260	6(3%)	0.604
Metabolic and Nutritional	8(4%)	5(2%)	0.575	5(3%)	0.578
Musculoskeletal	2(<1%)	1(<1%)	1.000	1(<1%)	1.000
Nervous	3(1%)	5(2%)	0.498	7(4%)	0.207
Respiratory	3(1%)	1(<1%)	0.623	4(2%)	0.716
Skin and Appendages	10(5%)	5(2%)	0.294	2(1%)	0.037*
Special Senses	0(0%)	2(<1%)	0.242	0(0%)	-
Urogenital	2(<1%)	2(<1%)	1.000	1(<1%)	1.000

^a P-value from two tailed Fisher's Exact test comparison versus Heparin.
^b Percents are based on number of patients in each treatment group.
* Indicates p<0.05.

PATIENTS WHO DIED DURING THE STUDY

Two patients, one in the enoxaparin 30 mg/q12h and one in the heparin group died of acute MI. A third patient in the heparin

group died of respiratory complications 65 days after discontinuation of study medication.

PATIENTS PREMATURELY DISCONTINUED FROM STUDY DUE TO ADVERSE EVENTS

Overall, 24 of 607 patients (4%) who received study medication experienced a total of 67 adverse events for which they were prematurely discontinued. Among these, were 5 of the 203 patients (2%) receiving enoxaparin 40 mg/qd, 7 of the 195 patients (4%) receiving enoxaparin 30 mg/q12h, and 12 of the 209 patients (6%) receiving heparin.

Approximately half of the adverse events were considered of mild or moderate severity and half were severe in nature. Forty-eight (48) of the 67 events that led to discontinuation of the study medication were considered to have been related to the study medication. These included 8/12 events in the enoxaparin 40 mg/qd group, 21/29 events in the enoxaparin 30 mg/q12h group, and 19/26 events in the heparin group.

PATIENTS WITH SERIOUS ADVERSE EVENTS

In addition to the three patients who died, 45 patients were classified as having serious adverse events: 11 of 203 patients (5%) in the enoxaparin 40 mg/qd reporting 21 events, 15 of 195 patients (8%) in the enoxaparin 30 mg/q12h reporting 29 events, and 19 of 209 patients (9%) in the heparin group reporting 33 events.

Seven of the 21 events in the enoxaparin 40 mg/qd, 13 of the 29 events in the enoxaparin 30 mg/q12h, and 7 of the 33 events in the heparin group were regarded as possibly or probably related to study drug.

CLINICAL LABORATORY EVALUATION

Post-operative increases from baseline in mean platelet counts, SGOT, SGPT, AP, LDH were observed in all three groups.

SHIFTS FROM THE NORMAL RANGE FOR LABORATORY PARAMETERS

Most of the patients in all groups had baseline low values of hemoglobin and hematocrit which remained below normal by the end of the study.

Elevation of the APTT occurred in 5% of the heparin patients and in 1% of the patients in the two enoxaparin groups. Shifts from normal range to above or below normal range and from below or

above normal range to normal range for the other hematologic parameters were similar in all groups. Among patients with normal baseline sodium values, 16% of the heparin patients, 9% of the enoxaparin 40 mg/qd patients and 13% of the enoxaparin 30 mg/q12h patients had values below normal.

Among patients with normal triglyceride values at baseline, a higher proportion of patients in the heparin group (32%) had values above normal at the end of the study compared with the two enoxaparin groups (15% and 17%).

Shifts from normal range to above or below normal range and from below or above normal range to normal of the other chemistry parameters were similar in all groups.

INCIDENCE OF 'POSSIBLY CLINICALLY SIGNIFICANT' VALUES FOR SELECTED LABORATORY PARAMETERS

Laboratory values of possible clinical significance were observed in all three treatment groups for platelet count, hemoglobin, SGOT, SGPT, Alkaline Phosphatase (AP), Total Bilirubin, and BUN. Creatinine value of possible clinical significance were recorded in the heparin group and in the enoxaparin 30 mg/q12h group. Thrombocytopenia, mostly of mild or modest severity, occurred in all three groups with similar frequency (18%, 15%, 15%). One patient treated with heparin developed heparin-induced thrombocytopenia and thrombosis.

The incidence of thrombocytosis (mild in 62%, moderate in 30% and severe in <1% of patients) was similar among all treatment groups.

Twenty-seven percent (27%) of all patients had a decrease in hemoglobin greater than 2 gm/dL and 16% had hemoglobin values less than 8 gm/dL. Similar results were seen in the two enoxaparin groups. Slightly higher proportion of patients in the heparin group experienced hemoglobin decrease of more than 2 gm/dL or had hemoglobin levels lower than 8 gm/dL.

One percent (1%) of all patients had elevated bilirubin, 4% and 5% had 3-6 fold elevation of SGOT and AGPT respectively, 1% or less had elevations of SGOT and SGPT greater than 6 folds above the investigator's upper limit of normal, and 5% had elevated AP values.

Five percent (5%) had clinically significant elevation of BUN and less than 1% had creatinine values elevated to levels of clinical significance. Similar results were observed among all three treatment groups.

The summary of the clinically significant laboratory parameters is shown in table 16.

Table 16
Summary of the On-Study Incidence of Patients with Clinically Significant Values for Selected Laboratory Parameters (Appendix B.19)

Parameter Value	Heparin		Enoxaparin		Overall n (%)
	5000 U q8h n (%)	40 mg QD n (%)	p-value ^a	30 mg q12h n (%)	
	209 (100%) ^b	203 (100%)		195 (100%)	607 (100%)
Platelets: Thrombocytopenia^b					
Mild	27 (13%)	27 (13%)	1.000	28 (14%)	82 (14%)
Moderate	5 (2%)	3 (1%)	0.724	7 (4%)	15 (2%)
Platelets: Thrombocytosis^c					
Mild	135 (65%)	124 (61%)	0.477	115 (59%)	374 (62%)
Moderate	56 (27%)	51 (25%)	0.512	63 (32%)	180 (30%)
Severe	1 (<1%)	3 (1%)	0.366	1 (<1%)	5 (<1%)
Hemoglobin:					
< 8 gm/dL	43 (21%)	28 (14%)	0.089	29 (15%)	100 (16%)
Dec \geq 2 gm/dL	65 (31%)	49 (24%)	0.124	51 (26%)	165 (27%)
Bilirubin:					
> 2 mg/dL	5 (2%)	1 (<1%)	0.216	1 (<1%)	7 (1%)
SGOT:					
3-6x Normal	9 (4%)	8 (4%)	1.000	9 (5%)	26 (4%)
> 6x Normal	2 (<1%)	1 (<1%)	1.000	2 (1%)	5 (<1%)
SGPT:					
3-6x Normal	9 (4%)	8 (4%)	1.000	14 (7%)	31 (5%)
> 6x Normal	2 (<1%)	2 (<1%)	1.000	4 (2%)	8 (1%)
Alk-Phosphatase:					
> 2x Normal	11 (5%)	11 (5%)	1.000	10 (5%)	32 (5%)
Creatinine:					
> 2 mg/dL	1 (<1%)	0 (0%)	1.000	2 (1%)	3 (<1%)
BUN:					
\geq 30mg/dL	15 (7%)	7 (3%)	0.124	9 (5%)	31 (5%)

^a P-values from two-tailed Fisher's Exact Test compared versus Heparin.

^b Platelets, thrombocytopenia:
Mild, $100,000/\text{mm}^3 \leq x <$ lower limit of normal;
Moderate, $20,000/\text{mm}^3 < x < 100,000/\text{mm}^3$;
Severe, $x < 20,000/\text{mm}^3$;

^c Platelets, thrombocytosis:
Mild, upper limit of normal $< x < 600,000/\text{mm}^3$;
Moderate, $600,000/\text{mm}^3 \leq x < 1,000,000/\text{mm}^3$;
Severe, $x \geq 1,000,000/\text{mm}^3$;
Dec, Decrease; Normal, upper limit of normal range.

* Indicates $p < 0.05$.

PATIENTS WITH MARKEDLY ABNORMAL LABORATORY VALUES

During or following study drug administration, 22 patients had hemoglobin levels lower than 7 gm/dL, 20 patients had platelet counts lower than $10^5/\text{mm}^3$ or greater than $10^6/\text{mm}^3$, 48 patients had elevations of SGOT or SGPT greater than 6x normal, AP greater than 300 U/L, and/or total bilirubin of more than 2 mg/dL; 31 patients had clinically significant elevation of renal function tests.

The incidence of markedly abnormal laboratory values was similar among the three treatment groups (table 16).

NONLABORATORY EVALUATIONS

VITAL SIGNS RESULTS

No clinically significant changes in mean values of vital signs were observed in any of the treatment groups.

POPULATION PHARMACOKINETICS

Increases from baseline in peak plasma anti-Xa and anti-IIa activities were observed in all three treatment groups from day 1 through the end of the study. In the enoxaparin groups, the anti-Xa activity was three times higher than the anti-IIa activity. The ratio of mean peak anti-Xa activity to mean peak anti-IIa activity was 1 or less in the patients treated with heparin.

CONCLUSION AND COMMENTS

This study compared the antithrombotic effectiveness of two enoxaparin regimen (30 mg q12h and 40 mg QD) with that of heparin 5000 U q8h. This study was conducted in US. The duration of therapy differed from the studies conducted in Canada for the duration of treatment which was limited to 7 days instead of 10-14 days.

The efficacy results showed that the regimen of enoxaparin 30 mg q12h was superior to the other two regimens for the prevention of DVT in patients undergoing elective orthopedic surgery. In the all treated group, the incidence of DVT was 12% in the heparin group, 15% in the enoxaparin 40 mg qfd group, and 5% in the

enoxaparin 30 mg q12h ($p < 0.05$). The results in the evaluable patients showed a rate of DVT of 6% for the enoxaparin 30 mg q12h group, 15% for the heparin group and 21% for the enoxaparin 40 mg QD group. The difference among the three groups was not statistically significant.

The incidence of major and minor bleeding complications and the total transfusion requirements were comparable in all three groups.

Among the serious adverse reactions encountered during the study, there were five cases of PE: one in a patient treated with enoxaparin 40 mg QD and four in patients treated with heparin. The PE of the enoxaparin patient occurred on day 4 of therapy and was associated with the finding of a superficial femoral vein phlebitis. The episodes of PE in the heparin patients occurred at the end of the study. One patient experienced PE concomitant with calf vein thrombosis. The other three patients developed PE between 2 and 3 weeks post-study, off medication, and beyond the follow-up time.

Among the serious adverse events regarded as associated with the study medication, one case of severe thrombocytopenia and thrombosis, resulting in bilateral lower extremities gangrene, occurred in a patients treated with heparin.

The effectiveness of enoxaparin 30 mg q 12h in preventing DVT in hip surgery patients was greater in this study than that obtained with the same regimen in study ENO 884 and PK 523 (5% treatment failure versus 10% and 17% respectively).

The study design presented numerous deficiencies, therefore the interpretation of the results is subject to such limitations. The study was not double-blind; moreover, the investigators were provided with the randomization list which introduced the additional bias of patients selection. The patients were assigned the study treatment either presurgery or postsurgery. The protocol underwent various amendments; several protocol variations were allowed in the evaluation of efficacy.

The study is, therefore, unacceptable for efficacy evaluation. The study can, however, contribute to the safety evaluation of enoxaparin.

STUDY NUMBER; PK 526

TITLE: Multiple-dose, double-blind clinical trial of the safety and efficacy of enoxaparin for the prevention of post-operative Deep Vein Thrombosis (DVT) following total hip replacement surgery.

The study was initiated on January 19, 1989. A total of 572 patients were enrolled by 32 investigators in US until August 24, 1990.

NDA Volumes: 59-61; 2.18

The investigators enrolling more than 10 patients were:

<u>Investigator</u>	<u>Study location</u>	<u>Patients Enrolled</u>
J.R. Roberson, M.D.	Emory Univ. Atlanta, GA	14
R.B. Brasier, M.D.	Ann Arbor VAH Ann Arbor, MI	27
R. Bona, M.D.	St. Francis H., Hartford CT	16
F.G. Ebaugh Jr, M.D.	VAMC Palo Alto, CA	17
J.J. Flechtner, M.D.	Dakota Clinic, Fargo, MD	27
D. MacFarlane, M.D.	U.Iowa Col.Med., Iowa City, IA	30
T. Siesholtz, M.D.	Grand View H., Sellerville, PA	19
G Johnson, M.D.	VAMC, Minneapolis, MN	34
R.M. Lyons, M.D.	Humana H., San Antoni, TX	45
M.D. Tremaine, M.D.	Anderson Clinic, Anderson, VA	45
J. Ansell, M.D.	U. Massachusetts, Worcester, MA	24
R. Rodvien, M.D.	Pacific Presb.H.San Francisco, CA	18
C.G. Savory, M.D.	Hughston Sports M.H., Columbus, GA	50
M. Rader, M.D.	Nyack Hospital, Nyack, NY	11
W.K. Furman, M.D.	Sarasota Mem.H., Sarasota, FL	48
W.L. Overdyke, M.D.	Highland Clinic, Shreveport, LA	19
M. Christie, M.D.	Vanderbilt Univ.H., Nashville, TN	18
G.B. Shaver, M.D.	Asheville Med.Ctr. Asheville, NC	23
R.E. White Jr, M.D.	Presbyt. Hosp., Albuquerque, NM	15
M. Ritter, M.D.	Kendrick Mem.H., Woosville, IN	14

STUDY OBJECTIVE: The objective of the study was to determine the safety and the efficacy of enoxaparin administered subcutaneously (sc) at doses of 10 mg once daily (10 mg/qd), 40 mg once daily (40 mg/qd), and 30 mg every 12 hours (30 mg/q12h) for up to 7 days for the prevention of DVT in patients undergoing elective hip replacement.

STUDY DESIGN

The clinical trial was conducted as a Phase III randomized, double-blind, parallel-group, multicenter study. The patients were randomly assigned to receive either enoxaparin 10 mg.qd,

enoxaparin 40 mg/qd, or enoxaparin 30 mg/q12h for a period of up to seven days beginning within the first 24 hours after surgery. The enoxaparin doses of 40 mg/qd and 30 mg/q12h were selected based on clinical PK studies and on the results of previous studies which demonstrated the effectiveness of these doses in preventing DVT. The dose of 10 mg/qd was used to provide efficacy and safety information for the low end of the dose response curve.

The primary efficacy assessment for DVT was bilateral contrast media venography (VG) on day 7, or earlier if clinically indicated. Additional efficacy assessment of DVT was obtained with non-invasive vascular examinations and clinical signs and symptoms of DVT.

Evaluation for safety was performed daily throughout the study period and within 14 days following termination of study drug treatment.

SELECTION OF STUDY POPULATION

The eligibility and ineligibility criteria were similar to those described for protocol PK 525.

DOSING SCHEDULE

Patients were randomly assigned to one of three treatment groups according to a randomization code supplied by the sponsor. The enoxaparin dose for the three treatment groups were:

1. 10 mg QD
2. 40 mg QD
3. 30 mg q12h

All doses were administered sc in the abdominal area. No dosage changes were allowed. Treatment was started within 24 hours after completion of surgery, provided that hemostasis at surgical site had been achieved. The treatment with enoxaparin was continued for up to seven days, unless it had to be terminated earlier because of patients discontinuation from the study or discharge from the hospital.

EVALUATION AND SCHEDULING

These are summarized in table 1.

TABLE 1
STUDY SCHEMATIC - OVERVIEW

Evaluation/Procedure	Prior to Surgery ¹	Upon Admission ²	Peridosing Interval							End of Study ⁷	Follow Up
			Calendar/Treatment Day ³								
			1	2	3	4	5	6	7		
Informed Consent	X										
Complete Medical History	X										
Complete Physical Examination	X									X	X
12-Lead ECG ⁴	X									X	
Chest X-Ray ⁴	X										
Interim History		X									
Brief Physical Examination		X									
Biochemistry and Urinalysis	X									X	X
Hematology and Coagulation ⁵	X		X	X	X	X	X	X	X	X	X
Noninvasive Vascular Examination ⁶	X				X					X	
Vital Signs ⁵	X		X	X	X	X	X	X	X	X	X
Assessment of Operative Site ⁵			X	X	X	X	X	X	X	X	X
Bleeding Assessment			X	X	X	X	X	X	X	X	
Adverse Experience Evaluation			X	X	X	X	X	X	X	X	X
Dosing			X	X	X	X	X	X	X		
Bilateral Venography										X	
Concomitant Medications			X	X	X	X	X	X	X	X	X

- ¹ Up to 14 days prior to surgery.
- ² If complete history and physical examination were performed more than 48 hours prior to surgery.
- ³ Day 1 was the first dosing day; the next calendar day was Day 2.
- ⁴ Only if results of chest X-ray done within the preceding six months were not available.
- ⁵ Immediately prior to first dose of study drug on a dosing day.
- ⁶ Several techniques were permitted, but each center was to select one technique to be used for all patients.
- ⁷ Within 24 hours of the last dose of study medication.

EFFICACY PROCEDURES

Bilateral venograms were scheduled within 24 hours following last dose of study medication at the end of the study or following premature discontinuation of study treatment.

Venography represented the primary assessment of DVT. At one study site, venography was performed with radionuclide imaging instead of radiocontrast imaging. This test was included among the non-invasive vascular tests.

The procedures for interpreting VG and the non-invasive evaluation of DVT were as described in protocol 525.

SAFETY PROCEDURES

The clinical and laboratory assessments of bleeding and other adverse reactions were as described in protocol 525.

CLINICAL MONITORING PROCEDURES

In addition to Rhone-Poulenc personnel, monitoring of the study was performed on a regular basis by the following contract research organizations:

PACKAGING, BLINDING, AND LABELING PROCEDURES

Study medication was supplied in identical, prefilled syringes containing either placebo or 10, 40 or 30 mg enoxaparin in a volume of 0.4 mL.

All enoxaparin syringes contained also mg); the 10 mg enoxaparin syringe contained the 30 mg enoxaparin syringe contained

Each enoxaparin placebo syringe contained and less than

To maintain the double-blind character of the study, all patients received an injection q12h. For the enoxaparin 10 mg qd and 40 mg qd, the enoxaparin was given for the odd doses and the placebo for the even doses. Each patient's daily supply of study medication was packaged in an individual blister pack pre-labeled with the patient's number and dose number (1,3,5,7,etc; 2,4,6,8,etc). Patients received the entire content of the syringe. No dose adjustment was allowed.

The following lot numbers were used in this trial:

Enoxaparin, 10 mg: CB 3424, CB 3965
Enoxaparin, 40 mg: CB 3427, CB3974
Enoxaparin, 30 mg: CB 3422, CB 3645, CB 4372
Enoxaparin Placebo: CB 3426P, CB 3951P, CB 4006P

Investigators were supplied with study medication for blocks of 6 or 12 patients.

All supplies of enoxaparin used in the study were tested by the sponsor.

STATISTICAL METHODS

The sample size was determined based on the reported incidence of DVT in patients treated with either 40 mg qd or 30 mg q12h, on the assumed incidence of DVT in patients treated with 10 mg of enoxaparin qd of 25%, and on an anticipated 80% rate of evaluable patients. It was calculated that approximately 200 patients in each group would give a 80% power using a two-tailed test at a significance level of 0.05.

PATIENTS RANDOMIZATION

Patients were assigned to treatment group in a 1:1:1 ratio in blocks of six using a computerized randomization schedule. The

patients number were assigned in an ascending, sequential order. The number were assigned either before or after surgery, and after the patient signed the IC.

EFFICACY EVALUATION

Definition of efficacy outcome: Efficacy was assessed by the incidence rate of DVT. The diagnosis of DVT by venogram had absolute priority. A positive VG was defined by a positive finding in either the operated or non-operated limb or both limbs. A negative VG was defined as a negative bilateral VG. An inadequate VG was one in which the diagnosis of DVT could not be made nor excluded. A unilateral negative VG was classified as inadequate.

Diagnosis of DVT by either a positive result of the ¹²⁵I-fibrinogen scan or IPG had second priority.

Clinical evidence of DVT was defined as: 1) either a positive result of fibrinogen scan or IPG, or 2) other clinical evidence such as pulmonary embolism (PE) or administration of therapeutic anticoagulant regimen for DVT.

All treated patients who had received any study medication and had had at least one clinical evaluation were classified into one of the following outcome groups:

Outcome Group	-----Clinical Evidence of DVT-----		
	Venogram	Other Vascular Procedures <u>¹²⁵I-Fibrinogen or IPG</u>	Other Clinical Findings
1	+	All	All
2	-	All	All
3	IN/ND	+	All
4	IN/ND	-, IN/ND	+
5	IN/ND	-, IN/ND	Not +

"IN/ND" indicates that the venogram was inadequate or not done.

"All" indicates all situations (+, -, IN/ND)

- Group 1 included patients with positive VG (unilateral or bilateral), regardless of the results of the other evaluations.

- Group 2 included patients with negative bilateral VG, regardless of the results of the other evaluations.

- Groups 3 and 4 included patients with inadequate VG, without bilateral VG in whom the diagnosis of DVT was made by noninvasive tests or other clinical evidence.

- Group 5 included patients in whom VG was inadequate or not done, noninvasive vascular tests were negative, inadequate or not done and in whom there was no clinical evidence of DVT.

Patients in Groups 1, 3 and 4 were classified as treatment failure; patients in Groups 4 and 5 as non failures.

STUDY POPULATION

The efficacy analysis for ALL RANDOMIZED PATIENTS included all patients who were randomized and received medication, all randomized patients who never received medication and had no efficacy evaluation and all randomized patients who received treatment but had no efficacy data.

The efficacy analysis for ALL TREATED PATIENTS WITH EFFICACY DATA included all treated patients with at least one on-study efficacy evaluation.

The efficacy evaluation for all EVALUABLE PATIENTS included all patients who received study medication, had at least one on-study efficacy evaluation, and for whom none of the following conditions occurred during the study:

- Presurgical noninvasive vascular tests positive for DVT
- Patients had undergone surgery of ipsilateral hip or knee within one month before hip surgery.
- Patients had undergone surgery other than hip replacement or revision
- Patients had received more than 1500 U/day of heparin within four days prior to or during administration of study medication.
- Patients received more than one dose of Warfarin within 4 days prior to study or during study drug administration.
- Patients received the first dose of study medication later than 24 hours after surgery
- Patients received insufficient therapy (less than 75% of dose or less than 4 days of therapy)
- VG was not performed, or bilateral VG was not definitive, or definitive VG was not performed within 4 days or less after final dose of study medication.

UNEVALUABLE PATIENTS in each treatment group included the complement of evaluable patients with respect to the all treated patient population.

EFFICACY ANALYSES

INTENT-TO-TREAT ANALYSES

ALL TREATED PATIENTS WITH EFFICACY DATA

For this patient population, the efficacy endpoints (incidence of treatment failure) was defined as follows:

Groups 1, 3, 4 (positive)
Groups 1, 3, 4 (positive + Groups 2, 5 (negative))

Within this patient population, the incidence of DVT was also summarized for the subsets of: 1) type of surgery (primary hip replacement or revision), 2) type of anesthesia (regional/epidural or inhalation/IV), 3) use of surgical cement, 4) use of graduated compression stockings (GCS), 5) demographic characteristics (sex, age and race).

ALL RANDOMIZED PATIENTS

Only four patients, two in the 40 mg qd group and two in the 30 mg q12h group, were randomized but not treated. Therefore, the all randomized and the intent-to-treat groups were considered similar for purpose of analysis.

EVALUABLE PATIENTS EFFICACY ANALYSIS

All evaluable patients had definitive VG, thus, the efficacy endpoint (treatment failure) was defined as:

Group 1 (positive)
Group 1 (positive) + Group 2 (negative)

Group 3 (noninvasive vascular evidence of DVT) and 4 (clinical evidence of DVT) were not considered in the evaluation of efficacy for the evaluable patients.

Within the population of evaluable patients, the incidence of DVT was also summarized for the subsets of type of surgery, type of anesthesia, use of surgical cement, use of GCS, sex, age and race.

SAFETY EVALUATION

PATIENT POPULATION: All patients who received at least one dose of study medication were included in the safety evaluation.

SAFETY ANALYSES; The primary safety endpoints determined for each of the treatment groups were:

- Incidence of death, premature discontinuation from treatment, adverse events (according to severity and relationship to study medication)
- incidence of patients with major or minor bleeding episodes and day of onset of major bleeding episodes
- the mean number of total units of blood transfused on study (aside from operative and recovery room units) and the incidence of 0, 1-2, and more than 2 units of blood transfused on study.
- the incidence of abnormal values of clinical concern for selected laboratory tests from day 1 through the end of the study, including:

Platelets: Thrombocytopenia-

- mild: equal or greater than $1 \times 10^5/\text{mm}^3$ and less than the investigator's lower limit of normal
- moderate: equal or greater than $2 \times 10^4/\text{mm}^3$ and lower than $1 \times 10^5/\text{mm}^3$
- severe: lower than $2 \times 10^4/\text{mm}^3$

Platelets: Thrombocytosis-

- mild: equal or greater than the investigator's upper limit of normal and lower than $6 \times 10^5/\text{mm}^3$
- moderate: equal or greater than $6 \times 10^5/\text{mm}^3$ and lower than $1 \times 10^6/\text{mm}^3$
- severe: higher than $1 \times 10^6/\text{mm}^3$

Hemoglobin: Values $< 8 \text{ gm/dL}$ or a decrease $\geq 2 \text{ gm/dL}$ from baseline.

SGOT and SGPT: 3- to 6-fold increase and > 6 -fold higher than the investigator's upper limits of normal.

Total Bilirubin: Values $> 2 \text{ mg/dL}$.

Alkaline Phosphatase: Any value > 2 -fold higher than the investigator's upper limits of normal.

Creatinine: Any value $\geq 2 \text{ mg/dL}$.

BUN: Any value equal or greater than 30 mg/dL .

- The mean changes from baseline for hematology (post-surgery and pre-study drug administration) laboratory tests at day 4, day 7, end of study and follow-up and for serum chemistry (pre-surgery) laboratory tests at end of study and follow-up.
- Shifts in the percentage of patients with hematology and chemistry laboratory values outside the normal range at the end of the study relative to baseline.
- the mean change from pre-surgery baseline for systolic and diastolic blood pressure and pulse rate and temperature at day 4, day 7, end of study and follow-up

STATISTICAL ANALYSIS

Demographic and Baseline Characteristics

The three treatments groups were compared at baseline for categorical variables (sex) and other demographic variables (age, weight, BP, medical and surgical histories, transfusions) using descriptive statistics. Each variable was summarized for all treated and all evaluable patients. All randomized patients and all unevaluable patients were summarized for demographic, surgical and transfusion data.

Efficacy Analyses

The endpoint was represented by development of DVT (treatment failure).

The incidence of DVT was analyzed for both all treated patients with efficacy data and for the evaluable patients.

Justification for pooling across centers was investigated using a two-way logistic regression model with factors of treatment group, center, and treatment-by-center interaction. The results of the DVT findings were also summarized by investigator to provide a qualitative assessment of the presence of interactions. A two-way logistic regression model including factors for treatment group and center was used to compare the treatments. These analyses were carried out using the SAS procedure CATMOD, the CONTRAST statement was used to compare the treatment groups pairwise. Since it was expected that the two higher enoxaparin doses would be superior to the low dose, the pairwise comparison of the two high doses to the low dose were considered to be the primary treatment comparisons.

A Bonferroni-adjusted significance level of 2.5% was used for each of the primary treatment comparisons (all p-values multiplied by 2). Throughout the study "Statistical significance" corresponded to p-value equal or lower than 5%, adjusted for two comparisons. Comparison between the two enoxaparin doses was based on a 5% significance level. All tests were two-sided.

An approximate 95% confidence interval for the odds ratio of treatment failure in placebo versus enoxaparin was computed. The odds of a treatment failure are defined as estimated incidence rate of treatment failure/estimated incidence rate of treatment success. The incidence rate of treatment failure by

treatment group was summarized in patients subpopulations by demographic characteristics, type of surgery, type of anesthesia, use of surgical cement, use of GCS.

ADVERSE EVENTS

The COSTART dictionary was used to classify the adverse events. Events for a particular COSTART occurring more than once were counted only once. Repeated reporting of the same adverse event in a patient was reported only as the most severe. Each type of event occurring within a body system was counted.

Adverse events incidence rates (all events excluding those unrelated to study medication) were summarized by treatment group. The adverse events were summarized for each body system and overall. Overall indices reflected the number of patients reporting any adverse event. Fisher's exact two-sided test was performed for the statistical comparison of the heparin group with the two enoxaparin groups for total adverse events in each body system, for each event with an incidence of 5% or higher in a treatment group for all adverse reactions, and for each event with an incidence of 2% or higher in a treatment group for all adverse events excluding those unrelated to study medication. These analyses were not initially planned and were performed and are presented as a result of a meeting with the FDA in March 1991.

Bleeding Assessment

The overall incidence rates of patients with major or minor bleeding at operative, non-operative, or unknown sites during the study period were summarized for each treatment group. Treatment comparisons were based on the overall incidence rates of patients with major bleeding and of patients with major or minor bleeding. A two-way logistic regression model with factors for treatment group and center was used.

Laboratory Data

Mean changes from baseline for hematology parameters were determined on Day 4, day 7, end of study and follow-up, and at the end of the study and at follow-up for all serum chemistry laboratory parameters. The mean changes from pooled parameters across investigators were summarized for the three treatment groups using descriptive statistics. No formal statistical analyses were performed for these laboratory data. Fisher's exact test was performed for the statistical comparison between the heparin group and the two enoxaparin groups for

selected laboratory values of clinical concern. Shift tables were generated that summarize the distribution (below, within, above normal range) of baseline and end of study hematology and chemistry values.

If more than one laboratory or vital sign determination was available for a parameter, the first evaluation was used for analysis.

Vital Signs

The mean changes from baseline for vital signs combined across investigators on day 4, day 7, at end of study and at follow-up were summarized for the three treatment groups. No formal statistical test of hypothesis was performed.

PROTOCOL AMENDMENTS

The protocol was amended on 6-15-1990 to include the following changes:

- increase of number of centers from 20 to 40
- the definition of hip replacement surgery was expanded to mean a prosthetic device inserted into the intramedullary space of the femur, with or without reconstruction of the acetabulum.
- the time frame for performing pre-study evaluation and presurgical non-invasive evaluation of DVT was increased from 7 to 14 days prior to surgery
- the use of graduated compression stockings was allowed
- the administration of small amounts of heparin to 200 U/day was allowed to maintain patency of intravenous lines
- The second criterion for major bleeding requirement of being "clinically overt and/or accompanied by either a fall in hemoglobin or requirement for blood transfusion" was changed to "clinically overt and accompanied by"

PROTOCOL VARIATIONS

Patients with the following protocol deviations were included in the study and considered evaluable for efficacy because the sponsor did not believe that these deviations may have sufficient impact on the outcome of the DVT analysis;

- patients 37 years of age or older (protocol age=40)
- any type of hip replacement employing insertion of a prosthetic device (total hip system, femoral bipolar component or acetabular component).
- presurgical exclusion of DVT by any noninvasive vascular examination, patients with positive results were, however, excluded.

- surgery on the ipsilateral hip within three months
- use of NSAID during the four days before surgery and concomitant with study medication throughout the study
- two or more doses of warfarin were required to exclude a patient from evaluability.
- infrequent administration of 1500 U of heparin throughout the study

RESULTS

PATIENTS DISPOSITION/ACCOUNTABILITY

The allocation of the patients to the three groups and the disposition of the patients are summarized in the following table:

Disposition	Treatment Group			Total n(%)
	10 mg qd n(%)	40 mg qd n(%)	30 mg q12h n(%)	
<u>Patients Randomized</u>	161	201	210	572
<u>Patients Randomized</u>				
<u>Not Treated:</u>	0	2	2	4
<u>Patients Treated:</u>	161 (100%)	199 (100%)	208 (100%)	568 (100%)
<u>Patients Completed:</u>	108 (67%)	139 (70%)	154 (70%)	392 (69%)
<u>Evaluable</u>	105 (97%)	133 (96%)	136 (94%)	374 (95%)
<u>Not evaluable</u>	3 (3%)	6 (4%)	9 (6%)	18 (5%)
<u>Patients Discontnd.:</u>	53 (33%)	60 (30%)	63 (30%)	176 (31%)
<u>Evaluable</u>	11 (21%)	16 (27%)	7 (11%)	34 (19%)
<u>Not Evaluable:</u>	42 (79%)	44 (73%)	56 (89%)	142 (81%)
<u>Protocol violat.</u>	40 (25%)	39 (20%)	41 (20%)	120 (21%)
<u>Adverse event</u>	8 (5%)	9 (5%)	9 (4%)	26 (5%)
<u>Interc. Illness</u>	0	1 (<1%)	1 (<1%)	2 (<1%)
<u>Death</u>	0	2 (<1%)	0	2 (<1%)
<u>Lost to F/U</u>	1 (<1%)	7 (4%)	5 (2%)	13 (2%)
<u>Other</u>	3 (2%)	2 (1%)	5 (2%)	13 (2%)
<u>Patients Evaluated for Efficacy:</u>				
<u>All Randomized:</u>	161	201	210	572
<u>All Treated:</u>	161 (100%)	199 (100%)	208 (100%)	568 (100%)
<u>Evaluable</u>	116 (72%)	149 (75%)	143 (69%)	408 (72%)
<u>Not Evaluable:</u>	45 (28%)	50 (25%)	65 (31%)	160 (28%)
<u>Inadequate or no venography</u>	42 (26%)	48 (24%)	64 (31%)	154 (27%)
<u>Insufficient therapy</u>	3 (2%)	2 (1%)	1 (<1%)	6 (1%)

A total of 572 patients were randomized to one of the three study groups. Fewer patients were enrolled in the enoxaparin 10 mg QD group because this arm of the study protocol was terminated early following an interim analysis of efficacy.

A total of 176 treated patients were prematurely discontinued. The most common reason for discontinuation was protocol violation which most often consisted of inadequate or missing venograms. Two patients, both in the enoxaparin 40 mg QD group, died of MI. In one of the two deaths, the event was regarded as possibly related to study medication.

A total of 480 of the 568 treated patients (72%) were included in the evaluable efficacy analysis. The most common reason for the exclusion of patients from the evaluable efficacy analysis was inadequate or missing venography in 27% of patients (154/568); the venogram was not done in 140/568 patients and it was inadequate or unilateral in 10/568.

The total of 95% of treated patients who completed the study were evaluable, while only 19% of the treated patients who were withdrawn from study were evaluable. The rates of evaluability and inevaluability were similar among the three treatment groups. Of the 568 treated patients, 63% were male, 93% were Caucasian, the average age was 64.7 years, the average body weight was 80.6 kg (range 45-140), the average height was 168.4 cm, 19% were smokers. The three treatment groups of all treated patients as well as of evaluable patients, were comparable with respect to patient demographic characteristics.

The most frequently administered class of concomitant medications in each of the enoxaparin treatment groups included opiate and opioids (95%), cephalosporins (90%), analgesics and antipyretics (83%), laxatives (74%), and hypnotics and sedatives (60%). The three treatment groups were similar for the incidence of use of some other antithrombotic therapy and of use of NSAID, including ASA.

Concurrent illnesses were present in 86% of all patients. The most common illnesses were diseases of the circulatory system which occurred in 50% of patients, followed by symptoms, signs and ill-defined conditions in 25% of patients, and diseases of the connective and muscular system in 22% of patients. The three treatment groups for all patients and for evaluable patients had similar incidence rates of these concurrent illnesses as well as all conditions predisposing to DVT.

All 568 treated patients and 97% of the evaluable patients had medical, orthopedic, or surgical histories which had similar distribution among the three treatment groups.

The primary diagnoses and the surgery data were similar in the all treated and in the evaluable patient populations. In addition, the three treatment groups of evaluable and unevaluable patients were similar with respect to primary diagnosis, surgical data and transfusion data.

EFFICACY RESULTS

The incidence of DVT was significantly lower in the two groups treated with enoxaparin 30 mg q12h and 40 mg QD than in the group treated with 10 mg qd group in both the all treated and the evaluable patients populations,

The incidence of DVT was 11% in both all treated and evaluable patient populations of the enoxaparin 30 mg/q12h group, compared to that of 25% in the all treated and 31% in the evaluable patients treated with enoxaparin 10 mg QD. The incidence rate of DVT in the group treated with enoxaparin 40 mg QD was 14% in both all treated and evaluable patients.

The results of the statistical analysis of the DVT findings by treatment group for the all treated patients are shown in table 8.2, and figures 1A and 1B. The results of the evaluable patients efficacy analysis are shown in table 8.3 and figures 2A and 2B reproduced from the NDA application.

Table 8.2
Summary of Statistical Results of DVT Findings
By Treatment Group for All Treated Patients
(Appendix B.9.1)

<u>Patients Treated</u>	<u>Treatment Group</u>			<u>Overall</u>
	<u>10 mg QD</u>	<u>40 mg QD</u>	<u>30 mg q12h</u>	
	<u>n (%)</u>	<u>n (%)</u>	<u>n (%)</u>	<u>n (%)</u>
All Treated Patients	161(100%)	199(100%)	208(100%)	568(100%)
Treatment Failures	40(25%)	27(14%)	22(11%)	89(16%)
Proximal DVT	17(11%)	9(5%)	8(4%)	34(6%)
Distal DVT	20(12%)	12(6%)	8(4%)	40(7%)
Noninvasive	3(2%)	6(3%)	6(3%)	15(3%)

Between-Group Comparisons of the Incidence of Treatment Failures:

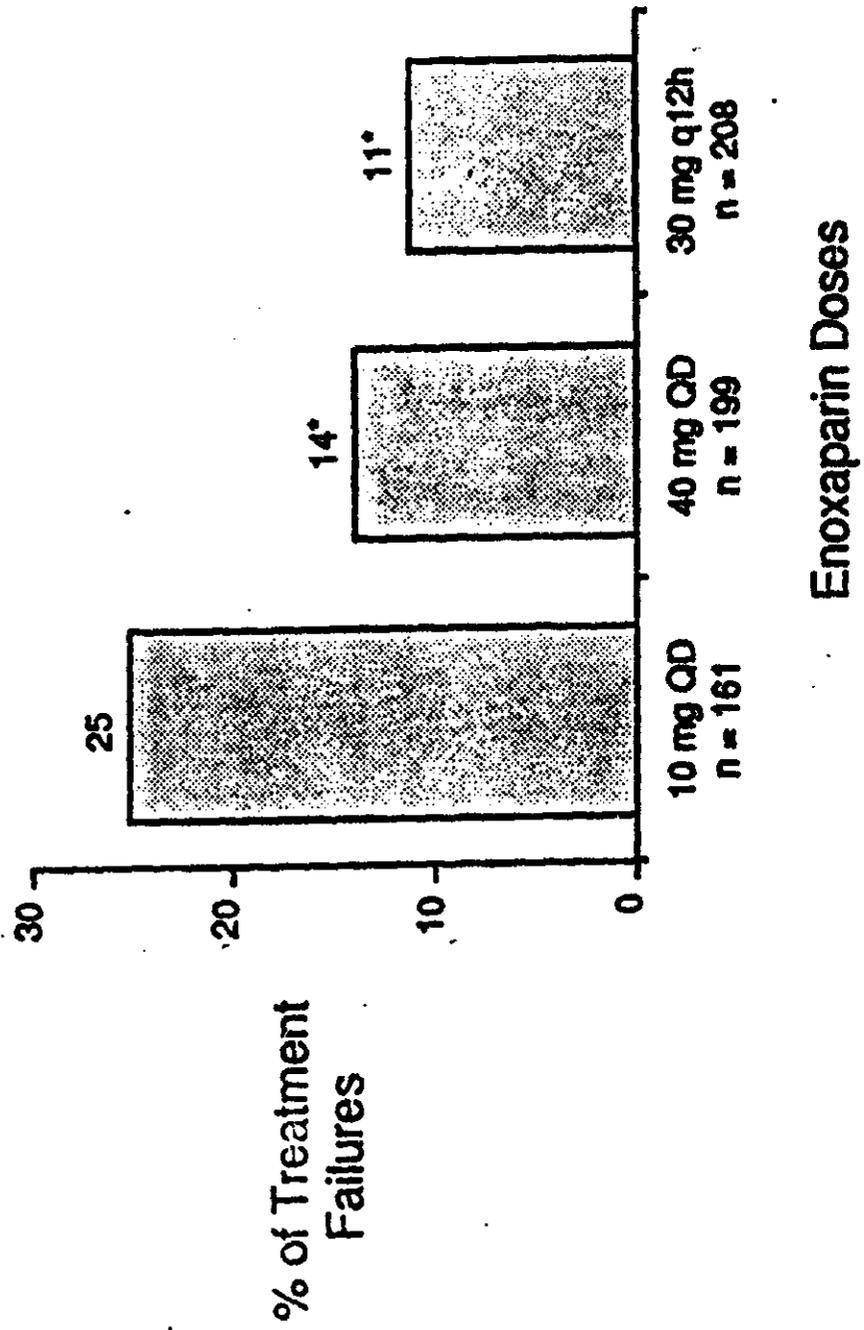
<u>Treatment Comparison</u>	<u>Odds Ratio^a</u>	<u>p-value</u>	<u>95% Confidence Interval for Odds Ratio</u>
Enoxaparin 10mg QD: 40mg QD ^b	2.16	0.0168*	(1.12, 4.15)
Enoxaparin 10mg QD: 30mg q12h ^b	2.93	0.0008*	(1.48, 5.81)
Enoxaparin 40 mg QD: 30 mg q12h	1.36	0.3369	(0.73, 2.53)

a Estimated from a logistic regression model with treatment and center effects.

b Two-sided p-values and confidence intervals are Bonferroni-adjusted (multiplied by 2).

* Statistically significant at the 5% level.

Figure 1A
Statistical Result of DVT Findings by Treatment Group
Percent of Treatment Failures
All Treated Patients
PK 526



* Statistically significantly favored over the 10 mg QD group at the 5% level

Figure 1B
Statistical Result of DVT Findings by Treatment Group
Confidence Intervals for Odds Ratio of Treatment Failures
All Treated Patients
PK 526

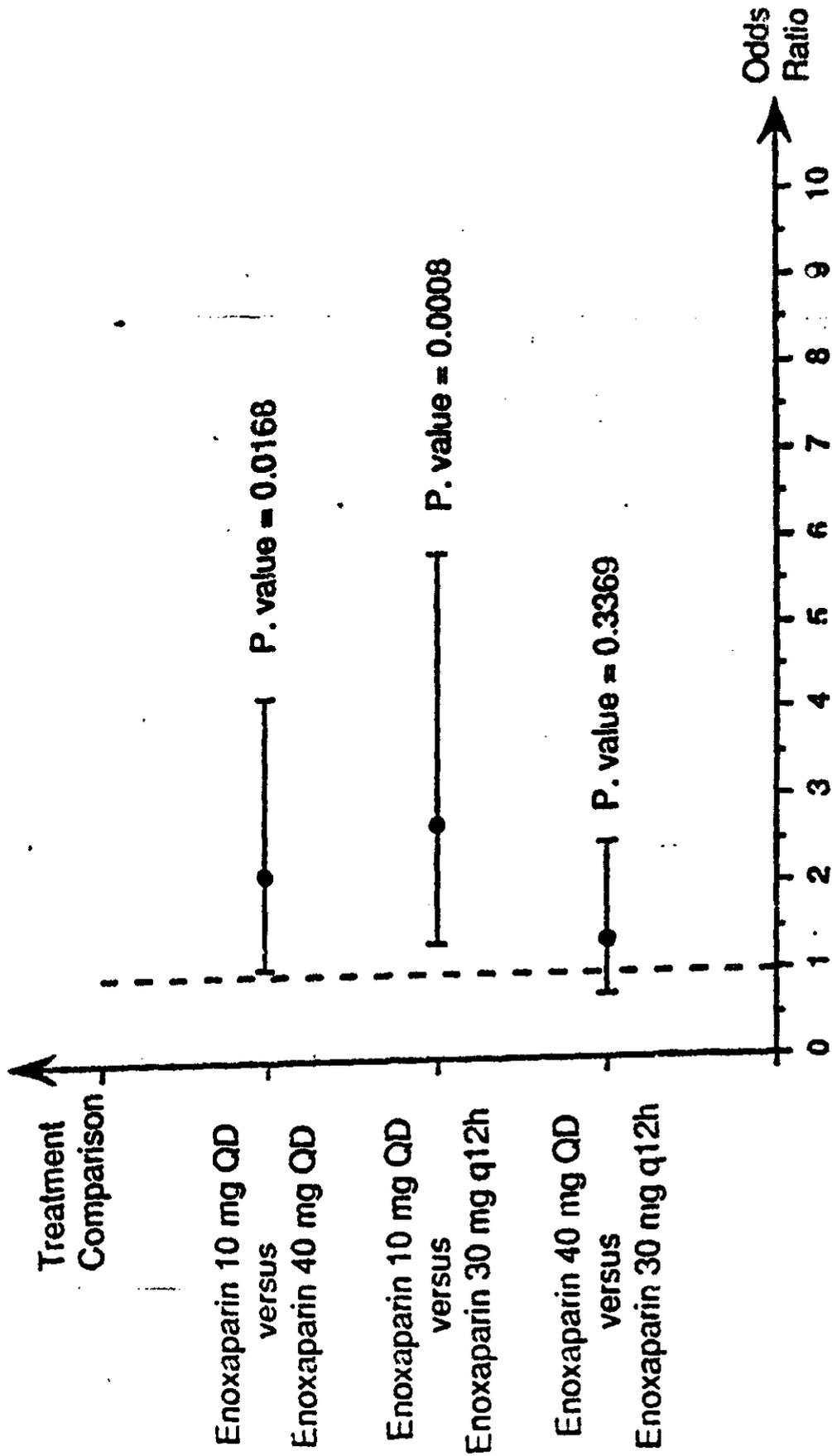


Table 8.3
Summary of Statistical Results of DVT Findings
by Treatment Group for Evaluable Patients
(Appendix B.9.2)

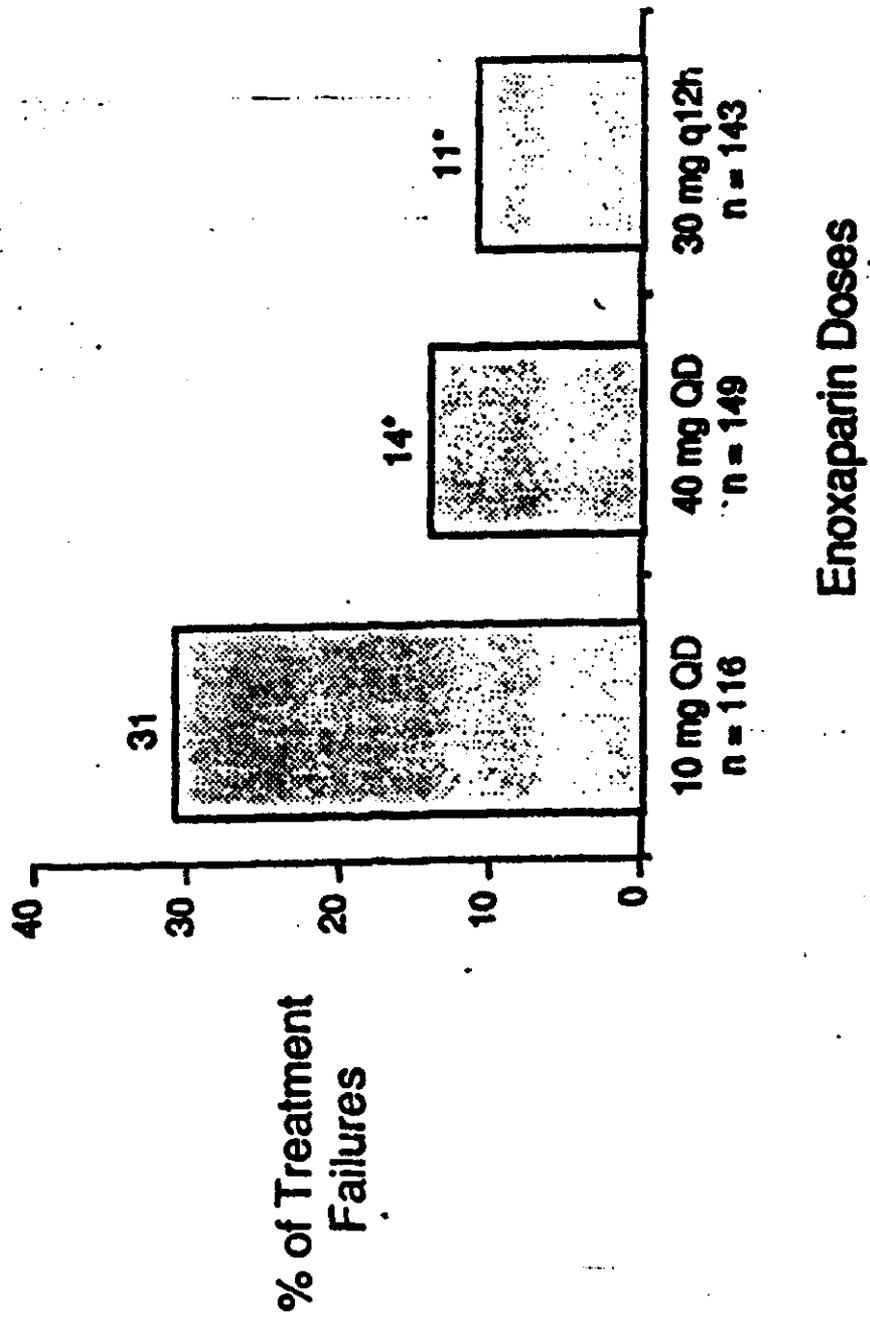
	-----Treatment Group-----			Overall n (%)
	10 mg QD n (%)	40 mg QD n (%)	30 mg q12h n (%)	
Evaluable Patients	116(100%)	149(100%)	143(100%)	408(100%)
Treatment Failures	36(31%)	21(14%)	16(11%)	73(18%)
Proximal DVT	16(14%)	9(6%)	8(6%)	33(8%)
Distal DVT	20(17%)	12(8%)	8(6%)	40(10%)

Between-Group Comparisons of the Incidence of Treatment Failures:

Comparison	Odds Ratio ^a	p-value	95% Confidence Interval for Odds Ratio
Enoxaparin 10mg QD: 40mg QD ^b	2.74	0.0054*	(1.29, 5.82)
Enoxaparin 10mg QD: 30 mg q12h ^b	3.57	0.0008*	(1.60, 7.98)
Enoxaparin 40 mg QD: 30 mg q12h	1.30	0.4783	(0.63, 2.70)

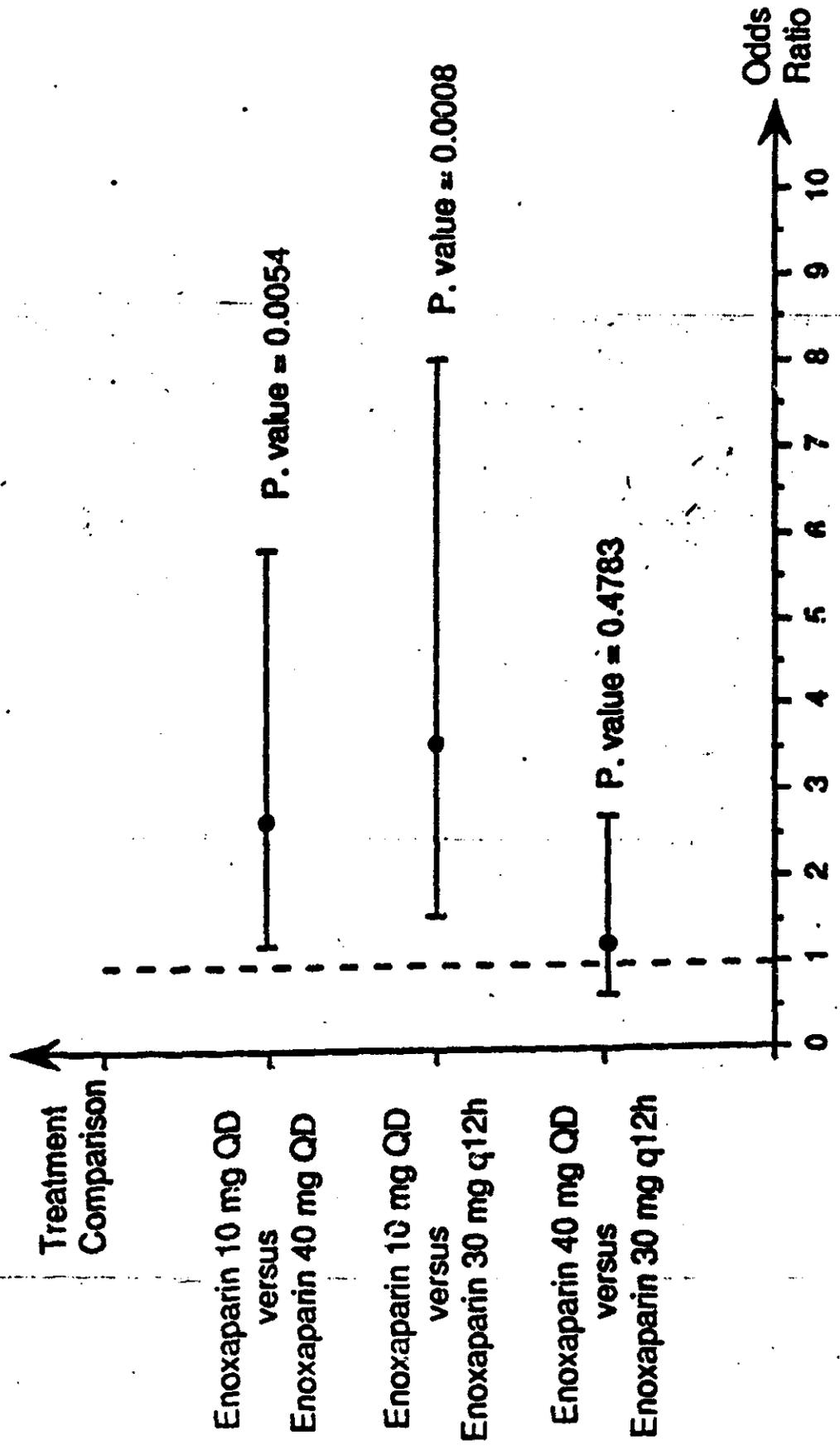
- a Estimated from a logistic regression model with treatment and center effects.
b Two-sided p-values and confidence intervals are Bonferroni-adjusted (multiplied by 2).
* Statistically significant at the 5% level.

Figure 2A
Statistical Result of DVT Findings by Treatment Group
Percent of Treatment Failures
Evaluable Patients
PK 526



* Statistically significantly favored over the 10 mg QD group at the 5% level

Figure 2B
Statistical Result of DVT Findings by Treatment Group
Confidence Intervals for Odds Ratio of Treatment Failures
Evaluable Patients
PK 526



DEMOGRAPHIC SUBSET OF ALL TREATED AND EVALUABLE PATIENTS:

No demographic variables were observed which affected the efficacy outcome for either the all treated or the evaluable patients groups. For all subsets, the incidence rates of DVT in the enoxaparin 30 mg q12h and the 40 mg QD groups were lower than those observed in the enoxaparin 10 mg QD group.

SURGICAL SUBSETS OF ALL TREATED AND EVALUABLE PATIENTS:

The incidence of DVT was similar among all patients with regard to type of surgery, type of anesthesia, use of surgical cement and use of GCS. The overall incidence of DVT and the incidence of DVT within each treatment group for each of the subpopulations demonstrated the same trends in the evaluable patients.

SAFETY RESULTS

All patients who received at least one dose of study medication were included in the safety analysis.

The mean exposure of patients to study medication, in terms of mean number of days (6.9 ± 1.30 days; range 1-11 days) and mean number of doses (12.7 ± 2.6 ; range 1-20), was similar in each of the three groups.

BLEEDING EVENTS: The incidence rate of bleeding episodes in the three treatment groups and the statistical analysis of the results are shown in 10.1.

Table 10.1
Summary of Patients with Episodes of Bleeding
(Appendix B.12.1)

Bleeding	Treatment Group			Overall n (%)
	10 mg QD n (%)	40 mg QD n (%)	30 mg q12h n (%)	
All Treated Patients	161(100%)	199(100%)	208(100%)	568(100%)
Major/Minor	8 (5%)	21(11%)	26(13%)	55(10%)
Major	3(2%)	7(4%)	11(5%)	21(4%)
Minor	5(3%)	14(7%)	15(7%)	34(6%)
None	153(95%)	178(89%)	182(88%)	513(90%)

Between-Group Comparison of the Incidence of Patients with Bleeding Episodes:

Comparison	Odds Ratio ^a	p-value	95% Confidence Interval for Odds Ratio
Major or Minor Bleeding Episodes:			
Enoxaparin 10 mg QD; 40 mg QD ^b	0.45	0.1482	(0.17, 1.22)
Enoxaparin 10 mg QD; 30 mg q12h ^b	0.37	0.0450 ^c	(0.14, 0.98)
Enoxaparin 40 mg QD; 30 mg q12h	0.83	>0.50	(0.44, 1.56)
Major Bleeding Episodes:			
Enoxaparin 10 mg QD; 40 mg QD ^b	0.63	>0.50	(0.13, 3.16)
Enoxaparin 10 mg QD; 30 mg q12h ^b	0.37	0.2950	(0.08, 1.72)
Enoxaparin 40 mg QD; 30 mg q12h	0.59	0.3049	(0.22, 1.62)

- a Estimated from a logistic regression model with treatment and center effects.
- b Two-sided p-values and confidence intervals are Bonferroni-adjusted (multiplied by 2).
- c Statistically significant at the 5% level.

A statistically significant difference was found between the enoxaparin 30 mg q12h and the 10 mg qd groups for combined major and minor bleeding. A numerical difference between the three groups suggestive of a relationship between incidence of major bleeding and enoxaparin dose persisted, but it was not statistically significant.

Most major bleeding episodes occurred at the operative site. The incidence of major bleeding at operative site was <1% in the enoxaparin 10 mg qd, 2 in the 40 mg qd and 4% in the 30 mg q12h. The incidence of major bleeding at extraoperative site was <1%. The majority of minor bleeding episodes occurred at extraoperative sites for all three treatment groups. The bleeding assessment by severity, site, and by treatment group for all treated patient population is summarized in the following table:

Number of Patients	-----Treatment Group-----			Total n=568
	10 mg qd n=161	40 mg qd n=199	30 mg q12h n=208	
Major/Minor Bleeding:	8 (5%)	21 (11%)	26 (13%)	55 (10%)
Major Bleeding:	3 (3%)	7 (4%)	11 (5%)	21 (4%)
Site:				
Wound	1 (<1%)	4 (2%)	8 (4%)	13 (2%)
Extra-operative	1 (<1%)	1 (<1%)	0	2 (<1%)
Unknown	1 (<1%)	2 (1%)	3 (1%)	6 (1%)
Minor Bleeding:	5 (3%)	14 (7%)	15 (7%)	34 (6%)
Site:				
Wound	0	1	4 (2%)	5 (<1%)
Extr-operative	3 (2%)	10 (5%)	10 (5%)	23 (4%)
Unknown	2 (1%)	3 (2%)	1 (<1%)	6 (1%)

Treatment Comparisons:

1. Incidence of Major or Minor bleeding episodes

	Odds Ratio	p-value	95% CI
10 mg QD/40 mg QD	0.45	0.1452	(0.17-1.22)
10 mg QD/30 mg q12h	0.37	0.0450	(0.14-0.98)
40 mg QD/30 mg q12h	0.83	>0.50	(0.44-1.56)

2. Incidence of Major bleeding episodes

	Odds Ratio	p-value	95% CI
10 mg QD/40 mg QD	0.63	>0.50	(0.13-3.16)
10 mg QD/30 mg q12h	0.37	0.2950	(0.08-1.72)
40 mg QD/30 mg q12h	0.59	0.3049	(0.22-1.62)

Onset of major bleeding occurred by post-operative day 3 for 18 of the 21 patients (median day 2). The mean weight (82.8 kg) of the patients with episodes of major bleeding was similar to that

of all treated patients (80.6 kg); only 4 patients weighed less than 60 kg (45.0, 50.9, 54.5, 56.8 kg).

One patient in the enoxaparin 10 mg qd and 4 patients in the 40 mg qd groups experienced clinically significant wound drainage (in excess of 1000 ml).

The transfusion requirements in the three treatment groups are summarized in the following table:

	-----Treatment Group-----			Total n=568
	10 mg qd n=161	40 mg qd n=199	30 mg q12h n=208	
Number of Patients				
Units Transfused:				
0 Units	128 (80%)	138 (69%)	151 (73%)	417 (73%)
1-2 Units	26 (16%)	36 (18%)	40 (19%)	102 (18%)
> 2 Units	7 (4%)	25 (13%)	17 (8%)	49 (9%)
Patients receiving Blood Transfusion				
N	33 (20%)	61 (31%)	57 (27%)	151 (27%)
Mean (Units)	2.2	2.8	2.5	2.5
S.D.	1.47	1.93	1.43	1.66
Range	1-8	1-13	1-8	1-13

ADVERSE EVENTS:

Overall, 562 of the 568 patients (99%) who received any study medication reported at least one adverse event. The overall incidence of adverse events was similar among the three treatment groups.

The majority of the adverse events were mild to moderate in severity. The incidence of adverse events regarded by these investigators to be severe was 18% in the enoxaparin 10 mg qd group (29/161 patients), 23% in the enoxaparin 40 mg qd (45/199 patients), and 20% in the enoxaparin 30 mg q12h group (42/208 patients).

The distribution of the adverse events by body systems is summarized in the table 12.1.

Table 12.1

Summary of Adverse Events By Body System
(All Adverse Events)
(Appendix B.13)

Body System Totals ^b	All Adverse Events Treatment Group				
	10 mg QD (n=161)	40 mg QD (n=199)	P-value ^a	30 mg q12h (n=208)	P-value ^a
Overall	159 (99%)	197 (99%)	1.000	205 (99%)	1.000
Body as a Whole	156 (97%)	192 (96%)	1.000	200 (96%)	0.782
Cardiovascular	39 (24%)	53 (27%)	0.629	69 (33%)	0.066
Digestive	104 (65%)	145 (73%)	0.108	163 (78%)	0.005*
Hemic/Lymphatic	13 (8%)	26 (13%)	0.172	40 (19%)	0.003*
Injection Site Reaction	16 (10%)	25 (13%)	0.506	25 (12%)	0.617
Metabolic and Nutritional	41 (25%)	58 (29%)	0.477	52 (25%)	1.000
Musculoskeletal	24 (15%)	18 (9%)	0.099	25 (12%)	0.442
Nervous	88 (55%)	117 (59%)	0.455	107 (51%)	0.599
Respiratory	36 (22%)	57 (29%)	0.185	51 (25%)	0.711
Skin and Appendages	65 (40%)	59 (30%)	0.035*	78 (38%)	0.591
Special Senses	12 (7%)	7 (4%)	0.104	7 (3%)	0.097
Urogenital	45 (28%)	60 (30%)	0.727	65 (31%)	0.566

- a P-value from two tailed Fisher's Exact test comparison versus enoxaparin 10 mg QD.
b Percents are based on number of treated patients in each treatment group.
* Indicates p<0.05.

The incidence rates of adverse events affecting the digestive system, specifically nausea and anorexia, were higher in the enoxaparin 30 mg q12h group.

The overall incidence of adverse events affecting the cardiovascular system (hemorrhage) and the hemic/lymphatic system was highest in the enoxaparin 30 mg q12h treatment group and lowest in the 10 mg qd group and reflected the incidence of major/minor bleeding and anemia.

The incidence of the adverse events which were regarded as related to study medication are summarized in table 12.3. With the exception of the adverse events involving the hemic/lymphatic system, the overall incidence rates of adverse

events regarded as related to study medication were similar for all three treatment groups. The most common adverse events were represented by fever, headache, pain, abdominal pain, nausea, vomiting, constipation, abnormal liver function tests, anorexia. The incidence of ecchymosis was greater among patients receiving enoxaparin 30 mg q12h than 10 mg qd. The majority of the adverse events regarded as related to study medication were of mild or moderate severity. The incidence of at least one severe adverse events considered study medication related was 2% in the enoxaparin 10mg qd group, 3% in the 40 mg qd group and 1% in the 30 mg q12h group.

Table 12.2

Summary of Adverse Events By Body System
-Excluding Those Not Study Drug Related-
(Appendix-B.14)

Body System Totals ^b	Adverse Events				
	10 mg QD (n=161)	40 mg QD (n=199)	P-value ^a	30 mg q12h (n=208)	P-value ^a
Overall	52 (32%)	64 (32%)	1.000	74 (36%)	0.580
Body as a Whole	19 (12%)	22 (11%)	0.868	25 (12%)	1.000
Cardiovascular	6 (4%)	12 (6%)	0.344	12 (6%)	0.468
Digestive	21 (13%)	20 (10%)	0.407	21 (10%)	0.411
Hemic/Lymphatic	3 (2%)	11 (6%)	0.100	17 (8%)	0.009*
Injection Site Reaction	4 (2%)	2 (1%)	0.414	6 (3%)	1.000
Metabolic and Nutritional	7 (4%)	8 (4%)	1.000	5 (2%)	0.378
Musculoskeletal	1 (<1%)	1 (<1%)	1.000	3 (1%)	0.635
Nervous	6 (4%)	6 (3%)	0.773	7 (3%)	1.000
Respiratory	6 (4%)	3 (2%)	0.309	7 (3%)	1.000
Skin and Appendages	11 (7%)	14 (7%)	1.000	12 (6%)	0.672
Special Senses	2 (1%)	1 (<1%)	0.589	1 (<1%)	0.583
Urogenital	4 (2%)	1 (<1%)	0.177	5 (2%)	1.000

^a P-value from two tailed Fisher's Exact test comparison versus enoxaparin 10 mg QD.
^b Percents are based on number of treated patients in each treatment group.
* Indicates p<0.05.

Two patients in the enoxaparin 40 mg qd group died of MI. In one patient, the MI was considered to be associated with blood loss secondary to study medication.

Overall, 26 of the 568 treated patients experienced adverse events requiring premature discontinuation of treatment. The occurrence of adverse events, serious adverse events and their classification are summarized in the following table:

	-----Treatment Group-----			Total n(%)
	10 mg qd n(%)	40 mg qd n(%)	30 mg q12h n(%)	
Patients treated:	161(100%)	199(100%)	208(100%)	568(100%)
Patient with Adverse Events	8(5%)	9(5%)	9(4%)	26(5%)
Number of Adverse Events	14(28%)	13(26%)	23(46%)	50(100%)
Events related to study medication	6/14	7/13	15/23	28/50
<u>Serious Adverse Events</u>				
Deaths	0	2	0	2/568
Patients with non-fatal adverse events:	13(8%)	16(8%)	10(5%)	39(7%)
Rehospitalization	6	4	1	
Prolonged Hospitalization	4	9	6	
Life-threatening Events	3	3	3	
Number of serious Adverse Events:	22(34%)	24(37%)	18(28%)	64(100%)

CLINICAL LABORATORY EVALUATION

Increase in platelet count occurred in all three treatment groups. A dose-dependent increase from baseline in SGOT and SGPT was observed. The elevations of the transaminases were reversible and the values had returned to baseline at follow-up evaluation. Elevation of alkaline phosphatase was noted in all groups and it was likely related to the bone surgery. The results of these laboratory tests are shown in table 15. Laboratory values of possible clinical significance noted in all three treatment groups are summarized in table 16.

Table 15
Mean Changes from Baseline[†] of Concern
in Laboratory Test Values
(Appendices B.15 and B.16)

Parameter	Treatment Group								
	10 mg QD			40 mg QD			30 mg q12h		
	n	Mean	Change	n	Mean	Change	n	Mean	Change
Hematology									
Platelets (# x 10 ³ /mm ³)									
Baseline	145	239.6	-	181	234.4	-	192	235.8	-
Day 7	110	366.9	123.1	151	361.4	127.2	160	369.9	127.1
End of Study	132	411.2	167.9	171	398.3	163.4	173	408.0	170.6
Follow-up	129	523.0	281.0	166	504.6	270.3	155	510.3	271.6
Serum Chemistry									
Alkaline Phosphatase (IU/L)									
Baseline	159	90.8	-	196	88.6	-	206	88.9	-
End of Study	143	101.9	10.0	179	104.1	16.1	193	107.5	17.8
Follow-up	135	120.3	30.3	171	119.4	31.9	170	120.3	30.6
SGOT (U/L)									
Baseline	158	24.4	-	196	28.0	-	205	25.3	-
End of study	141	37.6	13.1	180	47.0	18.7	192	46.3	20.8
Follow-up	136	27.6	3.1	173	25.5	-2.2	171	24.2	-1.7
SGPT (U/L)									
Baseline	136	24.6	-	168	35.2	-	164	24.0	-
End of Study	116	42.3	17.1	147	54.6	29.5	139	50.3	34.9
Follow-up	108	29.4	4.9	137	32.5	8.0	133	27.2	2.8

[†] Baseline for hematology parameters was post-surgery, day 1 of study drug treatment. Baseline for serum chemistry parameters was presurgery.

Table 16
Summary of the On-Study Incidence of Patients with Clinically Significant Values for Selected Laboratory Parameters
(Appendix B.19)

Parameter Value	Treatment Group		p-value ^a	30 mg q12h n (%)	p-value ^a	Overall n (%)
	10 mg QD n (%)	40 mg QD n (%)				
All Treated Patients	161(100%)	199(100%)		208(100%)		568(100%)
Platelets: Thrombocytopenia ^b						
Mild	17(11%)	23(12%)	0.866	28(13%)	0.427	68(12%)
Moderate	1(<1%)	2(1%)	1.000	1(<1%)	1.000	4(<1%)
Platelets: Thrombocytosis ^c						
Mild	98(61%)	134(67%)	0.224	138(66%)	0.325	370(65%)
Moderate	44(27%)	59(30%)	0.641	44(21%)	0.177	147(26%)
Severe	2(1%)	1(<1%)	0.589	2(<1%)	1.000	5(<1%)
Hemoglobin:						
< 8 gm/dL	15(9%)	35(18%)	0.400	32(15%)	0.086	72(13%)
Dec \geq 2 gm/dL	35(22%)	53(27%)	0.324	69(33%)	0.019*	157(28%)
Total Bilirubin:						
> 2 mg/dL	0	1(<1%)	1.000	1(<1%)	1.000	2(<1%)
SGOT:						
3-6x Normal	5(3%)	11(6%)	0.313	7(3%)	1.000	23(4%)
> 6x Normal	0	1(<1%)	1.000	1(<1%)	1.000	2(<1%)
SGPT:						
3-6x Normal	4(2%)	9(5%)	0.399	9(4%)	0.404	22(4%)
> 6x Normal	0	4(2%)	0.131	3(1%)	0.260	7(1%)
Alkaline Phosphatase:						
> 2x Normal	6(4%)	10(5%)	0.615	10(5%)	0.798	26(5%)
BUN:						
\geq 30 mg/dL	6(4%)	12(6%)	0.344	3(1%)	0.186	21(4%)
Creatinine:						
\geq 2 mg/dL	2(1%)	4(2%)	0.695	1(<1%)	0.583	7(1%)

^a P-values from two-tailed Fisher's Exact Test comparison versus the 10 mg QD group

^b Platelets, thrombocytopenia:
Mild, $100,000/\text{mm}^3 \leq x <$ lower limit of normal;
Moderate, $20,000/\text{mm}^3 \leq x < 100,000/\text{mm}^3$;
Severe, $x < 20,000/\text{mm}^3$;

^c Platelets, thrombocytosis:
Mild, upper limit of normal $< x < 600,000/\text{mm}^3$;
Moderate, $600,000/\text{mm}^3 \leq x < 1,000,000/\text{mm}^3$;
Severe, $x \geq 1,000,000/\text{mm}^3$.

Dec, Decrease.

Normal, upper limit of investigator's normal range.

* Indicates $p < 0.05$.

Mild thrombocytopenia occurred with similar frequency in all three groups. The proportion of patients with drop in hemoglobin greater than 2 gm/dL or with hemoglobin values of less than 8 gm/dL was higher in the enoxaparin 30 mg q12h group.

The number of patients in each of the three treatment groups with markedly abnormal laboratory values are summarized in the following table:

Laboratory Parameter	-----Treatment Group-----			Total
	10 mg qd	40 mg qd	30 mg q12h	
Hemoglobin < 7gm/dL	n	n	n	n
Hemoglobin < 7gm/dL	1	3	4	8
Platelet count <10 ⁵ /mm ³	1	2	1	4
platelet count >10 ⁶ /mm ³	2	1	2	5
ALP >300 U/L	3	3	6	12
SGPT >6x UNL	0	4	3	7
SGOT >6x UNL	0	1	1	2
Bilirubin >2mg/dL	0	1	1	2
BUN ≥30 mg/dL	6	12	3	21
Creatinin ≥ 2 mg/dL	2	4	1	7

CONCLUSIONS AND COMMENTS:

The study assessed the effect of three regimens of enoxaparin: 10 mg QD, 40 mg QD and 30 mg q12h on the prevention of DVT in elective hip replacement.

The study has shown that the post-operative administration of enoxaparin at the dose of 30 mg q12h was associated with a incidence rate of DVT of 11%; this represents a statistically and clinically significant reduction from the 25% incidence rate of DVT observed when 10 mg QD of enoxaparin were administered. The dose of 40 mg QD reduced the incidence of DVT to 14%; this represented a statistically significantly lower rate than that observed with 10 mg QD, but it was not significantly different from the effect of 30 mg q12h.

The incidence of combined major and minor bleeding complications was 13% in the 30 mg q12h dose group and 5% in the 10 mg QD dose group; this difference was not statistically significant. The incidence of major bleeding in the 40 mg QD and in the 30 mg q12h dose groups was 4% and 5% respectively, versus 2% in the 10 mg QD dose group. This difference was not statistically significant. More patients in the 30 mg q12h dose group experienced drop in hemoglobin of more than 2 gm/dL than in the other dose groups, however, the transfusion requirements were similar in all three groups.

An apparent dose-related increase from baseline in SGOT and SGPT was observed. This did not represent an unanticipated adverse event as similar dose-related increase in transaminases have been previously described with the administration of both heparin and enoxaparin. The etiology of this reversible abnormality is unknown.

OVERALL SUMMARY:

The sponsor has submitted the results of four controlled studies in support of the claim that enoxaparin is safe and effective for the prevention of thromboembolic complications following elective hip replacement. An overview of the four studies is presented in the following table:

Protocol Number	Study Design	Location	Treatment Start and Duration	Treatment Groups and Regimen
ENO 884	D-B Placebo- Controlled	Canada	Within 12-24 hr post-op. Up to 14 days post-op.	Placebo Control Enoxaparin 30 mg q12h
PK 523	D-B Controlled	Canada	Within 12-24 hr post-op. Up to 14 days post-op.	Heparin control 7500 IU q12h Enoxaparin 30 mg q12h
PK 525	Open-label Controlled	US	Within 2 days post-op. Up to 7 days post-op.	Heparin control 5000 U q8h Enoxaparin 40 mg QD Enoxaparin 30 mg q12h
PK 526	D-B Dose-ranging	US	Within 2 days post-op. Up to 7 days post-op.	Enoxaparin 10 mg QD Enoxaparin 40 mg QD Enoxaparin 30 mg q12h

Prior to the North American clinical trials, the efficacy and safety of enoxaparin in the prevention of DVT in orthopedic surgery had been investigated in Europe. Three clinical trials were conducted in Europe: one trial compared the effect of four regimens of enoxaparin: 40 mg qd, 60 mg qd, 30 mg q12h and 20 mg q12h; the second trial demonstrated that doses of 40 mg qd or 20 mg q12h were effective in preventing DVT in orthopedic patients; the third trial showed that the 40 mg qd regimen was more effective than unfractionated heparin 5000 U q8h in reducing the incidence of DVT in orthopedic patients.

In the European studies, the subcutaneous administration of enoxaparin was started few hours before surgery and was continued for 10-14 days.

In the North American clinical studies, the enoxaparin regimen was adapted to the current orthopedic practice which favors the post-operative initiation of prophylactic anticoagulation to reduce the risk of perioperative bleeding. Treatment was, in fact, initiated 12-24 hr post-surgery in the two Canadian studies and within 2 days post-operatively in the US studies.

The enoxaparin dosage used in these trials was selected on the basis of data from PK studies, from studies on experimental thrombosis and from the results of the European trials. As the preoperative dose of enoxaparin was omitted in the north american studies, a twice daily administration of enoxaparin was selected in the attempt to reduce the risk of thromboembolic events originating intra-operatively.

A total of 1940 patients received study drug therapy in the four North American trials included in this NDA: of them, 1349 received enoxaparin, 50 received placebo, and 541 received heparin. The number of patients, their demographic characteristics and selected surgery parameters of each treatment group for each trial are summarized in table 2.1. No significant differences were noted among treatment groups in each of the studies.

TABLE 2.1
SUMMARY OF DEMOGRAPHIC INFORMATION AND SELECTED SURGERY PARAMETERS FOR ALL TREATED PATIENTS
(By Trial/Regimen)
(Page 1 of 2)

Trial	EMO 224		PK 221		PK 226			PK 225		
	Placebo 30mg (q12h)	Enoxacin 30mg (q12h)	Enoxacin 30mg (q12h)	Netarsin 7500IU (q12h)	Enoxacin 10mg (QD)	Enoxacin 40mg (QD)	Enoxacin 30mg (q12h)	Enoxacin 40mg (QD)	Enoxacin 30mg (q12h)	Netarsin 5000IU (q8h)
Characteristics	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Number of Patients	50	50	333	332	161	199	208	203	195	209
SEX										
Male	19 (38%)	26 (52%)	145 (44%)	160 (48%)	107 (66%)	127 (64%)	124 (60%)	99 (49%)	90 (50%)	101 (48%)
Female	31 (62%)	24 (48%)	188 (56%)	172 (52%)	54 (34%)	72 (36%)	84 (40%)	104 (51%)	97 (50%)	108 (52%)
Age (Years)										
Number of Patients	50	50	333	332	161	199	208	203	195	209
Number of Patients < 65	21 (42%)	18 (36%)	138 (41%)	121 (36%)	69 (43%)	84 (42%)	90 (44%)	96 (47%)	81 (41%)	81 (39%)
Number of Patients ≥ 65	29 (58%)	32 (64%)	195 (59%)	211 (64%)	92 (57%)	115 (58%)	117 (56%)	107 (53%)	112 (57%)	128 (61%)
Mean	67.4	66.8	66.2	66.7	63.9	64.8	65.2	65.0	65.6	65.6
SD	8.9	8.6	10.4	9.1	10.5	10.3	10.6	11.3	11.0	10.7
Median	67.5	67.0	67.0	68.0	66.0	66.0	65.0	66.0	67.0	67.0
Range	44-82	43-84	40-91	40-91	31-83	39-85	40-88	40-91	40-89	37-88
Body Weight (Kg)										
No of Males ≤ Median	10 (53%)	21 (81%)	69 (61%)	90 (54%)	52 (40%)	54 (43%)	50 (40%)	43 (43%)	27 (30%)	51 (51%)
No of Males > Median	9 (47%)	5 (19%)	54 (37%)	60 (43%)	92 (56%)	69 (54%)	71 (57%)	55 (56%)	60 (61%)	47 (47%)
Males with no weight data	0	0	2 (1%)	2 (1%)	2 (2%)	4 (2%)	3 (2%)	1 (1%)	1 (1%)	3 (3%)
No of Females ≤ Median	10 (50%)	14 (50%)	100 (50%)	99 (50%)	22 (41%)	25 (49%)	40 (40%)	49 (47%)	52 (54%)	41 (38%)
No of Females > Median	13 (42%)	10 (42%)	75 (40%)	72 (42%)	32 (59%)	36 (50%)	42 (50%)	53 (51%)	44 (45%)	65 (60%)
Females with no weight data	0	0	4 (2%)	1 (<1%)	0	1 (1%)	2 (2%)	2 (2%)	1 (1%)	2 (2%)
Current Smoking Status										
Smoker	0	0	0	0	31 (19%)	39 (20%)	40 (19%)	33 (16%)	34 (17%)	32 (15%)
Non-smoker	0	0	0	0	130 (81%)	160 (80%)	160 (81%)	170 (84%)	161 (83%)	177 (85%)
Unspecified	50(100%)	50(100%)	333(100%)	332(100%)	0	0	0	0	0	0
Type of Surgery										
Primary	50(100%)	50(100%)	261 (78%)	254 (77%)	140 (87%)	154 (78%)	177 (85%)	169 (83%)	160 (82%)	161 (77%)
Revision	0	0	70 (21%)	76 (23%)	21 (13%)	45 (23%)	21 (10%)	30 (15%)	25 (13%)	38 (18%)
Unspecified/Other	0	0	2 (<1%)	2 (<1%)	0	0	0	4 (2%)	2 (1%)	0
Type of Anesthesia										
Regional/Epidural	0	0	8 (2%)	13 (4%)	47 (29%)	64 (32%)	57 (27%)	64 (32%)	56 (29%)	60 (29%)
IV/Inhalation	0	0	327 (98%)	319 (96%)	114 (71%)	135 (68%)	151 (73%)	114 (56%)	130 (67%)	128 (60%)
Unspecified	50(100%)	50(100%)	0	0	0	0	0	25 (12%)	19 (10%)	24 (11%)
Created Prosthesis										
Used	0	0	129 (39%)	120 (36%)	65 (40%)	87 (44%)	87 (42%)	55 (27%)	45 (23%)	60 (29%)
Not Used	0	0	204 (61%)	202 (61%)	96 (60%)	110 (55%)	121 (58%)	146 (73%)	149 (76%)	149 (71%)
Unspecified	50(100%)	50(100%)	0	0	0	2 (1%)	0	2 (<1%)	1 (<1%)	0
Graded Compression Stocking										
Used	0	0	0	0	91 (57%)	111 (56%)	125 (60%)	69 (34%)	70 (36%)	67 (32%)
Not Used	0	0	0	0	70 (43%)	88 (44%)	83 (40%)	109 (54%)	104 (53%)	118 (56%)
Unspecified	50(100%)	50(100%)	333(100%)	332(100%)	0	0	0	25 (12%)	21 (11%)	24 (11%)
HEARS/Ambly										
Used	5 (10%)	12 (24%)	25 (8%)	21 (6%)	56 (35%)	62 (31%)	77 (37%)	49 (24%)	39 (20%)	47 (23%)
Not Used	45 (90%)	38 (76%)	308 (92%)	311 (94%)	105 (65%)	137 (69%)	131 (63%)	154 (76%)	155 (80%)	161 (77%)
Unspecified	0	0	0	0	0	0	0	0	1 (<1%)	1 (<1%)

* Note: Some in the Regional/Epidural group may have received IV or inhalation anesthesia as a supplement.

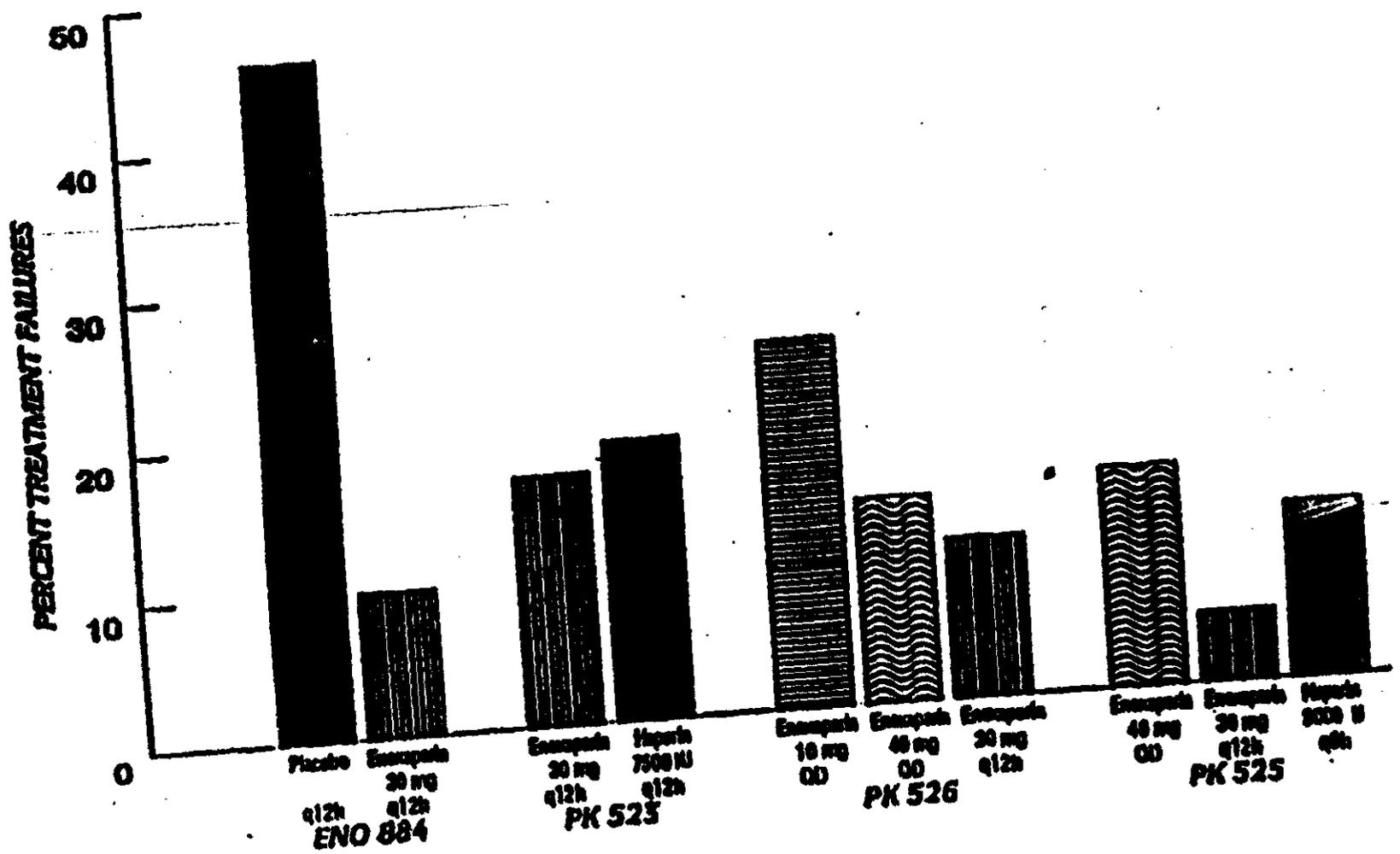
Table 1.4 summarizes the treatment groups, the treatment regimens, the total number of patients randomized, treated and evaluable, as well as the reasons for exclusion from analyses. Two efficacy analyses were performed in each study: one analysis included all the patients who had received study treatment and had undergone any evaluation of efficacy (all treated patients), the second analysis included all the patients who had received full treatment, had had definite evaluation of efficacy, and had not incurred any protocol violation (evaluable patients).

TABLE 1.4
SUMMARY OF PATIENT EVALUABILITY BY TRIAL
(By Trial/Regimen)

Trial	PK 524		PK 525		PK 526			PK 527		
	Placebo 30mg (q12h)	Enoxacin 30mg (q12h)	Enoxacin 30mg (q12h)	Enoxacin 30000 (q12h)	Enoxacin 10mg (QD)	Enoxacin 40mg (QD)	Enoxacin 30mg (q12h)	Enoxacin 40mg (QD)	Enoxacin 30mg (q12h)	Enoxacin 30000 (q24h)
Patients										
Number Treated	50	50	333	332	161	199	200	203	198	200
Number Evaluable (%)	31 (62%)	27 (54%)	236 (71%)	250 (75%)	116 (72%)	149 (74%)	143 (69%)	136 (67%)	136 (70%)	142 (69%)
Not Evaluable (%)	19 (38%)	23 (46%)	97 (29%)	82 (25%)	45 (28%)	50 (25%)	57 (28%)	67 (33%)	62 (31%)	58 (29%)
Reasons For Exclusion Prior to Mandatory Venography										
Mandatory Venography (%)	11 (22%)	19 (38%)	-	-	-	-	-	-	-	-
Mandatory Venography Not Done										
(%)	6 (12%)	5 (10%)	34 (10%)	38 (11%)	40 (25%)	46 (23%)	50 (25%)	57 (28%)	54 (27%)	61 (30%)
Mandatory Venography Inadequate										
(%)	0	1 (2%)	40 (12%)	27 (8%)	2 (1%)	2 (1%)	6 (3%)	4 (2%)	2 (1%)	0
Insufficient Therapy										
(%)	0	0	6 (2%)	2 (1%)	3 (2%)	2 (1%)	1 (1%)	2 (1%)	3 (2%)	5 (2%)
Inappropriate Surgery										
(%)	0	0	0	0	0	0	0	3 (1%)	0	1 (1%)
Prohibited Medication and/or Therapy										
(%)	2 (4%)	4 (8%)	17 (5%)	15 (5%)	0	0	0	1 (1%)	0	0

The overall DVT findings (defined as percentage of treatment failure) for all treated patients with efficacy data of each treatment group in each study are shown in Figure I.

FIGURE 1
Overall Percentage of Treatment Failures by Trial & Dosage Regimen



The efficacy results expressed as total numbers of DVT, overall incidence of DVT and incidence of proximal DVT in the all treated patients and in the evaluable patients groups in each treatment group are summarized in Table A.

-TABLE A-

Group Dosing Regimen	Plcb	Enoxap 10 mg QD	Enoxap 30 mg q12h	Enoxap 40 mg QD	Hepar 5000U q8h	Hepar 7500U q12h
Trial No.						
ENO 884						
All Treated:	50		50			
Overall No. DVT	23		5			
DVTs	46%		10%			
Proximal DVTs	22%		2%			
p-value			0.0002			
Evaluable Patients:						
Overall No. DVT	31		27			
DVTs	61%		15%			
PK 523						
All Treated:			333			332
Overall No. DVT			57			63
DVTs			17%			19%
Proximal DVTs			5%			5%
p-value versus Heparin			0.5317			
Evaluable Patients:						
Overall No. DVT			236			250
DVTs			43			58
DVTs			18%			23%
p-value versus Heparin			0.1611			
PK 526						
All Treated:	161	209		199		
Overall No. DVT	40	22		27		
DVTs	25%	11%		14%		
Proximal DVTs	11%	4%		5%		
p-value versus 10 mg QD			0.0008		0.0168	
p-value versus 40 mg QD			0.3369			
Evaluable Patients:						
Overall DVT	116	143		149		
DVTs	36	16		21		
DVTs	31%	11%		14%		
p-value versus 10 mg QD			0.0008		0.0054	
p-value versus 40 mg QD			0.4783			
PK 525						
All Treated:		194	203		207	
Overall No. DVT		9	30		24	
DVTs		5%	15%		12%	
Proximal DVTs		2%	4%		5%	
p-value versus Heparin			0.0278		0.2366	
p-value versus 40 mg QD			0.0002			
Evaluable Patients:						
Overall DVT		136	136		142	
DVTs		8	28		21	
DVTs		6%	21%		15%	
p-value versus Heparin			0.1030		0.0636	
p-value versus 40 mg QD			0.0003			

The enoxaparin regimen of 30 mg q12h was superior to placebo and to enoxaparin 10 mg QD in preventing DVT in elective hip replacement. When compared to heparin, enoxaparin 30 mg q12h was more effective than heparin 5000 U q8h and was as effective as heparin 7500 U q12h. The enoxaparin regimen of 40 mg once daily was as effective as enoxaparin 30 mg q12h in one study and was less effective in another study.

Table B shows the overall pooled incidence of DVT, proximal DVT and PE from all studies for each dose regimen. The studies differed in design and duration of therapy and their pooled results is not meant to represent a metanalysis, but rather to show the overall incidence of proximal DVT and PE in each treatment group. The incidence of proximal DVT was higher in the placebo, enoxaparin 10 mg QD, and heparin 5000 U q8h groups than in the other three groups, however, the difference was not statistically significant. No correlation is apparent between the number of proximal DVT and incidence of PE in each treatment group. The occurrence of PE was higher in the combined heparin groups (6/539) than in the enoxaparin 30 mg q12h group (1/786).

-TABLE B-

<u>Group</u> <u>Dosing Regimen</u>	<u>Plcb</u>	<u>Enoxap</u> <u>10 mg</u> <u>QD</u>	<u>Enoxap</u> <u>30 mg</u> <u>q12h</u>	<u>Enoxap</u> <u>40 mg</u> <u>QD</u>	<u>Hepar</u> <u>5000 U</u> <u>q8h</u>	<u>Hepar</u> <u>7500 U</u> <u>q12h</u>
Total Patients	50	161	786	402	207	332
Overall No. DVT	23	40	53	57	24	63
Overall DVT%	46%	25%	11.8%	14%	12%	19%
No. Proximal DVT	11	17	29	17	10	18
Proximal DVT%	22%	11%	3.6%	4.2%	5.0%	5.4%
No. PE	1	1	1	2	4	2

The incidence rates of DVT were analyzed in all subgroup by demographic parameters (gender, age, weight), current smoking status, type of surgery, anesthesia and surgical characteristics that may influence the outcome of the study. The effect of enoxaparin 30 mg q12h appeared to be consistent across the subgroups in all four studies. Two studies analyzed the incidence of DVT in smokers and non-smokers within the enoxaparin 30 mg q12h regimen, the incidence of DVT was 6% and 10% for smokers and 4% and 11% for non-smokers.

With respect to the type of surgery, the incidence of DVT ranged from 5% to 16% for primary hip replacement and from 0% to 23% for revision surgery, the latter group was, however, small.

Antithrombotic prophylaxis was started within 24 hours from surgery and was continued for 10-14 days in two studies, while it

was started within two days postoperatively and continued for only 7 days in the other two studies. The rates of treatment failures did not differ significantly according to initiation or duration of treatment.

No studies have been performed to compare directly the effectiveness of preoperative versus postoperative initiation of enoxaparin therapy. Only one study designed to assess the efficacy and safety of enoxaparin with subarachnoid block or general anesthesia compared 1) enoxaparin administered 12 hours prior to general anesthesia, 2) enoxaparin administered post-subarachnoid block and immediately preoperatively and 3) enoxaparin administered after subarachnoid block and after surgery. The results showed that the three groups were statistically comparable for both efficacy and safety.

Safety evaluation included all patients who had received any amount of study medication regardless of efficacy evaluation. The most pertinent adverse events for both enoxaparin and heparin were represented by bleeding complications. A summary of the combined major and minor bleeding events reported in the all treated patient population from each study is shown in Table C.

-TABLE C-

<u>Group</u> <u>Dosing Regimen</u>	<u>Plcb</u>	<u>Enoxap</u> <u>10 mg</u> <u>QD</u>	<u>Enoxap</u> <u>30 mg</u> <u>q12h</u>	<u>Enoxap</u> <u>40 mg</u> <u>QD</u>	<u>Hepar</u> <u>5000 U</u> <u>q8h</u>	<u>Hepar</u> <u>7500 U</u> <u>q12h</u>
Total Patients	50	161	786	402	207	332
<u>Bleeding:</u>						
Major + Minor	2 (4%)	8 (4.9%)	69 (8.7%)	42 (10%)	25 (12%)	31 (9.3%)
Major	2 (4%)	3 (2%)	31 (3.9%)	10 (2.4%)	13 (6.2%)	19 (5.7%)
Minor	0 (0%)	5 (3.1%)	38 (4.8%)	32 (7.9%)	12 (5.7%)	12 (3.6%)

The incidence of major and minor bleeding in the enoxaparin 30 mg q12h and 40 mg QD was higher than the placebo or the 10 mg QD and was similar to either heparin group. The incidence of major bleeding was lower in the enoxaparin 30 mg q12h group than in either heparin group, but greater than placebo or enoxaparin 10 mg QD groups. However, hemorrhage was reported as cause of study discontinuation by 5/786 enoxaparin 30 mg q12h-treated patients compared to 1/541 heparin-treated patients.

When analyzed for subgroups, no differences in bleeding were noted for gender, age and body weight in the enoxaparin regimen; however, a greater incidence of bleeding events occurred in the heparin groups in women. In all groups, bleeding manifestations, mainly ecchymosis, were more frequent in patients on concomitant therapy with aspirin or NSAID and other anticoagulants.

The analysis of all other adverse events (except bleeding) were performed on the two heparin regimens combined under the single group of Heparin 15,000 U/day. The incidence of serious adverse events is shown in Table D.

-TABLE D-

<u>Group</u> <u>Dosing Regimen</u>	<u>Picb</u>	<u>Enoxap</u> <u>10 mg</u> <u>QD</u>	<u>Enoxap</u> <u>30 mg</u> <u>q12h</u>	<u>Enoxap</u> <u>40 mg</u> <u>QD</u>	<u>Heparin</u> <u>15,000 U</u> <u>q24h</u>
Total Patients	50	161	786	402	541
Serious Adverse Events	2 (4%)	13 (8%)	32 (4%)	29 (7%)	26 (5%)
Termination due to Adverse Events	8 (16%)	8 (5%)	29 (4%)	15 (4%)	23 (4%)
Study-related Adverse Events	58% (?) (small sample)	32%	32%	27%	33%
Deaths	1		1	2	2

The incidence of overall adverse events in the enoxaparin 30 mg q12h dose group was more frequent in older patients.

No dose-related trends were observed among the three doses of enoxaparin for the overall incidence of adverse events. Among the related adverse events, a dose-related increased incidence of hemorrhage, anemia and edema were observed. The incidence of hemorrhage was 2% with the 10 mg QD dose, 3% with the 40 mg QD dose and 5% with the 30 mg q12h dose. The incidence of severe related adverse events also showed a dose-related trend (2% in both 10 mg QD and 40 mg QD doses and 7% in the 30 mg q12h dose). When the incidence of adverse events was compared between the selected dose regimen of enoxaparin 30 mg q12h and the conventional heparin regimens, no significant differences were noted in the incidence of all adverse events, related adverse events, and severe related adverse events. The adverse events reported in these two major groups are shown in Table 6.1.4.

Table 6.1.4

ADVERSE EVENTS OCCURRING AT >=2% INCIDENCE IN THE
ENOXAPARIN 30 MG Q12H OR HEPARIN TREATMENT REGIMENS
IN STUDIES PK523 AND PK525
(Excluding Unrelated Adverse Events)

Body System/ COSTART Term	Enoxaparin 30 mg q12h N=528		Heparin 15000 U/24h N=541	
	Severe	Total	Severe	Total
BODY AS A WHOLE	2%	6%	4%	9%
Fever	<1%	3%	<1%	3%
Pain	<1%	2%	1%	3%
CARDIOVASCULAR	2%	9%	3%	9%
Hemorrhage	<1%	6%	<1%	5%
DIGESTIVE	1%	6%	3%	7%
Nausea	<1%	2%	<1%	2%
Vomiting	0%	<1%	<1%	2%
HEMIC/LYMPHATIC	2%	7%	4%	11%
Echymosis	<1%	1%	<1%	2%
Hypochromic anemia	1%	4%	3%	7%
INJECTION SITE REACTIONS	<1%	2%	<1%	3%
Injection Site Hemorrhage	0%	<1%	<1%	2%
METABOLIC/ NUTRITIONAL	3%	8%	2%	9%
Edema	2%	3%	<1%	2%
Peripheral Edema	2%	4%	1%	5%
NERVOUS	<1%	4%	2%	4%
Confusion	<1%	2%	<1%	1%
Dizziness	0%	<1%	<1%	2%
RESPIRATORY	<1%	2%	<1%	2%
SKIN AND APPENDAGES	<1%	1%	<1%	4%
UROGENITAL	<1%	2%	<1%	2%

Extracted from Appendix A.6.2.

Mean increases from baseline were reported for platelets, alkaline phosphatase, LDH, SGOT and SGPT for both enoxaparin and heparin regimens. A dose-related increase in SGOT and SGPT was observed with enoxaparin, the increase seen with enoxaparin 30 mg q12h was similar to that seen with heparin 15,000 U/24h.

The increased levels of alkaline phosphatase were most likely attributable to bone reformation secondary to surgery. The increased platelet counts represented reactive thrombocytosis secondary to surgery. (The laboratory values which showed

changes considered as possibly clinically significant are summarized in Table 8.3.)

Table 8.3

SUMMARY OF THE ON-STUDY INCIDENCE OF PATIENTS WITH CLINICALLY SIGNIFICANT VALUES FOR SELECTED LABORATORY PARAMETERS

Parameter	Placebo	Enoxaparin			Heparin
		10 mg QD	40 mg QD	30 mg q12h	15000 U/24h
Value	N (%)	N (%)	N (%)	N (%)	N (%)
All Treated	50 (100%)	161 (100%)	402 (100%)	786 (100%)	541 (100%)
Platelets: Thrombocytopenia^a					
Mild	4 (8%)	17 (11%)	50 (12%)	141 (18%)	102 (19%)
Moderate	1 (2%)	1 (<1%)	5 (1%)	17 (2%) ^c	17 (3%)
Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)
Platelets: Thrombocytosis^b					
Mild	9 (18%)	98 (61%)	258 (64%)	499 (63%)	351 (65%)
Moderate	9 (18%)	44 (27%)	120 (30%)	215 (27%)	144 (27%)
Severe	0 (0%)	2 (1%)	4 (<1%)	5 (<1%)	4 (<1%)
Hemoglobins:					
<9 gm/dL	1 (2%)	15 (9%)	53 (13%)	102 (13%)	85 (16%)
Dec \geq 2 gm/dL	6 (12%)	35 (22%)	102 (25%)	204 (26%)	149 (28%)
SGOT:					
3-6x Normal	0	5 (3%)	19 (5%)	22 (3%)	19 (4%)
>6x Normal	0	0 (0%)	2 (<1%)	4 (<1%)	3 (<1%)
SGPT:					
3-6x Normal	0	4 (2%)	17 (4%)	34 (4%)	22 (4%)
>6x Normal	0	0 (0%)	6 (1%)	10 (1%)	7 (1%)
Bilirubin:					
> 2 gm/dL	0	0	2 (<1%)	3 (<1%)	5 (<1%)
Alk-Phosphatase:					
>2x Normal	2 (4%)	6 (4%)	21 (5%)	36 (5%)	39 (7%)
Creatinine:					
\geq 2 mg/dL	0	2 (1%)	4 (<1%)	8 (1%)	4 (<1%)
BUN:					
\geq 30 mg/dL	0	6 (4%)	19 (5%)	25 (3%)	32 (6%)

a Platelets, thrombocytopenia:
Mild, $100,000/\text{mm}^3 < x <$ lower limit of normal;
Moderate, $20,000/\text{mm}^3 < x < 100,000/\text{mm}^3$;
Severe, $x < 20,000/\text{mm}^3$;

b Platelets, thrombocytosis:
Mild, upper limit of normal $< x < 600,000/\text{mm}^3$;
Moderate, $600,000/\text{mm}^3 < x < 1,000,000/\text{mm}^3$;
Severe, $x \geq 1,000,000/\text{mm}^3$.

Dec, Decrease; Normal, upper limit of normal range.

c A data entry error was made for the end of study platelet count for patient number 7002 in the enoxaparin treatment group. The erroneous value of $30,000/\text{mm}^3$ remains in the database and is included in the total number of patients for whom moderate thrombocytopenia was reported. The correct value from the case report from is $306,000/\text{mm}^3$.

Extracted from Appendix A.15.

Mild thrombocytopenia was frequently observed in all treatment groups. It must be noted that moderate thrombocytopenia is defined here as a platelet count less than 100.000 cmm and as low as 20.000 cmm. However, given the fact that the clinical significance and the etiological implications of a platelet count of 100.00 cmm are quite different from those of a platelet count of 20.000 cmm, a lower value of 50.000 cmm seems more appropriate for the definition of moderate thrombocytopenia. It is of interest that the cases of thrombocytopenia reported with the administration of enoxaparin ranged between 100.000 and 75.000 cmm and occurred in the first few post-operative days. This degree of thrombocytopenia is likely related to the surgical procedure. On the other hand, in study PK 523 three patients in the heparin group experienced reduction of platelet count of 18.000, 28.000 and 34.000 cmm respectively. In these patients, the onset of thrombocytopenia was more delayed (day 9, 8 and 9) suggestive of heparin-induced thrombocytopenia. One heparin patient in study PK 525 was reported to have experienced thrombocytopenia with thrombosis. It must be emphasized, however, that the administration of enoxaparin in these studies has been of limited duration and that none of the patients had received the drug previously. Thus, at present, it is not possible to determine whether this compound is less immunogenic than unfractionated heparin or whether it cross-react with heparin-induced antibodies.

SUMMARY OF SAFETY FROM EUROPEAN STUDIES AND POST-MARKETING SURVEILLANCE:

Enoxaparin is approved in Europe and in several other countries for prophylaxis of DVT and PE in orthopedic surgery, and for anticoagulation in patients on hemodialysis.

A summary of the adverse events encountered during the European Phase II and III clinical trials, spontaneously reported during the post-marketing surveillance, or reported in the course of other clinical trials has been included with the NDA.

A total of 1463 patients received enoxaparin during phase II and III trials. The overall incidence of adverse events ranged from 13 to 36% across the treatment groups. The majority of adverse events were represented by injection site hematomas and wound hematomas. The incidence of wound hematoma with enoxaparin 30 mg q12h was higher than that reported in the North American trials and probably due to the preoperative administration of the drug. The adverse events encountered in the studies that assessed the enoxaparin for other indications (hemodialysis, cardiopulmonary bypass) consisted mainly in bleeding complications or lack of efficacy.

The European post-marketing clinical trials reporting of adverse events included eight patients who experienced serious and unexpected adverse events represented by hematoma, anemia, MI, intestinal necrosis, 2 reports of DIC, circulatory failure, CVA. Of these 8 patients, 3 died, 2 recovered with sequelae and 3 recovered.

Nineteen serious adverse events not reasonably associated with study medication were reported in 19 patients. They included 9 PE, 3 MI, 2 CVA, 2 DVT, 1 each of cardiac failure, sepsis and renal cyst.

Since approval of enoxaparin in Europe in 1987, 40,000,000 doses have been sold for an estimated patients population of 4,000,000. Post-marketing-spontaneous reporting of adverse events include 218 events involving 181 patients. Adverse events included 47 cases of hemorrhagic manifestations, 45 cases of thrombocytopenia and 25 cases of hypersensitivity including three cases of anaphylactoid reactions.

Twenty-five patients with heparin-induced thrombocytopenia were treated with enoxaparin iv or sc; one patient developed reversible renal failure, one patient developed LMWH-induced thrombocytopenia, one patient died following the development of acute ischemia of the lower extremities (?heparin-related thrombotic syndrome), and one patient died of GI bleeding after discontinuation of enoxaparin and initiation of oral anticoagulant therapy.

CONCLUSIONS:

In conclusion, enoxaparin at the dose of 30 mg q12h effectively reduced the risk of DVT in patients undergoing elective hip replacement surgery as compared to placebo or to a lower dose of enoxaparin. Compared to heparin, the enoxaparin regimen of 30 mg q12h was superior to heparin 5000 q8h and at least as effective as heparin 7500 bid. No assessment of risk reduction for PE could be made even by pooled incidence.

A regimen of enoxaparin 40 mg QD was evaluated in two studies. The efficacy results were comparable to those of the 30 mg q12h regimen in the better performed study. The enoxaparin 40 mg QD could represent an alternative regimen for patients in whom single daily injections are preferred. However, the only formulation proposed for marketing consists of prefilled syringes containing 30 mg of enoxaparin.

The risks of enoxaparin therapy were those expected of anti-thrombotic therapy and were at least comparable to those of

NDA 20-164
Page 162

heparin therapy. No adverse events unique to enoxaparin were observed.

RECOMMENDATION:

Approval of enoxaparin for the prevention of DVT in patients undergoing elective hip replacement surgery is recommended. The regimen of 30 mg q12h, subcutaneously, starting 12-24 hours post-operatively and continued for 7-14 days is recommended.



Lilia Talarico, M.D.

CC:
NDA 20-164
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HFD-180/SFredd
HFD-180/LTalarico
HFD-180/JChoudary
HFD-180/JGibbs
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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
 PUBLIC HEALTH SERVICE
 FOOD AND DRUG ADMINISTRATION
 CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 17, 1992
 FROM: Lilia Talarico, M.D., Medical Officer, HFD-180
 SUBJECT: Missing Table 7.1 in Medical Officer's Review
 TO: NDA 20-164

The table shown below should have been included on page 36 of the review of NDA 20-164.

Table 7.1
 Cross Tabulation of ¹²⁵I-Fibrinogen Scan Findings with
 Corresponding Venography Findings
 (Appendix B.7.3)

<u>Fibrinogen Findings</u>		<u>Corresponding Venography Findings</u>		<u>Findings In Agreement</u>
<u>Finding</u>	<u>n</u>	<u>Finding</u>	<u>n (%)^a</u>	<u>Finding n</u>
Negative	38	Negative	32 (84%)	Negative 32
		Positive	6 (16%)	
Positive	29	Negative	9 (31%)	Positive 20
		Positive	20 (69%)	
Total	67		67	52
Overall Agreement				(78%)

^a Percent of patients with non-venographic findings.

L. Talarico MD

*6/17/92
 Noted
 JG*

cc:
 HFD-181/CSO
 HFD-180/SFredd
 HFD-180/LTalarico
 HFD-180/JChoudary
 HFD-180/JGibbs
 f/t 6/17/92 jgw
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**DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW**

NDA: 20-164

DEC - 8 1992

Sponsor: Rhone-Poulenc Rorer Pharmaceuticals Inc.

Drug: Enoxaparin, Lovenox

Class: Low Molecular Weight Heparin

Indication: Prophylaxis of thrombosis

Submission: Safety Update Report

Date of Submission: 11-10-92

Date of Review: 11-23-92

Medical Reviewer: Lilia Talarico, M.D.

The sponsor has submitted an update of the Integrated Summary of Safety for the period 1-1-91 through 6-30-92. The safety update included all adverse events occurred in the course of European phase I trials, European Phase III clinical trials and North American phase III clinical trials, and the post-marketing spontaneous reports of adverse events.

The phase I studies were performed in normal subjects who received single or multiple doses of enoxaparin. Comparator regimens were heparin or dextran. No serious events occurred in the course of these studies; most adverse events were represented by injection site hematomas.

The European phase III studies consisted of 4 controlled studies in which a total of 825 patients participated. Enoxaparin was administered sc once or twice daily for 7 to 12 days.

PK 524 was a comparative study of enoxaparin and heparin in patients undergoing general surgery. In this study, 4 deaths were reported among patients who received enoxaparin and 7 deaths among patients who received heparin. One patient on enoxaparin developed heparin-induced thrombocytopenia.

Protocol PK 528 compared enoxaparin and heparin in the treatment of proximal DVT.

Protocols PK 534 and 536 compared enoxaparin and placebo in prevention of DVT in general surgery. No serious adverse events were reported in studies PK 528, 534, and 536.

The adverse events occurring in the course of these studies in the enoxaparin treated patients are summarized in table 2.2.

A total of 750 patients participated in the North American phase III trials. Enoxaparin was administered sc as a once daily dose of 40 mg or twice daily at the dose of 30 mg. The treatment duration ranged from 4 to 28 days.

Protocol PK 527 compared enoxaparin to placebo for prevention of DVT in patients undergoing knee surgery. No major bleeding complications occurred in the enoxaparin group, one major bleeding event occurred in the placebo group. More than three fold increases in ALT and AST occurred in 8 placebo and 10 enoxaparin patients. Three patients withdraw from the study. Protocol PK 540 compared enoxaparin to placebo in the prevention of restenosis following PTCA. A total of 458 patients participated in the study, 227 of them received enoxaparin 40 mg QD. The mean duration of treatment was 24.3 ± 8.18 days. The overall incidence of bleeding, major and minor, in the enoxaparin group was 108/227, 48%, compared to 79/231, 34% in the placebo group; the difference was statistically significant ($p < 0.05$). The incidence of major bleeding, however, was not significantly different in the two groups: 1% (3/231) in the placebo group and 4% (10/227) in the enoxaparin group. Ecchymoses were more frequent in the enoxaparin group. Two patients, one in each group, died during the study of arrhythmia unrelated to study treatment. Twenty-two patients in the placebo group and 16 patients in the enoxaparin group were discontinued because of various adverse events.

Protocol 547 is an ongoing study that compares enoxaparin and heparin for the prevention of DVT in knee replacement. One case of heparin-induced thrombocytopenia and two cases of PE were reported in the heparin group. Nine patients in the heparin group and 5 patients in the enoxaparin group were discontinued for various adverse events.

The adverse events occurring in the course of these studies in the enoxaparin treated patients are summarized in table 2.3.

A total of 124 spontaneous reports of adverse events occurring in 98 patients were collected during post-marketing surveillance. Twenty-six (26) of the events were serious and 98 non-serious. The serious events included 14 cases of bleeding, three of which intracerebral, one case of skin necrosis, two thrombophlebitis, one PE, five cases of thrombocytopenia and two of purpura (? thrombocytopenic), one thrombocytosis.

Review of the safety data from 1-1-91 to 6-30-92 shows 15 serious events, including 6 deaths, in which there was a reasonable possibility that the event may have been caused by the drug. Three of the deaths were considered unexpected events. Among these deaths there was a patient who developed heparin-induced thrombocytopenia and thrombosis associated with administration of enoxaparin. This case was reported in the medical literature. The second case was a patient with thrombocytopenia, CVA and peripheral ischemia. The third case was a patient who died of cardiac arrest.

Eleven cases of lack of efficacy were reported: six cases of PE and 5 cases of DVT.

The sales of enoxaparin during 1991 and the 1st half of 1992 exceeded those in the previous years 1989 and 1990. The total worldwide sales of enoxaparin for 1991 were 24.3 million of doses (11.4 and 12.9 million of doses for 20 mg and 40 mg respectively). Those for the period 1-1-92 to 6-30-92 were 16.3 million of doses (7.7 and 8.6 million of doses for 20 and 40 mg respectively).

The sponsor has submitted the CRF of all the 55 discontinued patients or patients who died in North American phase III clinical trials, inclusive of placebo or heparin controls. The safety data reports (CIOMS) were provided only for the eight patients with serious and unexpected events reasonably associated with the use of enoxaparin.

With the exception of 5 cases of heparin(enoxaparin)-induced-thrombocytopenia (HIT) and one case of thrombocytopenia with thrombotic complications (White-clot syndrome), the overall incidence and distribution of the other adverse events were similar to those reported with the NDA submission on 12-30-91. The cases of thrombocytopenia are listed below:

1. One patient in study PK 524 (European phase III studies). CRF from European studies were not provided.
2. Case DP04310= HIT with thrombotic complications and death.
3. Case PKS0092= HIT and CVA with positive test for heparin-dependent antiplatelet antibody.
4. Case PKS01160= Thrombocytopenia with CVA and lower limb ischemia (? HIT with arterial thrombosis).
5. Case PKS01071= Thrombocytopenia and phlebitis (no CRF or CIOMS form provided).

6. Case PKS01175= Thrombocytopenia; death secondary to CVA (no CRF or CIOMS form provided).

It is possible that more cases of thrombocytopenia have occurred. In fact, the cumulative spontaneous reporting tabulated from 1987 to June 1992 includes 64 cases of thrombocytopenia, beside 15 definitions of "purpura" or "decreased platelets".

The adverse reaction defined simply as "purpura and skin necrosis" may represent another case of HIT with thrombosis.

Comments and Recommendations: As expected, heparin-induced immune thrombocytopenia can occur with enoxaparin. At least one documented case of HIT with thrombosis has been described as well. At present, it is still unclear whether the frequency and the overall risk of these adverse reactions will be lower with enoxaparin and other low molecular weight heparins than with unfractionated heparin.

The sponsor should be requested to submit all safety reports of moderate or severe thrombocytopenia (platelet counts below 75,000/cmm) and any other report of possible HIT with thrombosis in order to better evaluate the risk and include the information in the labeling. The proposed labeling for enoxaparin makes reference to HIT, however there is no definite statement that enoxaparin itself can induce HIT and HIT with thrombosis. The sponsor should also be requested to analyze all adverse events reported by patient demographics, dose, dose duration, and indication.


Lilia Talarico, M.D.

cc:

NDA 20-164

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HFD-180/JChoudary

HFD-180/JGibbs

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4 of 7

Enoxaparin NDA #20-164
Safety Update Report

Table 2.2

DRUG RELATED ADVERSE EVENTS BY BODY SYSTEM FOR
PATIENTS WHO RECEIVED ENOXAPARIN ADMINISTERED SUBCUTANEOUSLY IN
PHASE III EUROPEAN CLINICAL TRIALS

Patient Exposure			
Study	Enoxaparin Dosage Group		
	1 mg/kg bid	20 mg od	40 mg od
PK 524	--	718	--
PK 528	67	--	--
PK 534	--	16	--
PK 536	--	--	24
Total	67	734	24

Number of Adverse Events			
Body System	Enoxaparin Dosage Group		
	1 mg/kg bid	20 mg od	40 mg od
<u>Injection Site</u>			
<u>Reaction</u>			
Hematoma	1	100	10
<u>Body as a Whole</u>			
Death	-	4	-
Retrosternal pain	-	-	1
Tiredness	-	-	1
Wound hematoma	-	101	2
Hematoma			
venipuncture	1	-	-
Hematoma from phlebography puncture site	1	-	-
<u>Cardiovascular</u>			
Bradycardia	-	-	1
Hypotension	-	-	1
<u>Digestive</u>			
Intestinal obstruction	-	-	1
<u>Hemic & Lymphatic</u>			
Heparin induced thrombocytopenia	-	1	-
<u>Respiratory</u>			
Dyspnea	-	-	1
Epistaxis	1	-	-
<u>Urogenital</u>			
Urinary retention	-	-	1

Table 2.3

DRUG RELATED ADVERSE EVENTS BY BODY SYSTEM FOR
 PATIENTS WHO RECEIVED ENOXAPARIN ADMINISTERED SUBCUTANEOUSLY IN
 PHASE III NORTH AMERICAN CLINICAL TRIALS

Study	Patient Exposure	
	Enoxaparin Dosage Group	
	30 mg q 12 hr	40 mg qd
PK 527	65	--
PK 540	--	227
PK 547	[161]	--
Total	227	

Body System Adverse event	Number of Adverse Events	
	Enoxaparin Dosage Group	
	30 mg q 12 hr	40 mg qd
<u>Injection site</u>		
<u>Reaction</u>		
Hematoma	-	34
Pain	-	11
<u>Body as a Whole</u>		
Death	-	1
Chest pain	1	11
Abdominal pain	-	4
Bleeding	7	118
Incision inflammation	1	-
<u>Cardiovascular</u>		
Angina pectoris	-	4
<u>Digestive</u>		
Nausea	-	6
<u>Hemic & Lymphatic</u>		
Ecchymosis	-	22
Bruising	1	-
<u>Metabolic & Nutritional Disorders</u>		
Increased ALT or AST	10	-
Knee edema	1	-
<u>Respiratory</u>		
Dyspnea	-	5
<u>Skin & Appendages</u>		
Pruritus	-	5
Rash	-	3

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MAR 3 1993

NDA 20-164
 Sponsor: Rhone-Poulenc Rorer
 Drug: Lovenox (Enoxaparin)
 Class: Low Molecular Weight Heparin
 Indications: Prevention of Thromboembolic complications of Hip replacement surgery.
 Submission: Review of medical literature to support indications of Lovenox in hip replacement
 Medical Reviewer: Lilia Talarico, M.D.
 Date of Review: 2-19-1993

On December 8, 1992, the sponsor requested a change in the proposed draft of Lovenox labeling to extend the proposed indication for the prevention of deep vein thrombosis (DVT) following surgery for hip replacement to include prevention of pulmonary embolism (PE). In support of the change, the sponsor has tabulated all cases of PE reported in the four studies submitted in the NDA for Lovenox. A total of 12 occurrences of verified PE were reported for the total study population of 1937 patients. The cases were distributed as follows:

One case was reported among the fifty patients treated with placebo;

One case was reported among the 785 patients who received Lovenox at the recommended dose of 30 mg q12h;

Five cases were reported in the two combined groups of patients who received heparin to a total dose of 15000 U/24h (5000 U/q8h or 7500 U q12h);

Five cases were reported in the two combined groups of patients who received a single daily dose of Lovenox (10 mg or 40 mg).

The incidence rates of PE are summarized in the following table:

Table V: Incidence Rates of Pulmonary Embolism in North American Enoxaparin Clinical Trials

<u>Trial</u>	<u>Enoxaparin 30 mg q12h</u>	<u>Heparin 15000 U/24 H</u>	<u>Placebo</u>	<u>Enoxaparin Once Daily</u>
ENO 884	2% (1/50)	ND	2% (1/50)	ND
PK 523	0% (0/333)	0.3% (1/332)	ND	ND
PK 525	0% (0/194)	1.9% (4/207)	ND	0.5% (1/203)
PK526	0% (0/208)	ND	ND	0.1% (4/360)
Total	0.1% (1/785)	0.9% (5/539)	2% (1/50)	0.9% (5/563)

ND: Not Dosed

Review of these data, however, indicate that the association between occurrence of PE and failure of the underlying prophylactic antithrombotic therapy to prevent DVT was not always documented. Seven of the 12 cases of PE occurred in patients who had had negative bilateral venograms at the end of study treatment and subsequently developed DVT and PE 8 to 11 days later. The reasons for these findings are unclear; beside erroneous reading of the venograms, the possibility that the thromboembolic event initiated after the termination of the prophylactic anticoagulation must be considered. Two of these six cases (patients 915 and 1110 from study PK525) were, in fact, allocated among the complications of venography by the sponsor. One patient included in the Lovenox 40 mg q 24h was a patient who had developed DVT on day 6 of therapy with Lovenox. The patient was started on unfractionated heparin therapy and three days later developed Heparin-Induced Thrombocytopenia with multiple thromboses and PE.

The relationship between DVT and PE has been adequately documented in the published medical literature. It is well recognized that DVT represents the source of PE in at least 90% of cases. The source of thromboembolism in the remaining less than 10% of cases is represented by upper extremities venous thrombosis, embolism from right-sided cardiac chambers, pelvic veins. The incidence of PE from sources other than DVT has increased with the introduction of subclavian veins access devices and with intravenous drug abuse. Clinically silent PE (detected by perfusion lung scan) occurs at the time of presentation in about 50% of patients with documented DVT. Conversely, asymptomatic DVT is found in approximately 70% of patients who present with confirmed symptomatic PE. Effective therapy of DVT effectively prevents the occurrence of PE. Antithrombotic prophylaxis is equally effective in preventing DVT and PE in patients at risk, as in the case of orthopedic surgery. Prior to the introduction of heparin therapy, the frequency of post-operative PE ranged from 20 to 60% and that of fatal PE from 5 to 20%.

A meta-analysis of the incidence of DVT and PE with perioperative administration of subcutaneous heparin from more than 70 randomized clinical trials with 16,000 patients undergoing general, orthopedic and urologic surgery was published in 1988 by Collins et al. (Collins R. et al.: Reduction in fatal Pulmonary Embolism and Venous Thrombosis by perioperative administration of subcutaneous Heparin, N.Engl.J.Med., 318:1162-1173, 1988).

The results showed that perioperative administration of heparin reduced the risk of thromboembolic complications (DVT and PE), irrespective of the type of surgery.

The data are summarized in the following tables:

Incidence Rates of DVT in the Meta-Analysis of PE and Heparin Clinical Trials¹

<u>Trial</u>	<u>No. of Patients</u>		<u>No. of DVT (%)</u>		<u>% Odds Red. (+ SD)</u>
	<u>Heparin</u>	<u>Control</u>	<u>Heparin</u>	<u>Control</u>	
General Surg.	3966	3396	355 (8.9%)	760 (22.3%)	67 ± 4
Orthopedic	635	619	151 (23.7%)	294 (47.4%)	68 ± 7
Urologic	129	129	18 (13.9%)	53 (41.0%)	75 ± 15
Tot. All Trials	4730	4144	524 (11.07%)	1107 (23.4%)	68 ± 3

1. Collins, R., et al.: Reduction in Fatal Pulmonary Embolism and Venous Thrombosis by perioperative administration of subcutaneous Heparin.

Table IV: Incidence Rates of Pulmonary Embolism¹ in the Metaanalysis of Pulmonary Embolism and Heparin Clinical Trials

<u>Subgroup of Trial</u>	<u>Nonfatal Pulmonary Embolism</u>		<u>Fatal Pulmonary Embolism</u>	
	<u>Heparin</u>	<u>Control</u>	<u>Heparin</u>	<u>Control</u>
International Multicenter Trial	14/2230	19/2250	6/2230	19/2250
Other 1:1 Trial ²	76/4546	117/4588	13/4136	36/4176
Other 2:1 or 3:1 Trials ²	15/1103	11/401	0/941	0/351
Tot. All Trials	105/7879	147/7239	19/7307	55/6777
% Incidence	1.33%	2.03%	0.26%	0.81%

Typical % Reduct. in Odds (± SD)

40±11

65±15

1. Collins, R., et al.: Reduction in Fatal Pulmonary Embolism and Venous Thrombosis by perioperative administration of subcutaneous Heparin.

The overall rate of DVT decreased from 23.7% in control patients to 11.1% in the heparin treated patients. The incidence of non-fatal PE was reduced from 2.0% in the control patients to 1.3% and that of fatal PE from 0.8 in the control patients to 0.2% in heparin treated patients.

The results of these studies clearly demonstrated that prophylactic therapy with heparin reduced the incidence of post-operative DVT and that this reduction was associated with a reduction of PE.

A statistical analysis of the incidence of PE among the various treatment groups in the clinical studies of the NDA of Lovenox has not been performed. However, counting all cases of PE, the overall incidence rate of 0.1% in the enoxaparin 30 mg bid group, compared to that of 0.95% in the pooled comparator groups (placebo, heparin, or inadequate enoxaparin therapy), indicate a noticeable risk reduction in the former group.

It seems, thus, appropriate that the labeling should reflect the association of effective treatment of DVT with reduced risk of PE. The sponsor has proposed the following wording for the Indication and Dosage: "Lovenox injection is indicated for the prevention of DVT and PE following hip replacement surgery." However, given the data available from the NDA, it may be more appropriate to use the following wording: "Lovenox injection is indicated for the prevention of DVT, which may lead to PE following hip replacement surgery".

The Safety Update Report submitted in November 1992 which included all adverse events reported from the US and European studies and from postmarketing spontaneous report, indicated that Heparin-Induced Thrombocytopenia (HIT) can be induced by Lovenox and that one case of HIT with thrombosis has been reported.

The sponsor should be requested to assess the risk of enoxaparin-induced thrombocytopenia and thrombosis and to submit the data in order to determine whether additional information should be included in the labeling.

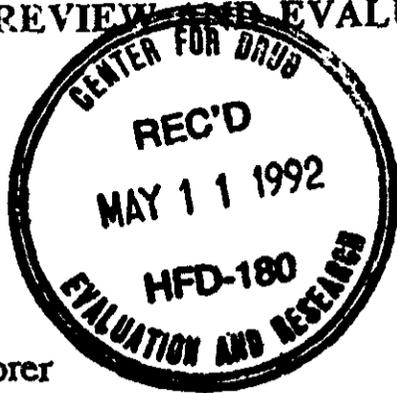
The sponsor was requested to provide this information as well as an analysis of all adverse events by patients demographics in December 1992.

Lilia Talarico
Lilia Talarico, M.D.

3/3/93

Concurrence
M

STATISTICAL REVIEW AND EVALUATION



Date

MAY - 9 1992

NDA #: 20-164

Drug: Enoxaparin

Applicant: Rhône-Poulenc Rorer

Indication: Prevention of Deep Vein Thrombosis (DVT) in patients undergoing elective total hip replacement (THR) surgery

NDA Drug Classification: 1P

Clinical Reviewer: Lilian Talarico, M.D.

Volumes Reviewed: 1.1, 1.32-1.74 July 31, 1991

Four controlled clinical trials are submitted in the statistical NDA package (see Table B.1).

Protocol #EN0884: double-blind, multicenter, randomized placebo controlled study with a total of 100 patients,

Protocol #PK526: multiple dose, double-blind, multicenter, randomized dose finding study with a total of 602 patients,

Protocol #PK523: double-blind, multicenter, randomized, Ca heparin controlled, with a total of 669 patients and

Protocol #525: Multiple dose, open label, multicenter with a total of 607 patients.

After our discussion with the medical review division, it was decided that the statistical review should concentrate on two studies: Canadian study #EN0884 and United States study #PK526.

Therefore, this review addresses the efficacy of enoxaparin 30 mg q12h in placebo controlled study #EN0884 and dose finding study #PK526.

Statistical Issues

1. In the placebo controlled study (EN0884), after 24 (24%) patients were randomized, the sponsor saw no events of DVT in either the active or placebo group. The sponsor then changed the protocol. After the protocol change, the data had a considerable number of DVTs in the placebo group and some in the enoxaparin group. How does this protocol change impact the statistical results claimed by the sponsor in favor of enoxaparin is a statistical issue for this trial.

2. The venography readings for the dose-response study (#PK626) were evaluated by two independent panels. The sponsor reported the comparison results with p-values for one panel only. Are the statistical results in favor of enoxaparin consistent for the two panels?

These (two) issues in the review have been discussed with the medical officer, Dr. Lilian Talarico, M.D.

I CANADIAN STUDY #EN0884 (placebo controlled)

1.1 STUDY DESIGN

This was a randomized, multicenter, double-blind, parallel-group, placebo controlled trial comparing the safety and efficacy of enoxaparin in the prevention of deep vein thrombosis (DVT) in patients after elective total hip replacement (THR) surgery. The patients were treated with enoxaparin 30 mg q12h or placebo (q12h), given subcutaneously twice daily for a period of 3-14 days. Three centers participated in the study.

Patients qualified for this trial if they

- were 40 or more years old
- were undergoing total elective hip replacement

Patients did not qualified if they had any of the following conditions:

- second or subsequent hip replacement
- generalized bleeding disorders
- allergic to iodine or radiopaque dye
- pregnancy and lactation
- participation in the evaluation of any non approved drug in the preceding four weeks
- diseases or treatments which can interfere with the kinetics of PK 10 169

Qualifying patients were randomized in blocks of size 10 in a double-blind fashion to receive either enoxaparin or placebo in a 1:1 ratio using a randomization schedule generated by the sponsor. Table 1 shows the schedule of evaluations for each patient. Patients evaluations included complete medical history, IPG, ¹²⁵I-fibrinogen scan, lung scan, RBC, PT, APTT, bleeding assessments, clinical labs, physical exam and bilateral venography. This table also contains the summary of patient demographics (bottom part).

Sample Size Estimation

A sample size of 100 randomized patients with 50 evaluables in each treatment group was planned. With 50 patients per treatment group, a power of more than 95% (by sponsor's recalculation) was postulated to detect a thrombosis rate of 15% for enoxaparin and 50% placebo.

Primary Efficacy Endpoints

The primary efficacy endpoint is the incidence rate of DVT, that is, incidence rate of treatment failure.

Evidence of the efficacy endpoint (DVT) was obtained from bilateral contrast media venography or clinical evidence of DVT. A positive venogram was defined by a positive finding in either the operative or non-operative limb, or both limbs. A negative finding was defined as a negative bilateral venogram.

Clinical evidence of DVT was defined as either a positive result from another vascular examination (IPG or ¹²⁵I-fibrinogen scan) or other clinical evidence such as pulmonary embolism or administration of anticoagulant therapy for the treatment of DVT.

The protocol stated a mandatory venography for all patients during days 10-14:

"If the leg scan becomes positive in the non-operation thigh, or if the IPG is positive a venogram will be performed immediately, otherwise it will be done between day 10 and day 14 postoperatively".

However, the mandatory venography was not done in some patients.

All treated patients who took study medication and had received at least one clinical evaluation after administration of study medication were classified into one of these five (5) groups:

- (a) Group 1: This group contained all patients whose DVT was confirmed by contrast media venography (VG +ve),
- (b) Group 2: This consisted of patients who had a negative bilateral VG (DVT was not confirmed by contrast media venography, VG -ve),
- (c) Group 3: This group had patients whose venography was not done (ND) or was inadequately (IN) performed but had a DVT confirmed by clinical evidence (that is, had a +ve result by the noninvasive procedure),
- (d) Group 4: This was composed of patients whose venography was not done (ND) or was inadequately (IN) performed and DVT was not confirmed by clinical evidence (that is, had a -ve result by the noninvasive procedure) and
- (e) Group 5: This group consisted of those patients who had no other clinical evidence of DVT; this group had no venography taken.

1.2.0 SPONSOR'S ANALYSIS RESULTS

The efficacy analyses were performed

1. by the intent-to-treat (ITT) principle,
2. for the evaluable subset, consisting of Group 1 and Group 2 only.

The sponsor reported 2-sided p-values for treatment comparison between enoxaparin and placebo as statistically significant if 2-sided $p < .05$.

A total of 100 patients were randomized; 50 in the placebo and 50 in the enoxaparin group. The ITT analyses included all patients who had at least one post-treatment clinical evaluation.

The sponsor claimed that the two treatment groups were comparable with respect to demographic characteristics (no statistical tests were carried by sponsor to support this claim). This reviewer's observations did not disagree with this claim.

1.2.1 Sponsor's DVT Results/ITT & Efficacy Subset

Below is a summary of the sponsor's findings for both the ITT and evaluable subset analyses (details are given in attached Table 2).

ITT			
Treatment Failure	Overall (N=100)	Placebo (N=50)	Enoxaparin (N=50)
Total	28 (28%)	23 (46%)	5 (10%)
Proximal	12 (12%)	11 (22%)	1 (2%)
Distal	14 (14%)	10 (20%)	4 (8%)
Indeterminate	2 (2%)	2 (4%)	0 (0%)
Odds Ratio	8.34		
p-value	0.0002		
95% CI	(2.72, 25.56)		
Evaluable			
Treatment Failure	Overall (N=58)	Placebo (N=31)	Enoxaparin (N=27)
Total	23 (40%)	19 (61%)	4 (15%)
Proximal	10 (17%)	9 (29%)	1 (4%)
Distal	13 (22%)	10 (32%)	3 (11%)
Indeterminate	0 (0%)	0 (0%)	0 (0%)
Odds Ratio	10.18		
p-value	0.0009		
95% CI	(2.57, 40.25)		

1.3 REVIEWER'S EVALUATIONS & COMMENTS/ STUDY # EN0884

Protocol Change

This reviewer was concerned about the change in the protocol. The sponsor changed the protocol after they saw no DVT in the first set of 24 (11 placebo and 13 enoxaparin) patients randomized. After the change in protocol, there were frequent DVTs in the placebo and some in the active group: 23/39 (placebo) and 5/37 (enoxaparin).

Failure Rates Before/After Protocol Change

	Placebo (P)	Enoxaparin (E)	(E-P) #	P*
Before Change	0/11 (=0%)	0/13 (=0%)	0%	No Result
After Change	23/39 (=59%)	5/37 (=14%)	45%	<.0001

*: 2-sided p Fisher's exact.

Sensitivity Analysis

This reviewer has looked into several scenarios (see table below) to evaluate the impact of the interaction effect due to the protocol change.

Consider scenario #4, where for the first 24 patients, it is assumed that all 11 placebo patients (before the change) had no DVT, but 8 of the enoxaparin patients (before the change) had DVTs. Under this scenario, this reviewer found that the difference between the two groups, although still in favor of enoxaparin, was not statistically significant at the .05 level of significance; Fisher's exact $p=.06$.

However, in this reviewer's assessment, a realistic scenario is the expected number of events for the 13 patients in the enoxaparin group (before the protocol change) under the null hypothesis of no treatment difference (see scenario #2). This expected number of events is equal to (placebo failure rate) \times (13 enoxaparin patients) $= .46 \times 13 = 6$ events. Enoxaparin 30 mg q12h is still significantly different from placebo, in favor of enoxaparin, under the penalty of 6 DVTs (the expected number of events under the null hypothesis); $p=.0196$.

Sensitivity Analysis

Scenario #	Placebo(P)	Enoxaparin(E)	(E-P) #	P*
1	(0+23)/50 (=46%)	(5+5)/50 (=20%)	-26%	.0102
2	(0+23)/50 (=46%)	(6+5)/50 (22%)	-24%	.0196
3	(0+23)/50 (=46%)	(7+5)/50 (=24%)	-22%	.0217
4	(0+23)/50 (=46%)	(8+5)/50 (=26%)	-20%	.0601
5	(0+23)/50 (=46%)	(9+5)/50 (=28%)	-18%	.0969

#: (enoxaparin-placebo) failure rate: negative difference favors drug

*: 2-sided p Fisher's exact

Scenario #: Out of 11 placebo patients none had DVT.

#1. 5 out of the 13 enoxaparin patients had DVT,

#2. 6 out of the 13 enoxaparin patients had DVT

#5. 9 out of the enoxaparin patients had DVT.

Therefore, in this reviewer's assessment, the data in this trial supported the sponsor's claim that enoxaparin 30 mg q12h was effective in the prevention of DVT in patients undergoing elective hip replacement surgery.

This reviewer also checked the randomization for this trial and it was OK.

II United States STUDY # PK526 (dose finding)

2.1 STUDY DESIGN

This was a randomized, multicenter, double-blind, parallel-group, placebo controlled trial comparing the safety and efficacy of three regimens of enoxaparin in the prevention of deep vein thrombosis (DVT) in patients after elective total hip replacement (THR) surgery. The patients were treated with enoxaparin 10 mg qd, or 40 mg qd, or 30 mg q12h, given subcutaneously for a period of 7 days. Thirty-two (32) centers participated in the study.

Patients qualified for this trial if they

- were 40 or more years old
- were undergoing total elective hip replacement
- pre-surgical noninvasive vascular examination performed within 14 days prior to surgery negative for DVT in lower extremities

Patients did not qualified if they had any of the following conditions (see Table A for more exclusion criteria):

- positive results from pre-surgical noninvasive vascular examination
- surgery on the ipsilateral hip within the preceding year
- history of previous venous thrombosis, generalized bleeding disorders, heparin associated thrombocytopenia
- females of child-bearing potential

Qualifying patients were randomized in blocks of size 6 in a double-blind fashion to receive either enoxaparin 10 mg qd, or 40 mg qd, or 30 mg q12h in a 1:1:1 ratio. The randomization was done by assigning the next available patient number using a randomization schedule generated by the sponsor.

Table 3 shows the schedule of evaluations for each patient. Patients evaluations included complete medical history, 12-lead ECG, chest X-ray, interim history, dosing, bleeding assessments, clinical labs, physical exam and noninvasive vascular operative site. This table also contains the summary of patient demographics (see bottom part).

Primary Efficacy Endpoints

See Canadian study (#EN0884)

Sample Size Estimation

A sample size of 600 randomized patients with 200 evaluables in each treatment group was planned in order to achieve 80% power.

2.2.0 SPONSOR'S ANALYSIS RESULTS

The efficacy analyses were performed

- 1) by the intent-to-treat (ITT) principle,
- 2) for the evaluable subset

The sponsor reported 2-sided p-values for treatment comparison between enoxaparin 10 mg qd and 30 mg q12h, 10 mg qd and 40 mg qd, and 30 mg q12h and 40 mg qd as statistically significant if 2-sided $p < .05$.

A total of 572 patients were randomized; 161 in the 10 mg qd, 201 in the 40 mg qd and 210 in the 30 mg q12h treatment group. The ITT analyses excluded four of the randomized patients (2 in 40 mg qd and 2 in 30 mg q12h) because they received no study medication and had no post-treatment clinical evaluation.

The sponsor claimed that the two treatment groups were comparable with respect to demographic characteristics (no statistical tests were carried by sponsor to support this claim). This reviewer's observation did not disagree with this claim.

2.2.1 Sponsor's DVT Results/ITT & Efficacy Subset

Below is a summary of the sponsor's findings for both the ITT and evaluable subset analyses (details are given in attached Table 4).

	ITT		
Treatment Failure	10 mg qd (N=161)	40 mg qd (N=199)	30 mg q12h (N=208)
Total	40 (25%)	27 (14%)	22 (11%)
Proximal	17 (11%)	9 (5%)	8 (4%)
Distal	20 (12%)	12 (6%)	8 (4%)
Noninvasive	3 (2%)	6 (3%)	6 (3%)

	Evaluable		
Treatment Failure	10 mg qd (N=116)	40 mg qd (N=149)	30 mg q12h (N=143)
Total	36 (31%)	21 (14%)	16 (11%)
Proximal	16 (14%)	9 (6%)	8 (6%)
Distal	20 (17%)	12 (8%)	8 (6%)

Comparisons:	# of Events (Percent) 2-sided p values		
ITT	10 mg qd (N=161)	40 mg qd (N=199)	30 mg q12h (N=208)
# of Patients 10 mg vs	40 (25%)	27 (14%) 0.0168*	22 (11%) 0.0008*
40 mg vs	-	-	0.3369
Evaluable	(N=116)	(N=149)	(N=143)
# of Patients 10 mg vs	36 (31%)	21 (14%) 0.0054*	16 (11%) 0.0008*
40 mg vs	-	-	0.4783

2.3 REVIEWER'S EVALUATIONS & COMMENTS/ U.S STUDY # PK526

Consistency of The Two VG Readings

This reviewer has looked at the sponsor's (ITT and evaluable subset) analyses results of the two venography readings:

1. the sponsor's analysis (ITT and evaluable subset) results according to investigator's interpretations of DVTs (submitted) with the NDA, and
2. the results according to the Yale centralized panel's interpretations of DVTs (submitted at the reviewer's request; see Table 4).

The two results were supportive of each other.

Results for 30 mg q12h & 40 mg qd

The sponsor's analyses results of the of DVTs efficacy data (based on ITT and efficacy methods) suggest that both the 30 mg q12h and the 40 mg qd doses were significantly superior over the 10 mg dose qd in their effectiveness in preventing deep vein thrombosis in patients undergoing elective hip replacement surgery. There was, however, no statistically significant difference between the 40 mg qd and the 30 mg q12h doses in their effectiveness in the prevention of DVT in patients after hip replacement surgery.

In this reviewer's assessments, the efficacy data in this trial supported the sponsor's claim that enoxaparin 30 mg q12h was more effective than enoxaparin 10 mg qd in the prevention of DVT in patients undergoing elective hip replacement surgery.

III. OVERALL CONCLUSION

The efficacy data in this trial (study #EN0884 & #PK526) supported the effectiveness of enoxaparin 30 mg q12h in the prevention of deep vein thrombosis in patients undergoing elective hip replacement surgery.

AJ Sankoh

A. J. Sankoh, Ph.D.

Mathematical Statistician

Concur:

Dr. Huque

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cc: Orig. NDA 20-164

HFD - 180

✓ HFD - 180/Dr. Fredd

HFD - 180/Dr. Talarico

HFD - 180/Mr. Hassell

HFD - 713/Dr. Dubey

[File:DRU 1.3.2 NDA]

HFD - 713/Dr. Huque

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Sankoh/x4710/AJS/05-07-92

Table B.1

**OVERVIEW OF STUDIES IN THE PREVENTION OF DEEP VEIN THROMBOSIS IN HIP REPLACEMENT SURGERY
(DATA FOR ALL TREATED PATIENTS)**

Protocol Number	Study Design	Length of Treatment	Treatment & Doses/Day	Number Treated/Evaluable ^a /Completed	Age Range ^b (Mean)	Male/Female ^b	White Black/Other ^b	No. (n) Non-evaluable ^b	No. (n) ^c Patients with DVT
DND 884	Placebo Controlled Double Blind	3-14 Days	Placebo (q12h)	50/31/23	44-81 (67.4)	38/62	NS	19 (38)	23 (46)
			Enox 60 mg (30 q12h)	50/27/25	41-84 (66.8)	52/48	NS	23 (46)	5 (10)
PK 523	Controlled Double Blind	3-14 Days	Hep 15000IU (7500 q12h)	332/250/260	40-91 (66.7)	48/52	NS	82 (25)	63 (19)
			Enox 60 mg (30 q12h)	333/236/280	40-91 (66.2)	44/56	NS	97 (29)	57 (17)
PK 526	Dose Ranging Double Blind	3-7 Days	Enox 10 mg	161/116/108	31-83 (63.9)	66/34	94/4/2	45 (28)	40 (25)
			Enox 40 mg	199/149/139	39-85 (64.8)	64/36	93/6/1	50 (25)	27 (14)
			Enox 60 mg	208/143/145	40-88 (65.2)	60/40	92/7/1	65 (31)	22 (11)
			(30 q12h)						
PK 525	Controlled Open Label	3-7 Days	Hep 15000U (5000 q8h)	209/142/150	37-88 (65.6)	48/52	86/14/1	67 (32)	24 (12)
			Enox 40 mg	203/136/144	40-91 (65.0)	49/51	90/9/1	67 (33)	30 (18)
			Enox 60 mg (30 q12h)	195/136/137	40-99 (65.6)	50/50	92/7/2	59 (30)	9 (5)

Enox = Enoxaparin

Hep = Calcium Heparin (PK 523), Sodium Heparin (PK 525).

NS = Not Specified

^a May include some discontinued patients who were evaluable.

^b Results for all-treated patients.

^c Based on all-treated patients. Three patients in PK 525 (two in the heparin group, one in the enoxaparin 30 mg q12h group) received medication but did not have a clinical assessment performed.

Table 1/Study #EN0884

STUDY SCHEMATIC - OVERVIEW

Evaluation/Procedure	Prior to Surgery	Periodosing Interval											End of Study			
		Calendar/Treatment Day ¹	2	3	4	5	6	7	8	9	10	11		12	13	14
Informed Consent	X															X
Complete Medical History	X															X
Complete Physical Examination	X															X
Laboratory Tests: Hematology and Coagulation, Serum Chemistry and Urinalysis	X															X
Vital Signs	X															X
Impedance Plethysmography (IPG)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
¹²⁵ I-Fibrinogen Leg Scan	X															X
Leg Scan	X															X
Pulmonary Angiography ⁵		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-Factor Xa Activity ⁶		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bleeding Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hemoglobin, Hematocrit, RBC		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Tests (PT, APTT)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Experience Evaluation		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dosing																X
Bilateral Venography ⁷		X														X
Concomitant Medications																X
Assessment of Operative Site																X

- 1 Day 1 was the first post-operative day; the next calendar day was Day 2.
- 2 Or at time of discontinuation of study medication.
- 3 IPG-Fibrinogen was injected immediately following surgery (study day 0); scans were performed daily post-operatively.
- 4 At entry and between days 10 and 14.
- 5 Selective pulmonary angiography performed to establish definitive diagnosis of pulmonary embolism, if necessary.
- 6 Plasma samples to be obtained 6 hours after first daily dose.
- 7 Mandatory venography was strictly enforced for the last 76 patients enrolled.

Summary of Demography and Baseline Conditions
All Treated Patients

	Overall	Placebo	Enoxaparin
Number of Patients	100	50	50
SEX			
FEMALE	50(50%)	31(62%)	24(48%)
MALE	50(50%)	19(38%)	26(52%)
AGE (yr)			
N	100(100%)	50(100%)	50(100%)
MEAN	67.1	67.4	66.8
STD	8.17	8.06	8.98
MEDIAN	67.0	67.5	67.0
RANGE	41-84	44-82	41-84
Blood Pressure (mmHg)			
N	100(100%)	50(100%)	50(100%)
MEAN	141.7	142.8	140.5
STD	21.56	20.70	22.23
MEDIAN	140.0	140.0	140.0
RANGE	100-190	110-192	100-190
N	100(100%)	50(100%)	50(100%)
MEAN	82.0	82.9	83.0
STD	10.00	10.44	11.20
MEDIAN	82.0	81.0	83.0
RANGE	60-110	60-110	60-110

Table 2/Study #EN0884

**Statistical Results of Deep Vein Thrombosis Findings by Treatment Group
All Treated Patients with Efficacy Data**

	<u>Overall</u>	<u>Placebo</u>	<u>Enoxaparin</u>
Number of Patients	100	50	50
Treatment Failures ^a	28(28%)	23(46%)	5(10%)
PROXIMAL	12(12%)	11(22%)	1(2%)
DISTAL	14(14%)	10(20%)	4(8%)
INDETERMINATE (OTHER)	2(2%)	2(4%)	0
Treatment Comparison:			
Incidence of Treatment Failures	Odds Ratio	p-value ^{b,c}	95% Confidence Interval
Placebo : Enoxaparin 30 mg q 12h	8.34	0.0002 ^b	(2.72, 25.56)

**Statistical Results of Deep Vein Thrombosis Findings by Treatment Group
Evaluable Patients**

	<u>Overall</u>	<u>Placebo</u>	<u>Enoxaparin</u>
Number of Patients	58	31	27
Treatment Failures ^a	23(40%)	18(58%)	4(15%)
PROXIMAL	10(17%)	9(29%)	1(4%)
DISTAL	13(22%)	10(32%)	3(11%)
INDETERMINATE (OTHER)	0	0	0
Treatment Comparison:			
Incidence of Treatment Failures	Odds Ratio	p-value ^{b,c}	95% Confidence Interval
Placebo : Enoxaparin 30 mg q 12h	10.18	0.0008 ^b	(2.57, 40.25)

^a For this All Treated efficacy analysis the % treatment failures is defined as the number of patients with any positive evidence of DVT (Outcome Groups 1, 3 and 4) out of all patients with at least one clinical evaluation (Outcome Groups 1 through 5).
^b Two-sided p-values from the logistic regression model with treatment and center effects.
^c * indicates p<0.05.

Table A/Study #PK526

EXCLUSION CRITERIA

- Female patients of child-bearing potential.
- Positive results from pre-surgical noninvasive vascular examination.
- Surgery on the ipsilateral hip within the preceding year.
- Documented history of previous venous thrombosis.
- History of generalized bleeding disorders.
- History of heparin-associated thrombocytopenia.
- Eye, spinal cord, or CNS surgery within three months of entry into study.
- Active ulcerative disease of the gastrointestinal tract.
- Uncontrolled hypertension (blood pressure greater than or equal to 180/105 mmHg).
- Uncontrolled asthma.
- Documented allergy to unfractionated heparin.
- Allergy to fish or swine products.
- Allergy to iodine or radiopaque dye.
- Allergy to sulfites.
- Regular use of the following medications for the four days preceding hospitalization or requirement for use during hospitalization: aspirin, aspirin-containing products, or non-steroidal anti-inflammatory drugs (NSAIDs).
- Current evidence of drug (excluding tobacco products) or alcohol abuse.
- Treatment with other investigational drugs within the previous four weeks.
- Any disease or requirement for treatments that might interfere with the action, kinetics, or evaluation of enoxaparin.
- Clinically significant abnormality on physical examination, chest X-ray, or electrocardiogram.
- Clinically significant abnormal laboratory value.

Table 3/Study #PK526

TABLE 3
STUDY SCHEMATIC - OVERVIEW

Evaluation/Procedure	Prior to Surgery ¹	Upon Admission ²	Peridosing Interval							End of Study ⁷	Follow Up
			Calendar/Treatment Day ³	1	2	3	4	5	6		
Informed Consent	X										
Complete Medical History	X										
Complete Physical Examination	X									X	X
12-Lead ECG	X									X	
Chest X-Ray ⁴	X										
Interim History		X									
Brief Physical Examination		X									
Biochemistry and Urinalysis	X		X	X	X	X	X	X	X	X	X
Hematology and Coagulation	X									X	X
Noninvasive Vascular Examination ⁵	X									X	X
Vital Signs ⁶	X		X	X	X	X	X	X	X	X	X
Assessment of Operative Site ⁵			X	X	X	X	X	X	X	X	X
Bleeding Assessment			X	X	X	X	X	X	X	X	X
Adverse Experience Evaluation			X	X	X	X	X	X	X	X	X
Dosing			X	X	X	X	X	X	X	X	X
Bilateral Venography										X	
Concomitant Medications											X

- ¹ Up to 14 days prior to surgery.
- ² If complete history and physical examination were performed more than 48 hours prior to surgery.
- ³ Day 1 was the first dosing day; the next calendar day was Day 2.
- ⁴ Only if results of chest X-ray done within the preceding six months were not available.
- ⁵ Immediately prior to first dose of study drug on a dosing day.
- ⁶ Several techniques were permitted, but each center was to select one technique to be used for all patients.
- ⁷ Within 24 hours of the last dose of study medication.

Summary of Patient Demographic Information by Treatment Group
All Randomized Patients

	Overall	Enoxaparin 10mg QD	Enoxaparin 40mg QD	Enoxaparin 30mg q12h
Number of Patients	572	161	201	210
SEX				
FEMALE				
MALE				
AGE (yrs)				
N	361(63%)	107(66%)	129(64%)	125(60%)
MEAN	211(37%)	54(34%)	72(36%)	85(40%)
STD				
MEDIAN				
RANGE				
Blood Pressure (mmHg)				
Systemic				
N	34(6%)	7(4%)	12(6%)	15(7%)
MEAN	531(93%)	151(94%)	187(93%)	193(92%)
STD	1(<1%)	0	0	1(<1%)
MEDIAN	6(1%)	3(2%)	2(<1%)	1(<1%)
RANGE				
Diastolic				
N	571(100%)	161(100%)	201(100%)	209(100%)
MEAN	64.7	63.9	64.8	65.1
STD	10.43	10.50	10.24	10.57
MEDIAN	66.0	66.0	66.0	65.0
RANGE	31-88	31-83	39-85	40-88

Table 4/Study PK526

Summary of Patient Evaluability by Treatment Group

	Overall	Enoxaparin 10mg QD	Enoxaparin 40mg QD	Enoxaparin 30mg q12h
All Randomized Patients	572	161	201	210
Randomized, Not Treated	4	0	2	2
All Treated Patients	568	161	199	208
Evaluable	408(72%)	116(72%)	148(75%)	143(68%)
Unevaluable	160(28%)	45(28%)	50(25%)	66(31%)
INADEQUATE OR NO CONTRAST MEDIA VENOGRAPHY INSUFFICIENT THERAPY	154(27%) 6(1%)	42(26%) 3(2%)	48(24%) 2(1%)	64(31%) 1(<1%)

ITT & Efficacy Subset

Statistical Results of Deep Vein Thrombosis Findings by Treatment Group
All Treated Patients with Efficacy Data

	Overall	Enoxaparin 10mg QD	Enoxaparin 40mg QD	Enoxaparin 30mg q12h
Number of Patients	568	161	199	208
Treatment Failures ^a	80(14%)	40(25%)	27(14%)	22(11%)
PROXIMAL DVT	34(6%)	17(11%)	9(5%)	8(4%)
DISTAL DVT	40(7%)	20(12%)	12(6%)	8(4%)
INDETERMINATE (NON-INVASIVE)	15(3%)	3(2%)	6(3%)	6(3%)
Treatment Comparisons:				
Incidence of Treatment Failures	Odds Ratio	p-value ^{b,c}	95% Confidence Interval	
Enoxaparin 10 mg QD ; Enoxaparin 40 mg QD	2.16	0.0188 *	(1.12, 4.18)	
Enoxaparin 10 mg QD ; Enoxaparin 30 mg q12h	2.92	0.0008 *	(1.48, 6.81)	
Enoxaparin 40 mg QD ; Enoxaparin 30 mg q12h	1.36	0.3309	(0.72, 2.53)	

Statistical Results of Deep Vein Thrombosis Findings by Treatment Group
Evaluable Patients

	Overall	Enoxaparin 10mg QD	Enoxaparin 40mg QD	Enoxaparin 30mg q12h
Number of Patients	408	116	148	143
Treatment Failures ^a	72(18%)	38(33%)	21(14%)	16(11%)
PROXIMAL DVT	33(8%)	16(14%)	9(6%)	8(6%)
DISTAL DVT	40(10%)	20(17%)	12(8%)	8(6%)
Treatment Comparisons:				
Incidence of Treatment Failures	Odds Ratio	p-value ^{b,c}	95% Confidence Interval	
Enoxaparin 10 mg QD ; Enoxaparin 40 mg QD	2.74	0.0054 *	(1.29, 6.82)	
Enoxaparin 10 mg QD ; Enoxaparin 30 mg q12h	3.57	0.0008 *	(1.60, 7.98)	
Enoxaparin 40 mg QD ; Enoxaparin 30 mg q12h	1.30	0.4782	(0.63, 2.70)	

^a For this Evaluable efficacy analysis the 3 treatment failures is defined as the number of patients with positive evidence of DVT in Contrast Media Venography (Outcome Group 1) out of all patients with definitive venogram results (Outcome Groups 1 and 2).
^b One-sided p-values from the logistic regression model with treatment and center effects. The p-values for the two primary comparisons, 10mg QD dose versus the 30mg q12h and 40mg QD doses respectively, are Bonferroni adjusted (multiplied by 2). A similar adjustment has also been made to the corresponding confidence intervals.
^c * indicates p<0.05.

TABLE 4/STUDY P3526 CONTINUED

Patients Treated	10 mg QD n (%)	40 mg QD n (%)	30 mg q12h n (%)	Overall n (%)
Number of Patients	161(100%)	199(100%)	208(100%)	568(100%)
Treatment Failures	47(29%)	42(21%)	30(14%)	119(21%)

Inter-Group Comparisons of the Incidence of Treatment Failures:

Treatment Comparison	Odds Ratio ^a	p-value	95% Confidence Interval for Odds Ratio
Enoxaparin 10mg QD:40mg QD ^b	1.70	0.0916	(0.95, 3.04)
Enoxaparin 10mg QD:30mg q12h ^b	2.65	0.0008*	(1.43, 4.91)
Enoxaparin 40 mg QD:30mg q12h	1.56	0.1029	(0.91, 2.66)

Treatment Group

Patients Treated	10 mg QD n (%)	40 mg QD n (%)	30 mg q12h n (%)	Overall n (%)
Number of Patients	116(100%)	149(100%)	143(100%)	408(100%)
Number of Failures	43(29%)	33(22%)	24(17%)	100(25%)

Inter-Group Comparisons of the Incidence of Treatment Failures:

Treatment Comparison	Odds Ratio ^a	p-value	95% Confidence Interval for Odds Ratio
Enoxaparin 10mg QD:40mg QD ^b	2.17	0.0174*	(1.12, 4.20)
Enoxaparin 10mg QD:30mg q12h ^b	2.88	0.0014*	(1.43, 5.81)
Enoxaparin 40 mg QD:30mg q12h	1.33	0.3629	(0.72, 2.45)

^a Estimated from a logistic regression model with treatment and center effects.

^b Two-sided p-values and confidence intervals are Bonferroni-adjusted (multiplied by 2).

* Statistically significant at the 5% level.

^c For patients without definitive Yale results, treatment failure was determined by investigators' findings and other clinical evidence.

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MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:

FROM: Mordecai Friedberg, Mathematical Statistician
Division of Biometrics, HFD-715

TO: Enoxaparin Injection, NDA 20-164

SUBJECT: Statistical deficiencies associated with the
Sponsor's submission dated May 1, 1992

The sponsor provided FDA with the statistical analyses of anti-Xa assay activity in the industrial enoxaparin lots within the 20 mg/syringe and 40 mg syringe lots separately. Only the lower confidence interval was stated. However, FDA needs the upper confidence interval as well.

Further, no analysis was provided for the anticoagulant assay data, which we also require. This should be accomplished in the same manner as the anti-Xa assay analyses.


Mordecai Friedberg
Mathematical Statistician

cc: Original NDA 20-164
HFD-180
HFD-180/Dr. Sieczkowski/MS. Collier
HFD-715/Chron
HFD-715/Dr. Fairweather/Dr. Tsong/Mr. Friedberg
HFD-715/ NDA 20-164 Enoxaparin Injection
HFD-715/MF 5/5/92 wp51/Memo19



Statistical Review and Evaluation

NDA #: 20-164

Date: JAN 4 1993

Applicant: Rhone-Poulenc Rorer Pharmaceuticals Inc.

Name of Drug: Lovenox (Enoxaparin) Injection

Documents Reviewed:

1. NDA Amendment, Date of Document, August 11, 1992 (corrected versions of Appendices XV of June 29, 1992 Amendment), "Statistical Evaluation of Enoxaparin Stability Data for the Anti-Xa and Anti-coagulant Activity: 20 mg and 40 mg per syringe", ARR 92-013, May 29, 1992.
2. NDA Amendment, Date of Document, Dec. 17, 1992.

Introduction

Rhone-Poulenc Rorer has asked for an expiration dating period of 24 months for Lovenox (Enoxaparin) injection, 30 mg pre-filled syringes. The reviewing chemist, Dr. Joseph Sieczkowski, HFD-180, has requested the Division of Biometrics to perform a statistical review and evaluation of the sponsor's stability data.

Design

Six industrial lots of enoxaparin injectable solution (10 mg/0.1 mL), packaged in 20 mg syringes (0.2-mL/syringe - lot # 2014, 2015, and 2016) and 40 mg syringes (0.4 mL/syringe - lot # 4007, 4008, and 4009) were placed in stability testing for 24 months under the room temperature storage condition. The test intervals were 0, 6, 12, 18, and 24 months. Additional six pilot lots packaged in 20 mg (lot #: CB 3125, CB 3323, CB 3324) and 40 mg (lot #: CB 3325, CB 3443, and CB 3444) were stored at room temperature for 36 months. The test intervals were 0, 6, 11, 12, 18, 24, and 36 months for 20 mg syringes, and 0, 5, 6, 12, 18, 24, and 36 months for 40 mg syringes. In the December 17, 1992 submission, the sponsor also included stability study of three lots of enoxaparin 30 mg (0.3 mL) pre-filled syringes. These three lots of enoxaparin (lots #: 34, 35, and 36 or called CB 5596, CB 5597, CB 5598) were manufactured at the industrial scale proposed to be tested at 4°C, 25°C, and 30°C for 3 years, and 37°C for 3 months. However, in this submission, the sponsor submitted only up to six weeks of data of 30 mg syringes. The test intervals are 0, 2, 4, and 6 weeks for 25°C, 30°C, and 37°C and 0 and 6 weeks for 4°C. Table 1 lists the test variables and their specifications for enoxaparin injection 30 mg pre-filled syringes.

Sponsor's Analyses

The sponsor conducted two sets of statistical analyses in these stability studies. The first set included the statistical analyses of enoxaparin 20 mg and 40 mg data. The second set included the statistical analyses of 30 mg data.

The simple linear regression analyses were applied to assays of anti-Xa and anti-coagulant activity of lots packaged in 20 and 40 mg syringes. The first regression model for each assay and size included terms for lot differences in initial potency and stability. The second and final models pooled three lots, provided that lot stability differences had a statistical significance level above 0.25. The final model had a common intercept if initial lot differences in the first model had a statistical significance level above 0.25.

Stability through 36 months was determined if the projected lower 95% one-sided confidence limits of the final regression were above the lower specification limit for both anti-Xa and anti-coagulant activity.

Analysis of covariance models for effects of size, lots within size, months, and the interaction terms with size and lots on anti-Xa and anti-coagulant activity were also evaluated to confirm similarity between lots packaged in 20 and 40 mg syringes.

In a secondary analysis, the Ruberg and Stegeman procedure ("Pooling Data for Stability Studies: Testing the Equality of Batch Degradation Slopes," Biometrics 47, pp. 1059 - 1069, 1991) was used to determine the critical significance for pooling. The alternative arrays of slopes for this analysis were chosen to give 80% power to detect slope differences equivalent to an anti-Xa assay difference of 12% or an anti-coagulant assay difference of 24% between two batches at 36 months. The sponsor reported critical values for each dose strength/assay/production-pilot batch combination. The reported critical value of each case is the largest value estimated under two slope difference arrays. These regression results were not submitted.

Based on the above statistical analyses of the 24 months of 20 mg and 40 mg data from the industrial batches as well as statistical analyses of the 36 months of 20 mg and 40 mg data from the pilot group, the sponsor concluded that "it is anticipated that the current formulation of enoxaparin (10 mg per 0.1 mL), packaged in a syringe containing between 0.2 mL (20 mg per syringe) and 0.4 mL (40 mg per syringe) will remain within acceptable limits at least 36 months under the room temperature condition. Anti-Xa and anti-coagulant assay stability profiles from the industrial batches through 24 months are generally similar to the pilot batches profiles through 36 months. The industrial batches show much less variability. Both dosage forms (20 mg and 40 mg per syringe) demonstrate similar stability."

Similar analyses as described above were performed on the assays of anti-Xa and anti-coagulant activity of three lots of enoxaparin 30 mg pre-filled syringes after 6 weeks of storage under various temperature conditions. These analyses indicate the following results: (1) Anti-Xa and anti-coagulant activity of the product are independent of the temperature of storage (4°C, 25°C, 30°C, or 37°C). (2) Even accelerated stability storage conditions for 6 weeks do not cause a change in anti-Xa and anti-coagulant activity. (3) All three lots of enoxaparin 30 mg pre-filled syringes exhibited the same stability profile for anti-Xa and anti-coagulant activity. (4) Enoxaparin 30 mg pre-filled syringes when stored at 25°C demonstrated an anti-Xa activity change with time which is not distinguishable from zero.

Noted that the sponsor used 90%-110% of labeled potency as the specification limits for assay of anti-Xa activity for enoxaparin 20mg, 30mg, and 40mg, 72%-141% of labeled potency for assay of anti-coagulant activity for 20 mg and 40 mg, and 67.6%-132.4% of label potency for assay of anti-coagulant activity for 30 mg.

Based on the stability data and analyses of enoxaparin 20 mg, 40 mg, and 30 mg pre-filled syringes, the sponsor stated that "accepting the fact that enoxaparin 30 mg pre-filled syringes have the same stability profile as enoxaparin 20 mg and 40 mg syringes and, based on the stability data in the NDA (which shows that the product is stable for at least two years when stored at $\leq 25^{\circ}\text{C}$), it is reasonable to also expect at least 24 months of stability for enoxaparin 30 mg pre-filled syringes when stored at $\leq 25^{\circ}\text{C}$."

Reviewer's Analyses

The statistical procedures given in the FDA "Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics" (February, 1987) was applied to the stability data provided by the sponsor. The reviewer analyzed the assays of anti-Xa and anti-coagulant activity of enoxaparin 20 mg and 40 mg for both industrial and pilot batches. The assay data of anti-Xa and anti-coagulant activity of enoxaparin 30 mg stored at 25°C and 30°C were also analyzed. The specification limits for assays of anti-Xa and anti-coagulant activity were applied as sponsor specified. The statistical analyses and results are as follows:

I. 20 mg and 40 mg syringes room temperature stability data

I.a. Statistical analyses

(1) The assay of anti-Xa activity of enoxaparin 20 mg, industrial batches, stored at room temperature.

Table 2 presents the data and analysis of variance table of lots

2014, 2015, and 2016 under room temperature condition. Based on the p-values of statistical tests for selection of degradation curve models, the model of common intercept and common slope was selected. The 95% lower confidence bound for the regression line was calculated.

(2) The assay of anti-Xa activity of enoxaparin 40 mg, industrial batches, stored at room temperature.

Table 3 presents the data and analysis of variance table of lots 4007, 4008, and 4009 under room temperature condition. Based on the p-values of statistical tests for selection of degradation curve models, the model of common intercept and common slope was selected. The 95% lower confidence bound for the regression line was calculated.

(3) The assay of anti-Xa activity of enoxaparin 20 mg, pilot batches, stored at room temperature.

Table 4 presents the data and analysis of variance table of lots CB 3125, CB 3323, and CB 3324 under room temperature condition. Based on the p-values of statistical tests for selection of degradation curve models, the models of separate intercepts and separate slopes were selected. The 90% upper and lower confidence bounds for the three individual regression lines were calculated.

(4) The assay of anti-Xa activity of enoxaparin 40 mg, pilot batches, stored at room temperature.

Table 5 presents the data and analysis of variance table of lots CB 3325, CB 3443, and CB 3444 under room temperature condition. Based on the p-values of statistical tests for selection of degradation curve models, the model of common intercept and common slope was selected. The 95% lower confidence bound for the regression line was calculated.

(5) The assay of anti-coagulant activity of enoxaparin 20 mg, industrial batches, stored at room temperature.

Table 6 presents the data and analysis of variance table of lots 2014, 2015, and 2016 under room temperature condition. Based on the p-values of statistical tests for selection of degradation curve models, the models of separate intercepts and separate slopes were selected. The 90% upper and lower confidence bounds for the three individual regression lines were calculated.

(6) The assay of anti-coagulant activity of enoxaparin 40 mg, industrial batches, stored at room temperature.

Table 7 presents the data and analysis of variance table of lots 4007, 4008, and 4009 under room temperature condition. Based on the p-values of statistical tests for selection of degradation curve

models, the model of common intercept and common slope was selected. The 95% upper confidence bound for the regression line was calculated.

(7) The assay of anti-coagulant activity of enoxaparin 20 mg, pilot batches, stored at room temperature.

Table 8 presents the data and analysis of variance table of lots CB 3125, CB 3323, and CB 3324 under room temperature condition. Based on the p-values of statistical tests for selection of degradation curve models, the models of separate intercepts and separate slopes were selected. The 90% upper and lower confidence bounds for the three individual regression lines were calculated.

(8) The assay of anti-coagulant activity of enoxaparin 40 mg, pilot batches, stored at room temperature.

Table 9 presents the data and analysis of variance table of lots CB 3325, CB 3443, and CB 3444 under room temperature condition. Based on the p-values of statistical tests for selection of degradation curve models, the models of separate intercepts and common slope were selected. The 95% lower confidence bound for the three individual regression lines were calculated.

I.b. Results of analyses

Based on the above analyses, we found that the assays of anti-Xa and anti-coagulant activity of enoxaparin 20 mg and 40 mg syringes are stable after 36 months storage under room temperature condition.

II. 30 mg syringes 25°C and 30°C stability data

II.a. Statistical analyses

(1) The assay of anti-Xa activity of enoxaparin 30 mg, stored at 25°C.

Table 10 presents the data and analysis of variance table of lots CB 05596, CB 05597, and CB 05598 stored at 25°C. Based on the p-values of statistical tests for selection of degradation curve models, the model of common intercept and common slope was selected. The 95% lower confidence bound for the regression line was calculated.

(2) The assay of anti-Xa activity of enoxaparin 30 mg, stored at 30°C.

Table 11 presents the data and analysis of variance table of lots CB 05596, CB 05597, and CB 05598 stored at 30°C. Based on the p-values of statistical tests for selection of degradation curve models, the models of separate intercepts and common slope were selected. The 95% lower confidence bound for the three individual regression lines

were calculated.

(3) The assay of anti-coagulant activity of enoxaparin 30 mg, stored at 25°C.

Table 12 presents the data and analysis of variance table of lots CB 05596, CB 05597, and CB 05598 stored at 25°C. Based on the p-values of statistical tests for selection of degradation curve models, the models of separate intercepts and separate slopes were selected. The 90% upper and lower confidence bounds for the three individual regression lines were calculated.

(4) The assay of anti-coagulant activity of enoxaparin 30 mg, stored at 30°C.

Table 13 presents the data and analysis of variance table of lots CB 05596, CB 05597, and CB 05598 stored at 30°C. Based on the p-values of statistical tests for selection of degradation curve models, the models of separate intercepts and common slope were selected. The 95% lower confidence bound for the three individual regression lines were calculated.

II.b. Results of analyses

Based on the above analyses, we found that the assay of anti-Xa activity of enoxaparin 30 mg syringes is stable after 18 weeks storage at 25°C, and after 11 weeks storage at 30°C. The assay of anti-coagulant activity of enoxaparin 30 mg syringes is stable after 22 weeks storage at 25°C, and after 24 weeks storage at 30°C.

Although the assay data suggest a 11-24 weeks expiration dating period for enoxaparin 30 mg syringes stored between 25°C and 30°C, however, in this study, every lot of enoxaparin 30 mg syringes configuration has sample data only up to 6 weeks. The above estimated expiration dating periods were based on the data extrapolation beyond the range of storage time actually observed.

Summary

Rhone-Poulenc Rorer has asked for an expiration dating period of 24 months for Lovenox (Enoxaparin) injection, 30 mg pre-filled syringe. To support his request, the sponsor conducted two sets of stability studies. The first set included the stability study of the 24 months enoxaparin 20 mg and 40 mg data from the industrial batches as well as the stability study of the 36 months enoxaparin 20 mg and 40 mg data from the pilot group. The second set included the stability study of three lots of enoxaparin 30 mg pre-filled syringes after 6 weeks of storage under various temperature conditions. Noted that the sponsor used 90%-110% of labeled potency as the specification limits for assay of anti-Xa activity for 20 mg, 30 mg, and 40 mg,

72%-141% of labeled potency for assay of anti-coagulant activity for 20 mg and 40 mg, and 67.6%-132.4% of label potency for assay of anti-coagulant activity for 30 mg.

The reviewer analyzed the assays of anti-Xa and anti-coagulant activity of enoxaparin 20 mg and 40 mg syringes for both industrial and pilot batches. The assays of anti-Xa and anti-coagulant activity of enoxaparin 30 mg stored at 25°C and 30°C were also analyzed. The degradation curves for each batch data or pooled data of batches were fitted and the two-sided 90% confidence bounds for the mean degradation curves were constructed for the above stability data.

The assays of anti-Xa and anti-coagulant activity of enoxaparin 20 mg and 40 mg syringes suggest a 36 months expiration dating period for enoxaparin 20 mg and 40 mg syringes stored under room temperature.

The assay of anti-Xa activity of enoxaparin 30 mg syringes is stable after 18 weeks storage at 25°C, and after 11 weeks storage at 30°C. The assay of anti-coagulant activity of enoxaparin 30 mg syringes is stable after 22 weeks storage at 25°C, and after 24 weeks storage at 30°C.

Although the assay data suggest a 11-24 weeks expiration dating period for enoxaparin 30 mg syringes stored between 25°C and 30°C, however, in this study, every lot of enoxaparin 30 mg syringes configuration has sample data only up to 6 weeks. The above estimated expiration dating periods were based on the data extrapolation beyond the range of storage time actually observed. The sponsor should be asked to submit data up to the expiration date requested and the statistical analyses on at least three batches when the results become available.

Daphne Lin

Daphne Lin, Ph.D.
Mathematical Statistician

Concur: Karl K. Lin 1/4/93
Karl K. Lin, Ph.D., Group Leader, SARB

- cc: Original NDA 20-164
- HFD-180/Dr. Fredd
- HFD-180/Dr. Sieczkowski
- HFD-180/Ms. Collier
- HFD-710/Chron
- HFD-715/Dr. Karl Lin
- HFD-715/Dr. Daphne Lin
- HFD-715/Chron (SARB)
- HFD-715/DRU 2.1.1, Lovenox, Rhone-Poulenc Rorer Pharm. Inc.

Table 1

ENOXAPARIN INJECTION

SPECIFICATIONS FOR 30 mg PREFILLED SYRINGES
(0.3 ml fill in a 0.5 ml syringe)

Control tests	Specifications
<p>1. <u>Appearance</u></p> <p>2. <u>Identification of enoxaparin</u></p> <p>2.1 Precipitation with protamine sulfate</p> <p>2.2 U.V. spectrum</p> <p>2.3 Sodium</p> <p>3. <u>Physical & chemical tests</u></p> <p>3.1 Extrudable volume</p> <p>3.2 pH</p> <p>3.3 Relative density (R.T.)</p> <p>3.4 Particulate matter, USP</p> <p>4. <u>Assays</u></p> <p>4.1 Anti-Xa activity</p> <p>4.2 Anticoagulant activity (EP or USP)</p> <p>4.3 Free sulfates</p> <p>5. <u>Biological tests</u></p> <p>5.1 Sterility test, USP</p> <p>5.2 Pyrogen test, USP</p>	

(a) As per the LMWH International Reference Standard (W.H.O.)
(b) Tentative limit

Table 2
ENOXAPARIN INJECTION
Anti-Xa Activity Assay
20mg / Industrial Batches

Stability Analysis

TIME	_1	_2	_3
0	96.0	99.0	97.0
6	97.3	94.8	97.0
12	94.5	95.3	94.3
18	96.5	95.8	97.0
24	95.5	95.0	97.5

Analysis of Variance Table

SOURCE	SS	DF	MS	F	P
A	4.46	4	1.11	0.56828	0.69236
B	1.16	2	0.58	0.29612	0.75067
C	3.30	2	1.65	0.84044	0.46277
D	17.65	9	1.96		
E	138726.90	6	23121.15		

Batch All
Fitted Line : $Y = 96.686666667 + -0.043333333 X$

95% One-Sided Lower Confidence Limit

Common Intercept and Common Slope

BATCH	ESTIMATED DATING PERIOD (MONTHS/WEEKS)
All	65

Table 3

ENOXAPARIN INJECTION
 Anti-Xa Activity Assay
 40mg / Industrial Batches
 Stability Data

TIME	_1	_2	_3
0	97.8	96.6	95.0
6	95.6	95.6	95.5
12	95.5	95.9	94.4
18	97.4	97.6	96.6
24	93.8	94.0	93.9

Analysis of Variance Table

SOURCE	SS	DF	MS	F	P
A	4.03	4	1.01	0.53721	0.71249
B	2.72	2	1.36	0.72410	0.51098
C	1.31	2	0.66	0.35032	0.71366
D	16.88	9	1.88		
E	137327.64	6	22887.94		

Fitted Line : $Y = \text{Batch All } 96.38 + -0.058333333 X$

95% One-Sided Lower Confidence Limit

Common Intercept and Common Slope

BATCH ESTIMATED
 DATING PERIOD
 (MONTHS/WEEKS)

All 56

Table 4

ENOXAPARIN INJECTION
Anti-Xa Activity Assay
20mg / Pilot Batches
Stability Data

TIME	_1	_2	_3
0	105.0	98.0	98.5
6	105.0	97.5	101.5
11	101.5	.	.
12	.	96.0	101.5
18	101.5	99.0	96.5
24	97.5	95.0	96.0
36	100.5	99.0	98.5

Analysis of Variance Table

SOURCE	SS	DF	MS	F	P
A	75.05	4	18.76	4.27964	0.02218
B	61.19	2	30.60	6.97882	0.00976
C	13.86	2	6.93	1.58047	0.24588
D	52.61	12	4.38		
E	177698.89	6	29616.48		

Batch 1

Fitted Line : $Y = 104.49450226 + -0.168073827 X$

Batch 2

Fitted Line : $Y = 97.207142857 + 0.0130952381 X$

Batch 3

Fitted Line : $Y = 100.00714286 + -0.078571429 X$

95% One-Sided Lower Confidence Limit

Separate Intercepts and Separate Slopes

ESTIMATED
DATING PERIOD
(MONTHS/WEEKS)

BATCH	
1	53
2	80
3	50

Table 5

**ENOXAPARIN INJECTION
Anti-Xa Activity Assay
40mg / Pilot Batches
Stability Data**

TIME	_1	_2	_3
0	99.0	96.5	95.1
5	.	98.3	100.3
6	97.5	.	.
12	98.3	98.2	99.6
18	94.3	92.9	92.2
24	94.3	96.0	95.1
36	95.3	93.3	94.8

Analysis of Variance Table

SOURCE	SS	DF	MS	F	P
A	7.86	4	1.97	0.33015	0.85243
B	0.80	2	0.40	0.06742	0.93516
C	7.06	2	3.53	0.59289	0.56814
D	71.43	12	5.95		
E	167449.61	6	27908.27		

Batch All

Fitted Line : $Y = 97.627290076 + -0.07444483 X$

95% One-Sided Lower Confidence Limit

Common Intercept and Common Slope

ESTIMATED
DATING PERIOD
(MONTHS/WEEKS)

All 57

Table 6

ENOXAPARIN INJECTION
 Anti-coagulant Activity Assay
 20mg / Industrial Batches
 Stability Data

TIME	_1	_2	_3
0	100.8	109.4	122.7
6	102.3	107.8	117.2
12	104.7	107.0	116.4
18	100.8	107.0	117.2
24	104.7	107.0	115.6

Analysis of Variance Table

SOURCE	SS	DF	MS	F	P
A	618.29	4	154.57	58.006	0.000002
B	597.10	2	298.55	112.035	0.000000
C	21.19	2	10.60	3.977	0.057868
D	23.98	9	2.66		
E	180062.26	6	30010.38		

Fitted Line : $Y = \text{Batch 1} + 101.4 + 0.105 X$

Fitted Line : $Y = \text{Batch 2} + 108.76 + -0.093333333 X$

Fitted Line : $Y = \text{Batch 3} + 120.66 + -0.236666667 X$

95% One-Sided Lower Confidence Limit

Separate Intercepts and Separate Slopes

BATCH ESTIMATED
 DATING PERIOD
 (MONTHS/WEEKS)

1	84
2	84
3	84

Table 7
ENOXAPARIN INJECTION
Anti-coagulant Activity Assay
40mg / Industrial Batches
Stability Data

TIME	_1	_2	_3
0	96.1	97.7	94.1
6	98.4	96.9	96.9
12	97.7	100.4	98.1
18	98.4	95.7	96.5
24	99.2	99.2	98.8

Analysis of Variance Table

SOURCE	SS	DF	MS	F	P
A	6.60	4	1.65	0.74131	0.58721
B	3.96	2	1.98	0.89041	0.44377
C	2.63	2	1.32	0.59221	0.57330
D	20.02	9	2.22		
E	142922.15	6	23820.36		

Batch All

Fitted Line : $Y = 96.47333333 + 0.0944444444 X$

95% One-Sided Upper Confidence Limit

Common Intercept and Common Slope

BATCH	ESTIMATED DATING PERIOD (MONTHS/WEEKS)
-------	--

All

84

Table 8

ENOXAPARIN INJECTION
 Anti-coagulant Activity Assay
 20mg / Pilot Batches
 Stability Data

TIME	_1	_2	_3
0	110.9	128.1	98.4
6	111.6	129.7	101.1
11	112.5	.	.
12	.	123.4	101.6
18	110.9	114.1	90.6
24	106.3	125.0	98.4
36	115.6	115.6	96.9

Analysis of Variance Table

SOURCE	SS	DF	MS	F	P
A	1923.39	4	480.85	26.9174	0.00001
B	1851.89	2	925.95	51.8337	0.00000
C	71.49	2	35.75	2.0011	0.17783
D	214.37	12	17.86		
E	222130.40	6	37021.73		

Batch 1

Fitted Line : $Y = 110.50537993 + 0.0501865305 X$

Batch 2

Fitted Line : $Y = 128.36428571 + -0.357142857 X$

Batch 3

Fitted Line : $Y = 99.46 + -0.101666667 X$

95% One-Sided Lower Confidence Limit

Separate Intercepts and Separate Slopes

ESTIMATED
 DATING PERIOD
 (MONTHS/WEEKS)

BATCH	1	84
	2	84
	3	81

Table 9

ENOXAPARIN INJECTION
Anti-coagulant Activity Assay
40mg / Pilot Batches
Stability Data

TIME	_1	_2	_3
0	127.3	114.8	100.8
5	.	106.6	94.9
6	119.1	.	.
12	124.2	107.0	99.2
18	113.3	105.5	99.6
24	118.8	103.9	99.8
36	120.3	105.5	99.2

Analysis of Variance Table

SOURCE	SS	DF	MS	F	P
A	1453.06	4	363.27	28.8573	0.00000
B	1424.96	2	712.48	56.5984	0.00000
C	28.10	2	14.05	1.1162	0.35926
D	151.06	12	12.59		
E	214862.54	6	35810.42		

Fitted Line : $Y = 122.32735198 + -0.114209499 X$ Batch 1

Fitted Line : $Y = 109.02498373 + -0.114209499 X$ Batch 2

Fitted Line : $Y = 100.72498373 + -0.114209499 X$ Batch 3

95% One-Sided Lower Confidence Limit
Separate Intercepts and Common Slope

ESTIMATED
DATING PERIOD
(MONTHS/WEEKS)

BATCH	ESTIMATED DATING PERIOD (MONTHS/WEEKS)
1	84
2	84
3	84

Table 10
ENOXAPARIN INJECTION
Anti-Xa Activity Assay
30mg / Industrial Batches
Stability Data at 25 Degrees Temp.

TIME	-1	-2	-3
0	99.7	98.0	97.3
2	96.0	96.0	94.3
4	97.3	96.0	95.3
6	98.3	97.3	97.0

Analysis of Variance Table

SOURCE	SS	DF	MS	F	P
A	7.10	4	1.78	0.67670	0.63246
B	6.86	2	3.43	1.30741	0.33784
C	0.24	2	0.12	0.04599	0.95538
D	15.74	6	2.62		
E	112624.69	6	18770.78		

Fitted Line : $Y =$ Batch All
 $97.12 + -0.08166667 X$

95% One-Sided Lower Confidence Limit
 Common Intercept and Common Slope

BATCH	ESTIMATED DATING PERIOD (WEEKS)
All	18

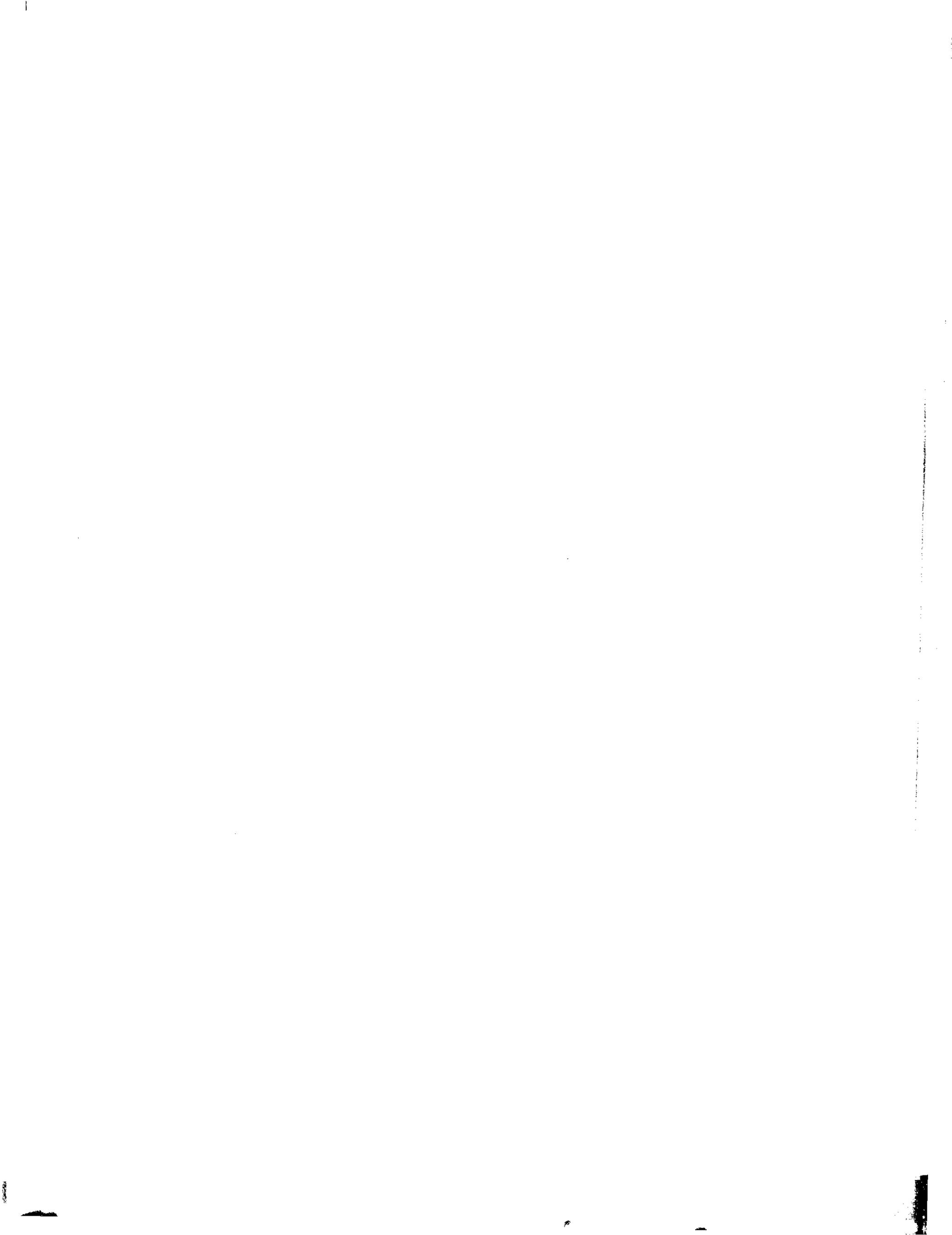


Table 11

ENOXAPARIN INJECTION
Anti-Xa Activity Assay
30mg / Industrial Batches
Stability Data at 30 Degrees Temp.

TIME	_1	_2	_3
0	99.7	98.0	97.3
2	96.0	96.7	94.6
4	96.3	96.7	96.7
6	98.0	96.7	93.7

Analysis of Variance Table

SOURCE	SS	DF	MS	F	P
A	8.70	4	2.17	0.99893	0.47564
B	8.04	2	4.02	1.84829	0.23692
C	0.65	2	0.33	0.14956	0.86420
D	13.06	6	2.18		
E	112224.42	6	18704.07		

Fitted Line : Y = $98.37 + (-0.29) X$ Batch 1

Fitted Line : Y = $97.895 + (-0.29) X$ Batch 2

Fitted Line : Y = $96.445 + (-0.29) X$ Batch 3

95% One-Sided Lower Confidence Limit

Separate Intercepts and Common Slope

BATCH	ESTIMATED DATING PERIOD (WEEKS)
1	15
2	14
3	11

Table 12

**ENOXAPARIN INJECTION
Anti-coagulant Activity Assay
30mg / Industrial Batches
Stability Data at 25 Degrees Temp.**

TIME	_1	_2	_3
0	88.2	90.8	89.8
2	86.6	89.8	89.8
4	86.6	90.8	89.8
6	88.7	94.0	88.7

Analysis of Variance Table

SOURCE	SS	DF	MS	F	P
A	34.27	4	8.57	6.2605	0.02470
B	29.28	2	14.64	10.6998	0.01050
C	4.98	2	2.49	1.8213	0.24092
D	8.21	6	1.37		
E	96086.97	6	16014.49		

Fitted Line : $Y =$ Batch 1 $87.3 + 0.075 X$

Fitted Line : $Y =$ Batch 2 $89.76 + 0.53 X$

Fitted Line : $Y =$ Batch 3 $90.02 + -0.165 X$

95% One-Sided Lower Confidence Limit

Separate Intercepts and Separate Slopes

BATCH	ESTIMATED DATING PERIOD (WEEKS)
1	22
2	24
3	24

Table 13

ENOXAPARIN INJECTION
Anti-coagulant Activity Assay
30mg / Industrial Batches
Stability Data at 30 Degrees Temp.

TIME	_1	_2	_3
0	88.2	90.8	89.8
2	86.6	87.7	89.8
4	85.6	88.7	88.7
6	86.1	89.8	89.8

Analysis of Variance Table

SOURCE	SS	DF	MS	F	P
A	21.62	4	5.41	4.50500	0.05066
B	20.50	2	10.25	8.54236	0.01756
C	1.12	2	0.56	0.46764	0.64753
D	7.20	6	1.20		
E	93939.64	6	15656.61		

Fitted Line : Y = Batch 1
 $87.145 + -0.173333333 X$

Fitted Line : Y = Batch 2
 $89.77 + -0.173333333 X$

Fitted Line : Y = Batch 3
 $90.045 + -0.173333333 X$

95% One-Sided Lower Confidence Limit

Separate Intercepts and Common Slope

BATCH	ESTIMATED DATING PERIOD (WEEKS)
1	24
2	24
3	24

000
C/M/

PHARMACOLOGISTS REVIEW COVERSHEET

MAR 11 1992

NDA No. : 20-164
SPONSOR : Rhone-Poulenc Rorer Pharmaceuticals, Inc.
DRUG : Enoxaparin
CATEGORY : Prevention of DVT
EVALUATION:

- * The submission generally consistent with Agency's Format
Guideline: Yes (X) No ()
- * Appropriate studies submitted: Yes (X) No ()
- * Primary adverse pharmacological effect: Hemorrhage
- * Target organs in toxicity studies: Liver, Kidney, exocrine Pancreas
and Parathyroid
- * Reproductive or developmental toxicity: Yes () No (X)
If Yes, explain briefly:
- * Carcinogenicity studies:
Number of studies: Rat () Mouse () Other ()
Results: +, -, ± () () ()
Site of tumors:
- * Sub-chronic/Chronic blood level studies: Rat () Dog () Other ()
- * GLP problems: Yes () No (X)
- * OTHER COMMENTS:

PRECLINICAL STUDIES AND TESTING LABORATORIES:

<u>Type of Study</u>	<u>Study/Report #</u>	<u>Drug Batch#</u>
Pharmacology		
Absorption:	464/061/	FP-573/608/
Rats & dogs	463/019	3055115
Distribution:		
Rats & Dogs		
Metabolism:		
Dogs		
Excretion:		
Rats & Dogs		
Acute Toxicity:		
<u>S.C.</u>		
Mice & Rats	027/02/064	812
<u>I.V.</u>		
Mice, Rats & Dogs	041/066/ 065/012	812
Subacute/subchronic/ Chronic Toxicity:		
<u>Rat</u>		
13-week (s.c.)	057	573
6-month (s.c.)	094	3214-01
26-week (i.v.)	054	781
<u>Dog</u>		
13-week (s.c.)	01	573
<u>Monkey</u>		
26-week (s.c.)	095	3214-01/3214-02
26-week (i.v.)	055	781
Reproductive Toxicity:		
Fertility & Reproductive Performance (Segment I)		
Rat (s.c.)	018	573R
Teratology (Segment II)		
Rat (i.v. & s.c.)	040/014	812/573R
Rabbit (i.v. & s.c.)	039/016	930/573
Perinatal/postnatal (Segment III)		
Rat (s.c.)	011	R573
Mutagenicity:		
Ames Test	04	573
Double Locus Cell Mutation Assay	05	573
Chromosomal aberration tests in cultured human lymphocytes	06	573
Chromosomal Aberration Test in Rat Bone Marrow	03	573
Special Toxicity Studies:		
Local Tolerance Study in Dogs	08	3055-32
Sensitization Test in Guinea Pigs	09	812
Hemolytic and Precipitating Properties	07	812

PHARMACOLOGY:

The coagulation mechanism consists of the plasma (intrinsic pathway) and tissue thromboplastin (extrinsic pathway) systems and both are important for normal hemostasis. Activation of factor X can be achieved by either intrinsic or extrinsic pathway. Extrinsic pathway is dependent on factor VII, calcium, and tissue factor, while intrinsic pathway is dependent on factors VIII, IX, X, XI, XII, calcium, PF3 and also on factor II. Once factor X is converted to factor Xa from either the intrinsic or extrinsic system, it forms a calcium mediated bridge complex with phospholipid, PF3 and factor V which in turn convert prothrombin to thrombin, and this thrombin is responsible for the formation of fibrin, activation of factor XIII and thrombus. Antithrombotic activity is defined as prevention of thrombosis (coagulation occurs within blood vessels). Heparin has been used for prevention of deep vein thrombosis in total hip replacement surgery. Heparin inhibits blood coagulation. It binds to antithrombin III (major effect) and the complex become much more powerful inhibitor of factor IIa (thrombin) than antithrombin III alone. Antithrombin III inhibits a number of coagulation factors (IXa, Xa, XIa and XIIa), and inhibition of these factors are strongly augmented by the presence of heparin. Heparin also inhibits the activation of prothrombin by Xa in the absence of antithrombin III. Heparin has also been reported to produce thrombocytopenia. Enoxaparin is a low molecular weight heparin which has anticoagulant activity as well as antithrombotic activity. Enoxaparin mainly inhibits factor Xa activity and inhibition of factor IIa activity was less than the unfractionated heparin. Furthermore the antithrombotic dose of enoxaparin has very little anticoagulant activity. In contrast, heparin has equivalent antithrombotic and anticoagulant activities.

In various experiments, enoxaparin dose was expressed in mg/kg, anti IIa unit/kg or anti Xa unit/kg. The anti IIa and Anti Xa units were assessed by utilizing enzyme specific chromogenic substrates for factor IIa and Factor Xa respectively. The potency of enoxaparin in terms of biological activities were as follows:

Enoxaparin:

1 mg = 53.2 anti IIa units = 133.2 anti Xa units

Heparin (comparator):

1 mg = 200 anti IIa units = 200 anti Xa units

Primary Activity

1. Antithrombotic Activity:

Antithrombotic activity of enoxaparin was assessed in various animals models:

Hamster (report # 100470): In hamster cheek pouch model, thrombus was induced by iontophoretic application of ADP to venule of the hamster cheek pouch. A s.c. dose of 312 anti-Xa units/kg of enoxaparin produced no inhibition of thrombus formation, while s.c. doses of 625 and 1250 anti-Xa units/kg reduced thrombus size and the maximum reduction was about 30% at the highest tested dose.

Rabbit (reports # 60, 100474, 100092, 100467 and 100469): Fourteen separate studies were conducted to assess the antithrombotic activity of enoxaparin in rabbits. In 4 of the studies drug was given via s.c. route (0.5-5 mg/kg or 25-200 codex units/kg) and in the remaining studies drug was given via i.v.

route (10-5000 mcg/kg, 5-10 codex units/kg or 2.5-1000 anti-Xa units/kg). In all these studies venous stasis model were used and thrombus was induced by various thrombogenic agents (tissue thromboplastin, factor Xa, rabbit serum, human serum and prothrombin complex with russell's viper venom). Both s.c. and i.v. doses of enoxaparin dose dependently block venous thrombus formation, when given prior to the thrombogen challenge in these studies. The ED50s were 45, 40 and 30 mcg/kg when prothrombin complex with RVV, bovine factor Xa and activated prothrombin were used as thrombogenic challenger respectively. In addition, enoxaparin prevented further development of a previously formed thrombus when given after the thrombogen challenge. In some experiment heparin (165 or 400 anti-Xa units/kg) was also compared for its antithrombotic activity with that of enoxaparin. There were no significant differences between the antithrombotic activities of enoxaparin and heparin.

Antithrombotic activities of enoxaparin (31-250 anti-Xa units/ml) and heparin (12.5-100 i.u./ml) were also measured in whole blood and platelet rich plasma in vitro by using chandler loop technique. Both drugs prolonged the thrombin induced platelet aggregation and thrombus formation in the loop.

Dog (report 100466 and 100474): Enoxaparin (0.625-10 mg/kg, s.c. or 2.5 mg/kg i.v. bolus) produced dose related inhibition of coronary artery thrombosis in dogs and also inhibited the reduction of coronary blood flow associated with thrombus formation. The drug also produced marked inhibition of factor Xa activity along with slight inhibition of factor IIa activity.

Enoxaparin (4.5 mg/kg i.v. bolus plus 1.6-3.2 mg/kg/hr for 3.5 hr) significantly reduced further development of previously formed thrombus when given 1 hr after thrombus induction. Most importantly there were no differences between circulating platelet counts in control and enoxaparin treated groups.

Monkey (report # 100092): Enoxaparin (1 mg/kg, s.c.) markedly inhibited (66-73%) generation of fibrinopeptide A in the monkey plasma. Thus suggesting that the drug has antithrombotic activity.

Sheep (report # 100468): Both enoxaparin (2 mg/kg, i.v.) and heparin (equivalent anti-Xa unit as enoxaparin) prevented clotting in arteriovenous shunt model in sheep.

2. Anticoagulant Activity:

Effect of enoxaparin on various parameters of hemostasis such as prothrombin time (PT), partial thromboplastin time (PTT) and thrombin time (TT) were assessed in rabbit, monkey, dog, sheep and human. PT is a screening test for extrinsic pathway of coagulation. It measures not only factor II but also measures factors I, V, VII and X. PTT is a screening test for intrinsic pathway of coagulation. It measures factors I, II, VIII, IX, X, XI and XII. It does not measure factor VII and platelet factor 3. PTT is widely used for monitoring heparin therapy, an increased APTT is indicative of decreased levels of one or more of the coagulation factors in the intrinsic pathway. TT is a one-stage clotting method, in this test thrombin is added to plasma and the time required for clot formation is a measure of the rate at which fibrin is formed and the test is unaffected by the levels of the other coagulation factors. This test is generally used for D.I.C. diagnosis, monitoring thrombolytic therapy and for screening for the presence of heparin. Additionally, in some experiment Anti-Xa and Anti-IIa activities were also measured by using enzyme specific chromogenic substrates.

In Vitro

Rabbit (report # 100474): In rabbit plasma both enoxaparin and heparin prolonged TT (thrombin time) and APTT (activated partial thromboplastin time), and enoxaparin was less active than heparin. Furthermore, enoxaparin potentiation of thrombin inhibition by antithrombin III was significantly less than heparin under the same experimental conditions, while enoxaparin and heparin both were equipotent in potentiation of the inhibition of factor Xa activity by antithrombin III.

	<u>TT (sec)</u>	<u>APTT (sec)</u>
control	10.9 ± 0.3	19.3 ± 0.5
Heparin (2 anti-Xa units/ml)	150	150
Enoxaparin (2 anti-Xa units/ml)	19.3 ± 0.6	30.9 ± 0.9

Collagen induced aggregation of washed rabbit platelets was inhibited dose dependently by heparin (0.25-50 anti-Xa units/ml) and as well as enoxaparin (0.25-50 anti-Xa units/ml). Heparin was much more effective than enoxaparin, since a heparin dose of 5 anti-Xa units/ml (34 mcg/ml) inhibited collagen induced aggregation by 62±9% while enoxaparin (25 anti-Xa units/ml = 312.5 mcg/ml) produced only 16% inhibition of the aggregation. In vitro, heparin has been reported to both induce and inhibit platelet aggregation, and precise mechanism has not been established.

Monkey (reports # 100474 and 100092): In monkey plasma, enoxaparin prolonged both TT and APTT. The effect on TT was much greater than APTT since TT was doubled at 1.25 mcg/ml while 10 mcg/ml was needed to double the APTT. Furthermore, heparin was much more active than enoxaparin in this experiment because a concentration of 1.25 mcg/ml of heparin was sufficient to triple the thrombin time and 5 mcg/ml

was sufficient to prolonged the APTT from 30 sec to greater than 200 sec.

	<u>TT (sec)</u>	<u>APTT (sec)</u>
control	31.1 ± 6.0	30.6 ± 3.5
Enoxaparin (1.25 mcg/ml=0.16 anti-Xa units/ml)	78.4 ± 12.0	31.2 ± 3.0
Enoxaparin (10 mcg/ml=1.3 anti-Xa units/ml)	300	65.4 ± 7.1

In another in vitro experiment it was shown that enoxaparin (2.5 mcg/ml) produce no change in PT (prothrombin) but prolonged TT (thrombin time) and APTT (activated partial thromboplastin time) and inhibited factor Xa activity. Similar results were seen when heparin was used but with respect to APTT and TT heparin was more effective than enoxaparin.

	PT (sec)	APTT (sec)	TT (sec)	Anti-Xa Activity % inhibition
Control	10.5±0.7	32.3±5.7	16.9±2.0	0.0
Enoxaparin (2.5 mcg/ml)	10.3±0.4	54.9±5.6	81.1±7.9	73.1±1.0
Heparin (2.5 mcg/ml)	11.4±0.6	70.2±8.4	150	67.7±5.0

Dog (report # 100474): In dog plasma, heparin and enoxaparin (0.25-12 mcg/ml) each dose dependently prolonged APTT and TT. Five mcg/ml of heparin triple the APTT time while 12 mcg/ml of enoxaparin was not sufficient to double the APTT, and 1 mcg/ml of heparin triple the TT while 7-8 mcg/ml of enoxaparin was required to get the same effect. Thus heparin was much more active than enoxaparin in these experiments.

Sheep (report # 100468): In sheep plasma, enoxaparin (0-10 mcg/ml) dose dependently increased anti-Xa activity (up to 6 fold), anti-thrombin activity (up to 0.3 fold) and prolonged APTT (from about 49 sec to about 85 sec). Furthermore, on mcg/ml basis, enoxaparin was less active than heparin in this experiment.

In Vitro Amount (mcg/ml) Needed to Have the Same Effects

	Anti-Xa Activity	Anti-IIa Activity	Anti-Coagulant Activity (APTT)
--	------------------	-------------------	-----------------------------------

Heparin	0.48	0.19	0.23
Enoxaparin	1.0	1.0	1.0

Human (report # 100092): In human, enoxaparin (0.62-10 mcg/ml) had no significant effect on platelet aggregation induced by ADP, epinephrine, collagen and arachidonate. Thrombin induced platelet aggregation was inhibited completely at 2.5 mcg/ml since this agent has direct anti-IIa activity. In whole blood, enoxaparin or heparin (3.12-100 mcg/ml) both dose dependently increase the production of TXB2 and PF4, and enoxaparin was less active than heparin in this experiment.

	TXB2 (pg/ml)	PF4 (ng/ml)
Saline	128 ± 11	130
Enoxaparin (3.12-100 mcg/ml)	164-310	100-400
Heparin (3.12-100 mcg/ml)	194-490	200-780

In human plasma, heparin (0.03-1.00 anti-Xa units/ml) significantly and dose dependently prolonged PT, APTT, and inhibited factor-IIa and factor-Xa

activities. Similar results were seen with enoxaparin but of a lesser magnitude. It should also be noted that enoxaparin inhibited factor-Xa generation only when antithrombin III was present. Additionally enoxaparin concentration dependently inhibited fibrinopeptide A generation and several components of contact activation system: factor XII, Factor XI, Kallikrein and Fitzgerald factor.

	<u>PT (sec)</u>	<u>APTT (sec)</u>	<u>TT (sec)</u>
Control	10.4-11.4	31.2	9.9
Enoxaparin (0.03-1 anti-Xa units/ml)	11.3-12.4	31.2-53.5	9.8-30.2
Heparin (0.03-1 anti-Xa units/ml)	10.7-16.8	31.6- 150	9.4- 150

Ex Vivo/In Vivo

Effect of enoxaparin on various parameters of hemostasis were assessed in rabbits and monkeys:

Rabbit (report # 100470): Enoxaparin (313-1330 anti-Xa units/kg, s.c.) increased bleeding time, clotting time, APTT, TT and increased plasma anti-Xa activity in ex-vivo hemostasis test. With respect to anti-Xa activity, enoxaparin was more potent than heparin. Both enoxaparin and heparin had no significant effect on PT, plasma fibrinogen levels, plasma antithrombin levels, and the amounts of protamine (in vitro) needed to neutralize high doses of PK-10169 (1334 anti-Xa units/kg) and heparin (260 i.u./kg) were not significantly different.

	<u>Bleeding Time (min)</u>	<u>Post 1 hr Whole Blood Clotting Time (min)</u>
Control	1.00±0.10	2.00±0.25
<u>Enoxaparin</u>		
313 (anti-Xa units/kg)	1.50±0.16	3.80±0.22
534 (anti-Xa units/kg)	1.50±0.16	4.45±0.31
1334(anti-Xa units/kg)	1.40±0.13	6.10±0.40
<u>Heparin</u>		
105 i.u./kg	1.50±0.14	2.85±0.06
167 i.u./kg	1.46±0.13	5.80±0.37
105 i.u./kg	1.51±0.10	4.82±0.32

	<u>Post 1 hr After drug Administration</u>		
	<u>APTT (sec)</u>	<u>TT (sec)</u>	<u>Anti-Xa Activity (usp units/ml)</u>
Control	16.17±0.83	6.40±0.23	0.32±0.12
<u>Enoxaparin</u>			
313 (anti-Xa units/kg)	23.74±0.52	10.16±0.45	2.49±0.08
534 (anti-Xa units/kg)	28.10±0.64	8.74±0.30	3.18±0.13
1334(anti-Xa units/kg)	33.14±0.91	16.02±1.09	not done
<u>Heparin</u>			
105 i.u./kg	21.90±0.82	7.78±0.13	0.29±0.02
167 i.u./kg	24.80±1.14	12.04±0.42	not done
105 i.u./kg	27.66±1.86	11.98±0.67	0.61±0.09

A single i.v. dose (1 mg/kg) of enoxaparin to rabbits also gave similar results. Furthermore protamine (in vivo) neutralized enoxaparin induced anti-IIa activity but had no effect on anti-Xa activity or on TT and APTT prolongation.

Monkey (report # 100092 and 100474): When enoxaparin (80 anti-Xa units/kg) was given to monkeys intravenously, it produced equivalent degree of inhibition of factor IIa and factor Xa activities. However if the same dose was given via s.c. route then inhibition of factor Xa activity was significantly greater than the inhibition of factor IIa activity (data presented graphically). In another experiment, 1 mg/kg i.v. dose to monkeys resulted in marked prolonged TT and slight prolonged APTT and no significant effect on PT, along with marked inhibition of factor Xa activity and slight inhibition of factor IIa activity. Inhibition of factor Xa activity lasted up to 12 hours after the drug administration.

3. Fibrinolytic Activity

Rabbit (report # 100470 and 100467) Subcutaneous administration of enoxaparin (1330 anti-Xa units/kg) or heparin (260 i.u./kg) had no effect on plasma concentrations of fibrin and fibrinogen degradation products and lysis time of the euglobulin fraction. However, in rabbit venous stasis model, aminocaproic acid (fibrinolysis inhibitor) decreased the anti thrombotic activity of enoxaparin (2.5 and 5.0 mg/kg, i.v.) by approximately 50%, thus indicating that enoxaparin had fibrinolytic activity.

Monkey (report # 100092): Enoxaparin (10,000 anti-Xa unit, i.v.) elevated tissue-plasminogen activator concentrations in monkeys, thus indicating that the drug has fibrinolytic activity.

Human (report # 100092): In human daily administration of enoxaparin (2500-12500 anti-Xa unit/day for 5 days) increased tissue plasminogen activator and B beta 15-42 related peptide concentrations in plasma and decreased the lysis time for euglobulin fraction in whole blood, thus indicating enoxaparin had fibrinolytic activity. However in in vitro experiments, concentrations of 5-25 mcg/ml of enoxaparin had no significant effect on fibrinolytic activity (fibrinogen, fibrinogen degradation products or plasminogen concentrations) in human plasma.

Prevention of Experimental Disseminated Intravascular Coagulation (DIC) by Enoxaparin in Rats (study # 100474): Enoxaparin 5 mg/kg s.c. or i.v.) protected rats from E.Coli induced experimental DIC.

In conclusion, enoxaparin and heparin both are antithrombotic in various animal models, and both prolonged APTT and TT and inhibited factor IIa and factor Xa activities. One important distinction between the two drugs is that enoxaparin markedly inhibited factor Xa activity and slightly inhibited factor IIa activity, while heparin inhibited both factors equally. Furthermore, heparin had greater anticoagulant activity and produced greater inhibition of platelet aggregation induced by various agents than enoxaparin at similar dose levels. Hence the antithrombotic activity of enoxaparin may be related to its relative specific inhibition of factor Xa and drug may cause less bleeding and/or thrombocytopenia compared to heparin at similar biologically active dose.

Secondary Activity

1. Effect on CNS: In mice, 3 different tests (acetic acid test, hot plate test and tail clip test) were used to assess the analgesic potential of enoxaparin. A s.c. dose of enoxaparin (1250 anti-Xa units/kg) did not produce analgesia in these tests, while morphine (10 mg/kg, s.c.) was active in all 3 tests.

2. Effect on Cardiovascular Parameters: In rabbits, no significant differences were observed in heart rate, blood pressure and ECG between enoxaparin (1330 anti-Xa units/kg) treated and saline treated (control) animals.

3. Effect on Renal Function: In rabbits, a s.c dose of 1330 anti-Xa units/kg had no significant effect on the renal functions (water intake, urine volume, excretion of Na⁺, K⁺, Cl⁻, urea and creatinine).

4. Anti-Inflammatory Activity: Enoxaparin doses of 312, 625 and 1250 Anti-Xa units/kg (s.c.) significantly reduced carrageenin induced edema in rats. No positive control was included in the test.

5. In Vitro Effect on Smooth Muscles:

Portal Vein from rats: Enoxaparin (32-500 Anti-Xa units/ml) had no effect on noradrenaline-induced contraction of portal vein of female rats. However, the highest tested dose inhibited the spontaneous activity of the portal vein.

Ileum from Guinea Pigs: Enoxaparin (63-250 Anti-Xa units/ml) had no effect on acetylcholine- or histamine-induced contraction of ileum in guinea pigs. However, the highest tested dose increased the spontaneous activity of the ileum in guinea pigs.

Duodenum from Rabbits: Enoxaparin (63-250 Anti-Xa units/ml) had no effect on the spontaneous activity of the duodenum in rabbits nor any effect on adrenalin-induced relaxation.

6. Effect on Plasma Lipase Activity and Lipid Constituents: Enoxaparin (1330 Anti-Xa units/kg, s.c.) significantly increased (58 %) plasma lipase activity in rabbits at 20 min after the drug administration, at 60 min after the drug administration lipase activity returned to base line values. Heparin (260 i.u./kg) had no effect on plasma lipase activity in rabbits. In another experiment, both enoxaparin (313 and 534 Anti-Xa units/kg, s.c.) and heparin (105 and 167 i.u./kg, s.c.) significantly increased non-esterified fatty acids

in rabbit's plasma, and enoxaparin produced no marked changes in plasma cholesterol, plasma triglycerides and phospholipids levels.

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION (ADME):

The ADME studies were conducted in rats and dogs. Sponsor has submitted additional ADME studies in rats, dogs and monkeys in the resubmission dated December 30, 1991.

RAT:

Pharmacokinetics of ^{99m}Tc-enoxaparin
After Intra-arterial Administration
(Report # 61 and 100464)

Methods: Male Wistar rats were given 286 (n=2), 800 (n=7) and 2860 (n=2) mcg/kg (39, 114 and 371 anti-Xa unit/kg respectively) of ^{99m}Tc-enoxaparin. Blood samples (0.25 ml) were collected from left carotid at 5, 15, 30, 45, 60, 75, 90, 105 and 120 minutes after the injection. After each sample collection animals were injected 0.25 ml of saline to maintain constant volume. Plasma radioactivity was determined by LSC and plasma anti-Xa activity was also monitored by a photometric assay (Tein and Lie: Thrombosis Research, 10, 399-410, 1977).

Results:

Pharmacokinetics of ^{99m}Tc-enoxaparin in Rats
After I.A dose

Dose (Anti-Xa Unit/kg)	Anti-Xa Activity		Radioactivity		
	t _{1/2} alpha (min)	t _{1/2} beta (min)	t _{1/2} alpha (min)	t _{1/2} beta (min)	t _{1/2} beta (min)
39	-	-	5.0		59
114	2.7	106	2.1		169
371	3.5	83	5.0		92

Both plasma radioactivity and anti-Xa activity falls bi-exponentially as a function of time. No pharmacological effect (anti-Xa activity) was seen in low dose treated rats, while the mid dose showed a clear anti-Xa activity (without any severe modification in coagulation). The highest dose induced severe bleeding and 1 out of 2 rats had urinary hemorrhage. Even though this animal was not included in the calculation, nevertheless, due to exaggerated pharmacological effect, changes in the blood volume and coagulation might affect the assays. The pharmacokinetics of radioactivity-fall was independent of enoxaparin dose. It should be noted here that enoxaparin is made up of heparin fractions with molecular weights ranging between 1800-10,000 dalton, and therefore will have variable pharmacological activity. It is not possible to correlate pharmacological activity (anti-Xa) and the amount of enoxaparin detected via radioactivity count. Furthermore one cannot compare the half-lives obtained via biological assay of the drug with that of heparin (comparator), because anti-Xa activity was needed to measure enoxaparin while a different method (namely APTT) was used to measure heparin. However, sponsor tried to compare the half-lives of enoxaparin and heparin in rats as measured by a fall in radioactivity. The t_{1/2}s were 80.6 minutes and 169 minutes for heparin and enoxaparin respectively. This long half-life of enoxaparin compared to heparin might be of some therapeutic value.

Biodistribution of ^{99m}Tc-enoxaparin After
Intra-arterial Administration
(Report # 61 and 100474)

Methods: Male Wistar rats were given ^{99m}Tc-enoxaparin (114 anti-Xa units/kg = 0.880 mg/kg) intra-arterially. Three animals were sacrificed at each time point. The time points were 5, 15, 30, 90, 105 and 120 minutes after the drug administration. Various organs were collected and radioactivity was determined by LSC (blood samples were not collected).

Results: The radioactivity accumulated in liver and kidneys. The C_{max} of radioactivity in tissues were seen at 30 minutes after injection. Radioactivity was also detected in heart, lung, spleen, and thyroid gland. The detected radioactivity may represent the unchanged drug and/or its metabolite(s) and it is also not known whether metabolite(s) have anti-coagulant activity or not.

Pharmacokinetics of ^{99m}Tc-enoxaparin After
S. C. Administration
(Report # 100464)

Methods: Male Wistar rats were given 0.5 (n=6), 1.14 (n=5) and 2.5 (n=3) mg/kg (65, 148 and 325 anti-Xa unit/kg respectively) of ^{99m}Tc-enoxaparin. Blood samples (0.25 ml) were collected from left carotid at 0, 1, 2, 3, 4, 5, 6, 7, and 22 hours after the injection. After each sample collection animals were injected 0.25 ml of saline to maintain constant volume. Plasma radioactivity and plasma anti-Xa activity were monitored.

Results: The kinetic radioactivity fall for all three doses were similar (no kinetic parameters were calculated). The maximum plasma concentration of radioactivity was seen between 2-4 hours after the drug administration and remaining constant until 22 hours (last sampling time point). However, the anti-Xa activity at mid and high dose (no anti-Xa activity was detected at low dose) reached maximum at 4-5 hours after the drug administration and then declined rapidly. Thus the curves of anti-Xa activity and radioactivity do not match. One can only conclude that after 7 hours of the drug administration the observed radioactivity might represent biologically inactive enoxaparin and/or its metabolites.

Biodistribution of ^{99m}Tc-enoxaparin After
S. C. Administration
(Report # 100464)

Methods: Male Wistar rats were given ^{99m}Tc-enoxaparin (1.142 mg/kg, 52 anti-Xa unit/rat) via S. C. Route. Three rats were sacrificed at 2 and 4 hours after the drug administration and various organs (heart, spleen, lung, liver, thyroid, artery, vein, kidney and skin) were collected. Urine sample was also drawn via paracentesis vesicae. In all samples, total radioactivity was determined by LSC.

Results: There was a large accumulation of radioactivity in kidneys and urine and the next highest concentration was in the liver. Radioactivity was also detected in heart, spleen and lungs. Two additional observations should be mentioned here:

(1) thyroid had significant amount of radioactivity, which indicates the presence of free TcO₄⁻, since per-technetate ion follows the same metabolic pathway as iodine and heparin does not bind thyroid (Perdrisot et al; Biomedicine et pharmacotherapy, soumis a publication).

(2) Vascular endothelium (arterial or venous) also had significant amounts of radioactivity.

Excretion of ^{99m}Tc-enoxaparin After
S. C. Administration
(Report # 100464)

Methods: Five male Wistar rats were given ^{99m}Tc-enoxaparin (1 mg/kg, 0.8 mci/rat) via s.c. route. Urine samples were collected from each rat at every 8 hour intervals through 48 hours, and the intervals for feces collection were 0-8, 8-24, and 24-48 hours. In all samples radioactivity was determined by LSC.

Results: At the end of 48 hours, about 50% of the radioactivity was excreted in the urine while about 1.28% of the radioactivity was eliminated in the feces. About 25% of the administered radioactivity was excreted in the urine by the end of the first 8 hours.

Pharmacokinetics of ³⁵S-enoxaparin After I. V. and S. C.
Administration of the Drug to Rats
(Report # 6800-963/1A)

Methods: Male Crl:SD(CD)BR strain rats (n=5/dose group) were given a single dose of ³⁵S-enoxaparin either subcutaneously (0.425, 0.85 and 1.7 mg/kg) or intravenously (0.425, 0.85 and 1.7 mg/kg). Additionally, one group of rats were given ³⁵S-enoxaparin (0.85 mg/kg) intravenously for 7 consecutive days. Blood samples were collected from tail vein at 3, 6, 15, 30 minutes 1, 2, 4, 8, 16, 24, 48 and 72 hours after single dose administration, and on day 7 from rats receiving multiple dose. Additionally blood samples were also collected at 24 hour after each dose (day 1-6) from rats receiving multiple dose of the drug. The concentration of the radioactivity in whole blood was measured by LSC. The above procedure was repeated using non-radiolabelled enoxaparin and blood samples were collected by cardiac puncture at the above specified time period and analyzed for anti-Xa activity in plasma.

Urine and feces samples were collected from 0.85 mg/kg dose group (i.v. and s.c.) following the administration of ³⁵S-enoxaparin. The collection time intervals were 0-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-168 hours after single dose administration and after 7 daily i.v. doses of the drug. Additionally, urine and feces samples were also collected every 24 hours on days 1-6 from rats receiving multiple i.v. doses.

For assessing biliary excretion, ten bile duct cannulated rats were given a single dose of 0.85 mg/kg of ³⁵S-enoxaparin via S.C or I.V. route (5 rats/route). Bile samples were collected at 0-0.5, 0.5-1, 1-2, 2-4, 4-8, 8-24 and 24-48 hours after the drug administration. Additionally, urine samples were collected during 0-4, 4-8, 8-24, and 24-48 hours after drug administration and feces were collected during 0-8, 8-24 and 24-48 hours after drug administration. The total radioactivity in the samples were measured by LSC.

In the above pharmacokinetics experiment, 3 rats/dose group were killed at 6, 30 minutes, 1 and 8 hours after single dose administration and after 7 daily i.v. doses of the drug. Plasma radioactivity was assessed and percent protein bound was determined.

Results: Irrespective of route of administrations, the C_{max} values of radioactivities in whole blood after single dose were linear with dose (Table

I: Sponsor's table 7.1, volume 2.8, page 48). Furthermore, C_{max} value after 7 daily i.v. doses of 0.85 mg/kg (4.401 ± 0.415 mcg equivalent/g) was similar to C_{max} value obtained after a single dose (4.090 ± 0.384 mcg equivalent/g). Thus the data indicate that there is no significant accumulation of the drug. Similar conclusions can be drawn if one compares AUC values. The T_{max} values were 0.45-0.7 hour, and 0.05 hour after s.c. and i.v. dose respectively. The $t_{1/2}$ ranged from 5.574 ± 0.421 hour to 10.48 ± 4.308 hour. This wide range in $t_{1/2}$ value is due to secondary and/or tertiary rise in whole blood radioactivity, and this rise may be due to the appearance of enoxaparin metabolites and/or ^{35}S -sulphate ions.

TABLE ^a I
Summary of whole blood radioactivity parameters following either subcutaneous or intravenous administration of (³⁵S)-enoxaparin to male rats

Route of administration	Dose level (mg/kg)	C _{max} (ng equiv/g)	t _{max} (h)	AUC _(0-24h) (ng equiv.h/g)	t _{1/2β} (h)
Subcutaneous	0.425	0.346 (0.046)	0.450 (0.112)	1.848 (0.324)	10.40 (4.308)
Subcutaneous	0.850	0.659 (0.088)	0.700 (0.274)	6.900 (1.250)	6.367 (0.213)
Subcutaneous	1.700	1.632 (0.212)	0.700 (0.274)	15.07 (0.883)	10.39 (2.968)
Intravenous	0.425	2.359 (0.409)	0.920 (0.027)	2.036 (0.268)	11.22 (3.368)
Intravenous	0.850	4.090 (0.384)	0.010 (0.022)	5.305 (0.971)	5.574 (0.421)
Intravenous	1.700	9.701 (0.814)	<0.95 (0.000)	14.54 (3.028)	9.877 (2.674)
Intravenous ^a	0.850	4.401 (0.415)	0.950 (0.000)	8.470 ^{**} (0.186)	8.333 (0.815)

^a Pharmacokinetic parameters following the last of 7 daily doses

^{**} AUC over the dosing interval (0-24h)

() = standard deviation

a = Sponsor's table 7.1, Volume 2.8, Page 48

Plasma mean maximum anti-Xa activity over the tested s.c. or i.v. dose range also increased linearly with dose (Table II: Sponsor's table 7.16, volume 2.8, page 63). Comparison of AUC values (plasma anti-Xa activity vs time curve) at various s.c./i.v. doses confirm this linear relation. The $t_{1/2}$ after single s.c. dose ranged from 0.837-2.149 hour and 0.330-0.679 hour after single i.v. dose. Due to a secondary rise in plasma anti-Xa activity (similar to that observed for whole blood radioactivity) it was difficult to assess the $t_{1/2}$ values. Therefore sponsor used 0.5 hr - 2 hr sampling points to calculate $t_{1/2}$ of single low s.c. dose and 1-8 hour sampling points to calculate $t_{1/2}$ s of mid and high s.c. single doses. Similarly, 0.05-1 hour and 0.5-2 hour sampling points were used to calculate $t_{1/2}$ s of single mid and high i.v. doses respectively. After 7 daily i.v. doses of enoxaparin (0.85 mg/kg), plasma anti-Xa activity did not accumulate significantly and the kinetics were similar to that obtained after a single i.v. dose of 0.85 mg/kg of enoxaparin.

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TABLE^a II

Summary of plasma anti Xa activity parameters following either subcutaneous or intravenous administration of enoxaparin to male rats

Route of administration	Dose level (mg/kg) ⁺	A_{max} (IU/mL)	t_{max} (h)	AUC _(0-t) (IU.h/mL)	AUC _(0-∞) (IU.h/mL)	$t_{1/2}$ (h)	Cl/F (mL/h/kg)
Subcutaneous	0.425	0.132	0.5	1.015 (0-24)	0.391	0.837 (0.5-2)	43.55
Subcutaneous	0.850	0.332	0.5	1.722 (0-24)	1.010	2.149 (1-8)	51.34
Subcutaneous	1.700	0.767	1.0	3.071 (0-24)	2.239	1.015 (1-8)	57.57
Intravenous	0.425	0.301	0.1	ID	NA	ID	ID
Intravenous	0.850	0.684	0.05	0.371 (0-1)	NA	0.330 (0.05-1)	238.3
Intravenous	1.700	2.008	0.05	1.253 (0-2)	NA	0.679 (0.5-2)	141.1
Intravenous [*]	0.850	1.082	0.05	0.724 (0-2)	NA	0.558 (0.05-2)	122.1

⁺ 0.425 mg/kg = 44.2 IU/kg; 0.85 mg/kg = 88.4 IU/kg; 1.7 mg/kg = 176.8 IU/kg

^{*} After the last of 7 daily doses

() = Time range for estimate

ID = Insufficient data for estimate

NA = Not applicable

a = Sponsor's table 7.16, Volume 2.8, Page 63

Following s.c., i.v. or repeat i.v. administration of ³⁵S-enoxaparin (0.85 mg/kg), about 64-72% of radioactivity was excreted in the urine and 7.6-10.9% of radioactivity was eliminated in the feces (biliary excretion = 2%) by the end of 168 hours after the drug administration (Table III: Sponsor's table 7.25, volume 2.8, page 73). A major portion of the administered radioactivity was excreted during the first 12 hours after drug administration.

TABLE^a III

Summary of excretion of radioactivity following either subcutaneous or intravenous doses of (³⁵S)-enoxaparin to the rat

	Subcutaneous (0.85 mg/kg)	Intravenous (0.85 mg/kg)	Intravenous (repeat) ^b (0.85 mg/kg)
Urine	63.91	66.216	72.548
Capacities	5.716	4.774	3.984
Feces	16.92	7.826	8.138
Capacities	0.838	ND	0.644
Carcass	11.57	0.664	0.114
Total	92.15	91.27	92.73

^a 7 daily doses

^b - Sponsor's table 7.25, volume 2.8, page 73

In-vivo, about 85-90% of the drug was bound to rat plasma proteins but 8 hours after the drug administration (s.c., i.v., or 7 daily i.v. doses) the plasma protein binding decreased to approximately 10-20%.

Thus pharmacokinetics of radioactivity after single s.c., single i.v., or 7 daily i.v. doses of ³⁵S-enoxaparin were linear with tested doses and independent of route of administration. Furthermore, biological activity (anti-Xa activity) profile is similar to pharmacokinetics profile.

Distribution of ³⁵S-enoxaparin After I.V. and S.C.
Administration of the Drug to Rats
(Report # 963/1B)

Methods: Male rats were given a single dose of ³⁵S-enoxaparin (0.85 mg/kg) or ³⁵S-heparin (equivalent to enoxaparin anti-Xa activity) by i.v. and s.c. route. At 5 minutes, 1, 2, 24, 72 and 168 hours after the drug administration, one rat/dose group was sacrificed and 6 sagittal sections (about 25 mcm) were obtained and auto-radiographed. Three rats/dose group/time point were sacrificed at the above mentioned time intervals and various organs were collected and radioactivity was measured by LSC.

Additionally, rats were also given ³⁵S-enoxaparin (0.85 mg/kg, i.v.) for 7 consecutive days. Three rats/time point were sacrificed at 24 hours after the 1st, 3rd, 5th, and 7th dose and on 3, 7, 14 and 28 days after the last dose (7th dose).

Results: The pattern of distribution of radioactivity was similar whether the drug was given as single s.c., i.v. or multiple i.v. doses of ³⁵S-enoxaparin (Table IV: Sponsor's table 7.1, volume 2.8, pages 53 and 54; Table V: Sponsor's table 7.11, volume 2.8, pages 64 and 65; Table VI: Sponsor's table 7.21, volume 2.8, pages 75 and 76). The radioactivity distribution was rapid and wide spread. Kidney, liver and cartilage (aorta and trachea) had high levels of radioactivity and very low amounts of radioactivity was found in CNS. Clearance of radioactivity from the systemic circulation was rapid (blood conc. of radioactivity was below detection limit by 72 hours) but clearance from tissues were prolonged (moderate level of radioactivity was seen even 28 days after dosing). In multiple dose study (7 daily doses), radioactivity in all tissue accumulated and the levels were 3-5 fold greater than the initial values. However, the anti-Xa activity after 7 daily doses were comparable to what was found after single dose (see above). Therefore, one can conclude that radioactivity remaining in tissues is inactive drug and/or its metabolite(s). ³⁵S-Heparin gave similar results.

TABLE^a IV

Mean concentrations of radioactivity in tissues following a single subcutaneous administration of (³⁵S)-enoxaparin to male rats at a nominal dose level of 0.85 mg/kg body weight.

Tissue	µg equivalents of (³⁵ S)-enoxaparin /g				
	5 min	30 min	1 h	2 h	4 h
Adrenals	0.134	0.363	0.452	0.732	0.424
Aorta	0.650	4.041	3.361	1.339	0.799
Bladder	0.325	2.661	3.053	4.723	1.036
Blood	0.397	0.727	0.577	0.261	0.217
Brain	0.004	0.013	0.017	0.017	0.012
Caecum	0.082	0.497	0.556	0.783	0.781
Fat	0.063	0.176	0.218	0.922	0.142
Heart	0.116	0.333	0.423	0.380	0.330
Kidney	0.763	2.742	2.480	2.517	2.052
Large Intestine	0.097	0.334	0.495	0.828	0.650
Liver	0.123	0.492	0.937	1.305	1.587
Lungs	0.149	0.394	0.439	0.462	0.394
Mesenteric Lymph Nodes	0.113	0.449	0.679	0.937	0.765
Muscle	0.031	0.144	0.176	0.187	0.170
Pancreas	0.114	0.461	0.599	0.817	0.773
Pituitary	0.138	0.319	0.653	0.294	0.897
Plasma	0.591	1.117	0.892	0.393	0.299
Prostate Gland	0.106	1.731	2.398	0.921	0.510
Skin	0.056	0.343	0.466	0.498	0.432
Small Intestine	0.097	0.293	0.564	0.876	0.917
Spleen	0.091	0.314	0.416	0.489	0.472
Stomach	0.087	0.330	0.524	0.544	0.521
Testes	0.006	0.140	0.161	0.233	0.237
Thymus	0.049	0.190	0.206	0.235	0.189
Thyroid	0.444	1.231	1.882	1.554	1.339
Trachea	0.229	0.795	0.697	1.032	0.712
Vena Cava	0.195	0.388	0.408	1.270	0.483

a = Sponsor's table 7.1, Volume 2.9, Page 53

TABLE^a IV Cont.

Mean concentrations of radioactivity in tissues following a single subcutaneous administration of (³⁵S)-enoxaparin to male rats at a nominal dose level of 0.85 mg/kg body weight.

Tissue	µg equivalents of (³⁵ S)-enoxaparin /g			
	8 h	24 h	72 h	168 h
Adrenals	0.414	0.253	0.176	0.135
Aorta	0.555	0.353	0.254	0.122
Bladder	0.924	0.542	0.267	0.208
Blood	0.193	0.050	ND	ND
Brain	0.026	0.009	0.009	ND
Caecum	0.948	0.735	0.283	0.197
Fat	0.129	0.022	0.041	0.031
Heart	0.276	0.171	0.133	0.082
Kidney	2.133	1.719	1.225	0.624
Large Intestine	0.760	0.607	0.248	0.152
Liver	1.392	0.862	0.575	0.349
Lungs	0.389	0.246	0.155	0.112
Mesenteric Lymph Nodes	0.707	0.278	0.355	0.165
Muscle	0.129	0.079	0.055	0.034
Pancreas	0.600	0.431	0.280	0.200
Pituitary	0.424	0.249	0.180	ND
Plasma	0.253	0.069	0.015	ND
Prostate Gland	0.462	0.191	0.115	0.083
Skin	0.398	0.246	0.180	0.115
Small Intestine	0.918	0.605	0.266	0.191
Spleen	0.470	0.560	0.210	0.205
Stomach	0.485	0.420	0.220	0.174
Testes	0.207	0.134	0.078	0.049
Thymus	0.205	0.109	0.079	0.052
Thyroid	0.983	1.338	0.698	0.281
Trachea	0.913	0.677	0.532	0.380
Vena Cava	0.410	0.346	0.206	0.116

ND = Not Detected

a = Sponsor's table 7.1, Volume 2.9, Page 54

TABLE^a v

Mean concentration of radioactivity in the tissues following a single intravenous administration of (³⁵S)-enoxaparin to male rats at a nominal dose level of 0.85 mg/kg body weight.

Tissue	µg equivalents of (³⁵ S)-enoxaparin /g				
	5 min	30 min	1 h	2 h	4 h
Adrenals	1.747	0.776	0.484	0.425	0.382
Aorta	4.537	1.794	0.753	0.712	0.628
Bladder	16.42	2.697	2.985	1.758	0.935
Blood	3.054	0.849	0.250	0.151	0.132
Brain	0.282	0.025	0.008	0.009	0.014
Caecum	1.191	0.914	0.979	0.741	0.825
Fat	0.594	0.269	0.347	0.173	0.144
Heart	1.124	0.462	0.369	0.319	0.285
Kidney	9.753	4.083	2.895	2.544	2.649
Large Intestine	1.169	0.664	0.598	0.637	0.479
Liver	1.018	1.129	1.219	1.242	1.108
Lungs	1.324	0.622	0.460	0.406	0.366
Mesenteric Lymph Nodes	1.659	1.243	0.942	1.002	1.374
Muscle	0.412	0.249	0.214	0.172	0.152
Pancreas	1.126	0.820	0.896	0.702	0.662
Pituitary	1.207	0.676	1.586	1.235	1.029
Plasma	5.235	1.325	0.385	0.224	0.170
Prostate Glands	2.389	0.818	1.090	0.409	0.365
Skin	0.845	0.707	0.667	0.521	0.417
Small Intestine	1.232	0.785	0.984	0.950	0.790
Spleen	0.868	0.661	0.642	0.574	0.490
Stomach	1.069	0.597	0.618	0.465	0.478
Testes	0.258	0.193	0.221	0.203	0.198
Thymus	0.554	0.282	0.241	0.205	0.201
Thyroid	3.126	1.120	2.597	2.126	1.014
Trachea	1.905	0.940	1.065	0.724	0.898
Vena Cava	2.814	0.596	0.600	0.538	0.428

a = Sponsor's table 7.11, Volume 2.9, Page 64

TABLE^a V Cont.

Mean concentration of radioactivity in the tissues following a single intravenous administration of (³⁵S)-enoxaparin to male rats at a nominal dose level of 0.85 mg/kg body weight.

Tissue	µg equivalents of (³⁵ S)-enoxaparin /g			
	8 h	24 h	72 h	168 h
Adrenals	0.314	0.214	0.139	0.090
Aorta	0.311	0.282	0.250	0.089
Bladder	0.592	0.400	0.239	0.178
Blood	0.125	0.033	ND	ND
Brain	0.017	ND	0.025	0.003
Caecum	0.547	0.509	0.278	0.186
Fat	0.095	0.059	0.017	0.007
Heart	0.197	0.170	0.144	0.071
Kidney	2.760	2.413	1.990	0.785
Large Intestine	0.631	0.325	0.213	0.129
Liver	0.966	0.686	0.456	0.293
Lungs	0.323	0.231	0.151	0.100
Mesenteric Lymph Nodes	0.574	0.525	0.341	0.181
Muscle	0.124	0.080	0.055	0.030
Pancreas	0.486	0.391	0.266	0.160
Pituitary	0.268	0.159	0.071	ND
Plasma	0.174	0.037	0.009	ND
Prostate Glands	0.407	0.108	0.096	0.061
Skin	0.378	0.251	0.180	0.115
Small Intestine	0.747	0.362	0.253	0.177
Spleen	0.449	0.335	0.256	0.160
Stomach	3.491	0.370	0.201	0.150
Testes	0.171	0.639	0.066	0.044
Thymus	0.187	0.091	0.085	0.050
Thyroid	0.768	0.495	0.473	0.240
Trachea	0.478	0.532	0.387	0.285
Vena Cava	0.248	0.190	0.143	0.103

ND = Not Detected

a = Sponsor's table 7.11, Volume 2.9, Page 65

TABLE^a VI

Mean concentrations of radioactivity in tissues following multiple intravenous administrations of (³⁵S)-enoxaparin to male rats at a nominal dose level of 0.85 mg/kg body weight.

Tissue	µg equivalents of (³⁵ S)-enoxaparin /g			
	24 h pd 1	24 h pd 3	24 h pd 5	24 h pd 7
Adrenals	0.206	0.452	0.804	1.035
Aorta	0.200	0.506	0.733	1.069
Bladder	0.452	0.725	1.466	1.895
Blood	0.036	0.041	0.052	0.053
Brain	0.007	0.025	0.043	0.052
Caecum	0.584	1.050	2.182	2.267
Fat	0.054	0.130	0.158	0.208
Heart	0.145	0.356	0.549	0.644
Kidney	2.474	6.737	10.33	12.49
Large Intestine	0.389	1.013	1.107	1.586
Liver	0.698	1.773	2.782	3.005
Lungs	0.197	0.539	0.906	1.024
Mesenteric Lymph Nodes	0.395	0.841	1.026	1.899
Muscle	0.071	0.178	0.247	0.364
Pancreas	0.390	0.806	1.208	1.825
Pituitary	0.256	0.341	0.861	1.025
Plasma	0.032	0.057	0.056	0.061
Prostate Gland	0.237	0.501	0.506	0.686
Skin	0.252	0.575	0.943	1.218
Small Intestine	0.477	1.004	1.812	1.735
Spleen	0.375	0.865	1.520	1.573
Stomach	0.354	0.722	1.049	1.428
Testes	0.088	0.224	0.351	0.448
Thymus	0.107	0.306	0.503	0.482
Thyroid	0.631	1.494	2.303	1.629
Trachea	0.555	1.076	2.208	2.253
Vena Cava	0.233	0.332	0.908	1.029

a = Sponsor's table 7.21, Volume 2.9, Page 75

TABLE^a VI Cont.

Mean concentrations of radioactivity in tissues following multiple intravenous administrations of (³⁵S)-enoxaparin to male rats at a nominal dose level of 0.85 mg/kg body weight.

Tissue	µg equivalents of (³⁵ S)-enoxaparin /g			
	3 days pd 7	7 days pd 7	14 days pd 7	28 days pd 7
Adrenals	0.732	0.642	0.394	0.204
Aorta	1.136	0.663	0.503	0.358
Bladder	1.234	1.107	0.771	0.529
Blood	0.034	0.015	ND	ND
Brain	0.051	0.136	0.040	0.029
Caecum	2.033	1.369	0.907	0.536
Fat	0.194	0.089	0.051	0.020
Heart	0.677	0.394	0.284	0.191
Kidney	9.236	5.869	2.750	0.751
Large Intestine	1.281	0.829	0.532	0.155
Liver	2.620	1.920	0.962	0.510
Lungs	0.943	0.569	0.555	0.244
Mesenteric Lymph Nodes	1.480	0.616	0.719	0.445
Muscle	0.338	0.176	0.144	0.081
Pancreas	1.427	1.191	0.584	0.352
Pituitary	0.889	1.147	0.530	0.379
Plasma	0.040	0.018	0.005	ND
Prostate Gland	0.527	0.684	0.216	0.137
Skin	0.972	0.689	0.351	0.203
Small Intestine	1.764	1.217	1.033	0.475
Spleen	1.456	1.533	0.812	0.642
Stomach	1.444	0.802	0.667	0.303
Testes	0.386	0.287	0.226	0.157
Thymus	0.542	0.295	0.290	0.154
Thyroid	2.604	1.581	1.582	0.817
Trachea	2.199	1.644	1.300	0.802
Vena Cava	0.671	0.494	0.418	0.966

ND = Not Detected

a = Sponsor's table

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Furthermore, the nature of the radioactivity in rat plasma, urine, feces, bile, kidney and liver were also characterized by HPLC and protamine sulphate-sepharose chromatography. Early time point, samples of plasma, urine and bile mainly contained radioactivity species similar to ³⁵S-enoxaparin, but desulphated, while later-time point samples contained mainly lower molecular weight species (also desulphated). Both early and late time point samples of kidney and liver contained mainly radioactive species similar to ³⁵S-enoxaparin but desulphated. The above phenomena was independent of dose or frequency of dosing. Therefore, ³⁵S-enoxaparin metabolized by desulphation and/or depolymerization to lower molecular weight species, and the desulphated enoxaparin is probably biologically less potent than the parent drug. It can also be said that the drug is initially excreted as intact compound but later as the lower molecular weight species.

TABLE VII
Quantitative Assessment of the Distribution of Radioactivity in Various Extract Following the Administration of 0.85 mg/kg of ³⁵S-enoxaparin to Male Rats

<u>Sample Time</u>	<u>Peak</u>	<u>Percent Radioactivity Detected</u>		
		<u>Single s.c. dose</u>	<u>Single i.v. dose</u>	<u>7 daily i.v. dose</u>
<u>Plasma</u>				
6 min.	A	70	71	69
	B+C	30	29	31
8 hr.	A	16	25	18
	B+C	84	75	82
<u>Urine</u>				
0-12 hr.	A	76	83	76
	B+C	24	17	24
24-48 hr.	A	15	17	23
	B+C	85	83	77
<u>Bile</u>				
0-4 hr.	A	65	ND	
	B+C	35	100	
8-24 hr.	A	ND	ND	
	B+C	100	100	

Peak A = Desulphated enoxaparin
Peak B+C = Low molecular weight species of desulphated enoxaparin
ND = not detected

Pharmacokinetics of ³⁵S-enoxaparin in Dogs
(Report # 100463)

Methods: Beagle dogs (n=2-3/dose group) were given ³⁵S-enoxaparin intravenously (1 mg/kg) or subcutaneously (0.7 mg/kg). Blood samples were drawn at 5, 10, 15, 20, 30, 45 minutes and 1, 1.5, 2, 3 and 4.5 hours after the i.v. administration of the drug and 15, 30, minutes, 1.5, 2, 3, 4, 6, 7, 24 and 48 hours after the s.c. administration of the drug from jugular vein for measuring plasma anti-Xa activity (using specific chromogenic substrate) as well as radioactivity. Urine and feces samples were also collected up to

96 hours (intervals not clearly identified) from 2 dogs which received i.v. dose and from 3 dogs which received s.c. dose. Two dogs were sacrificed, one at 1 hour and the other at 6 hours after s.c. administration of the drug. Blood, bile, urine, cerebrospinal fluid and various organs were collected and radioactivity was measured by LSC.

Results: After i.v. administration, the plasma anti-Xa activity decreases in a monophasic manner, while decline in radioactivity is triphasic. It should be noted here that biological activity disappeared from the plasma faster than the radioactivity, and the apparent volume of distribution was greater for radioactivity than for biological activity. Thus the biological activity appears to be limited to the plasma volume whereas volume of distribution as measured by radioactivity reflects a distribution of radioactivity in the extravascular compartments.

Pharmacokinetics of ³⁵S-enoxaparin in Dogs (n=2) After I.V. Dose

<u>Parameters</u>	<u>Anti-Xa Activity</u>	<u>Radioactivity</u>
T _{1/2} (hr)	1.48	alpha = 0.05 beta = 0.38 Term = 3.58
VD _{apparent} (L/kg)	0.083	0.45
CL _{plasma} (L/hr)	0.578	1.3115

After s.c. administration, the plasma anti-Xa activity and radioactivity both declined in biphasic manner. The C_{max} for anti-Xa activity was almost double than that for radioactivity, and the t_{1/2} alpha and t_{1/2} beta for anti-Xa activity as well as radioactivity were comparable. According to sponsor, the ratio of area under s.c. and i.v. curves (corrected for dose administered) is greater than one. Hence, enoxaparin is completely bioavailable via s.c. route.

Pharmacokinetics of ³⁵S-enoxaparin in Dogs (n=3) After s.c. Dose

<u>Parameters</u>	<u>Anti-Xa Activity</u>	<u>Radioactivity</u>
C _{max} (mcg/ml)	3.28	1.45
T _{max} (hr)	2.5	1.67
T _{1/2} alpha (hr)	2.57	3.0
T _{1/2} beta (hr)	20.35	17.67
VD apparent (L/kg)	0.41	1.18
CL plasma (L/hr)	0.286	0.65

Distribution of ³⁵S-enoxaparin After s.c. Administration
of the Drug to Dogs (n=1)

<u>Organs</u>	<u>Radioactivity (mcg/g or ml)</u>	
	<u>1 hr</u>	<u>6 hr</u>
Plasma	2.23	0.73
Blood	1.17	0.49
Bile	-	0.38
Urine	75.6	150.20
CSF	0.023	0.032
Liver	4.80	8.84
Kidney	5.19	3.20
Adrenals	1.30	2.57
Spleen	1.05	1.57
G.I. Tract	0.97	1.15
Lungs	0.97	0.87
Blood Vessels	0.73	0.60
Heart	0.55	0.54
Brain	0.04	0.07

The highest concentrations of radioactivity were measured in liver, kidneys, adrenals, spleen, G.I. tract and low concentrations were found in lungs, heart, and blood vessels. The low concentrations in the blood relative to plasma indicate that there is no intraerythrocytic accumulation of the radioactivity. Substantial amounts of radioactivity in the urine indicates elimination of the labelled product by renal route, while bile excretion was negligible.

Excretion: Irrespective of the route of administration, about 56-68% of the administered radioactivity was excreted in the urine in 96 hours, and fecal elimination amounted to less than 5%. About 45% of the administered radioactivity was excreted in the 1st 24 hours in the urine.

Metabolism: About 38-60% of urinary radioactivity (0-24 hr) after i.v. dose represented unchanged drug or biologically active drug (ie having anti-Xa activity), while 34-40% of urinary radioactivity (0-24 hr) after s.c. dose represented biologically active drug.

The above ADME study in dogs after i.v. administration of the drug (1mg/kg) was repeated with the following exceptions:

(1) Blood samples were collected up to 24 hours after 1mg/kg dose and up to 48 hours after 3 mg/kg dose administration.

(2) Anti-IIa activities (via chromogenic substrate) in the plasma samples were also monitored.

(3) Only one dog was given 1 mg/kg i.v. dose, and two dogs received higher dosage (3 mg/kg).

The data indicated that at 6 hours after 1 mg/kg of enoxaparin administration, no anti-IIa activity was evident. In contrast anti-Xa activity and radioactivity were found until 24 hour after the drug administration. Plasma anti-Xa activity was greater than the plasma radioactivity expressed in ³⁵S-enoxaparin equivalents. Following pharmacokinetics parameters were obtained.

Pharmacokinetics Parameters of ³⁵S-enoxaparin in Dog (n=1)
After I.V. Administration of 1 mg/kg

Parameters	Anti-Xa Activity	Anti-IIa Activity	Radioactivity ³⁵ S-enoxaparin
T1/2 ((hr) alpha	1.21	0.37	0.12
beta			0.86
term	7.04	1.10	13.40
VD _{apparent} (L/kg)	0.28	0.12	1.08
Cl _{plasma} (L/hr)	0.468	1.34	0.922
AUC (mcg/ml/hr)	33.20	11.6	14.4

When the dogs were given 3 mg/kg of ³⁵S-enoxaparin, then t_{1/2} for anti-IIa activity (19.9 hr) was much greater than what was obtained when lower dose level was administered (1.1 hr) and VD was increased (0.12 L/kg at 1 mg/kg VS 1.24 L/kg at 3 mg/kg) and plasma clearance was decreased (1.34 L/hr at 1 mg/kg VS 0.613 L/hr at 3 mg/kg). Additionally, AUC value indicated that at higher dose anti-Xa activity was increased proportionally while there were increases in anti-IIa activity and radioactivity but increases were not proportional to dose.

Pharmacokinetic Parameters of ³⁵S-enoxaparin in Dogs (n=2)
After I.V. Administration of 3 mg/kg

Parameters	Anti-Xa Activity	Anti-IIa Activity	Radioactivity ³⁵ S-enoxaparin
T1/2 (hr) alpha	1.12	0.75	0.16
beta			0.95
Term	8.11	19.90	7.88
VD _{apparent} (L/kg)	0.29	1.24	1.25
CL _{plasma} (L/hr)	0.36	0.63	1.57
AUC (mcg/ml/hr)	101.4	52.2	24.6

Multidose Pharmacokinetics Study in Dogs (n=2)

Methods: In this study two dogs were given s.c. doses of 1 mg/kg/day of ³⁵S-enoxaparin for 7 consecutive days. Blood samples were collected at 30 minutes, 1, 2, 3, 4, 5, 6, 7, 8, and 24 hours after the drug administration on day 1 and on day 7 of the study. Radioactivity and anti-Xa activity were measured in each sample.

Results: The Cmax of radioactivity on day 7 was about 2 times the Cmax on day 1, and the Cmax of anti-Xa activity on day 7 was about 1.4 times the Cmax on day 1. Additionally, the concentrations measured by anti-Xa activity was at least 2 times greater than the levels expressed in ³⁵S-enoxaparin equivalent. The kinetic curves were parallel and no parameters were calculated. No evidence of a significant accumulation (may be slight) of the drug was seen after 7 daily s.c. doses, since 24 hour after drug administration on day 1 and day 7 the concentrations of the drug were comparable.

Plasma Concentration (mcg/ml)

<u>Parameters</u>	<u>Radioactivity</u>		<u>Anti-Xa Activity</u>	
	<u>Day 1</u>	<u>Day 7</u>	<u>Day 1</u>	<u>Day 7</u>
C _{max}	1.75	3.18	4.8	6.7
C _{24hr} (after dosing)	0.11	0.14	0.35	0.6

Plasma Protein Binding: In dogs, after i.v. administration of ³⁵S-labelled drug, about 24% of the radioactivity was bound to plasma protein (mainly to antithrombin III) while 76% was unbound. The bound and unbound fractions were separated by HPLC and their biological anti-Xa activities were measured. The bound enoxaparin inhibited factor-Xa activity and the free form had no anti-Xa activity.

Excretion: Urinary and fecal excretion of radioactivity was also studied after administration of 3 mg/kg i.v. dose. The results were similar to that obtained after 1 mg/kg i.v. dose (see page 27).

Subcutaneous Pharmacokinetics of Enoxaparin in Primates
(Report # 19)

Methods: In this report biological activities (antithrombotic, anti-coagulant and fibrinolytic activity) were assessed in monkeys (n=5/dose group) after single s.c. dose of enoxaparin (50, 100 or 200 anti-Xa unit/kg). Blood samples were drawn prior to and at 1, 3, 6, 12, 18 and 24 hours after the drug administration. Platelet counts, bleeding time, coagulation parameters (PT, PTT and TT) and fibrinopeptide A levels were measured at the above mentioned time intervals. Anti-IIa and anti-Xa activities were also monitored. Anti-IIa and anti-Xa activities were measured by amidolytic assays and radioimmunoassay was used to measure fibrinopeptide A levels.

Results: In monkeys, a dose as high as 200 anti-Xa U/kg of enoxaparin had no significant effect on platelet count up to 24 hours (last sampling time point). Prothrombin time was not affected at any time (up to 24 hr). This indicates that s.c. administration of enoxaparin had no effect on extrinsic pathway. Furthermore, PT time is of limited value in assessing the action of enoxaparin because in this assay thrombin is generated by activation of factor VIIa which is largely resistant to inhibitory action of AT-III-heparin fraction complex. Significant prolongation of TT (which return to normal by 18 hour) were seen at mid and high dose, which indicated that anti-IIa fragments were also absorbed during treatment. The drug also increased the anti-IIa activity in circulating blood significantly, however this increase in anti-IIa action was not able to produce any profound effect on PT or PTT. A dose dependent anti-Xa activity was seen in monkeys, and at 100 u/kg the anti-Xa activity lasted up to 18 hours, while at 200 u/kg, marked inhibition was seen at 1 hour after the drug administration and even post 24 hour residual inhibition was seen in circulating blood. Fibrinopeptide A generation test assesses the collective anti-Xa and anti-IIa action of enoxaparin. This test is more sensitive than amidolytic anti-Xa and IIa test. The data indicated

that enoxaparin inhibited fibrinopeptide A generation and the inhibition lasted up to 18 hours after the drug administration.

Effect of S.C. Administration of Enoxaparin to Monkeys (n=5)

Parameters	Time (hour)	Dose (anti-Xa unit/kg)		
		50	100	200
Thrombin Time (Sec)	0	24.2±1.5	24.8± 0.9	24.7±0.7
	1	27.2±3.7	40.7±13.2	--
	3	29.2±3.6	78.1±13.4	90.0±8.3
	6	28.3±3.7	37.0± 4.7	56.3±4.7
	12	27.9±2.8	32.7± 6.2	37.8±2.4
	18	24.0±2.0	30.7± 5.6	27.1±2.3
	24	23.0±0.9	26.1± 1.9	24.2±2.2
	IIa Inhibition (%)	0	0.6±1.3	0±0
1		23±9	22±6	24±9
3		23±12	28±6	37±7
6		22±7	18±10	40±20
12		4±5	4±6	10±8
18		4±5	3±4	15±7
24		2±3	0±0	9±10
X ₂ Inhibition (%)		0	0±0	1±3
	1	32±10	67±13	79±5
	3	36±4	79±5	83±5
	6	30±4	68±5	81±3
	12	12±4	20±4	65±4
	18	4±1	14±4	37±4
	24	4±4	10±9	17±5
	Fibrinopeptide A Generation (ng/ml)	0	>40	>40
1		17±5	10±7	10±3
3		5±1	13±6	9±4
6		11±3	20±9	8±5
12		>40	27±11	8±4
18		>40	--	7±4
24		>40	>40	>40

Thus the drug is absorbed rapidly and completely in both rats and dogs following s.c. administration of ³⁵S-enoxaparin. In rats, plasma mean maximum anti-Xa activity over the tested s.c. or i.v. dose range increased linearly with dose. Due to a secondary rise in plasma anti-Xa activity as well as in whole blood radioactivity it was difficult to assess the t_{1/2} values. Variable sampling time durations were used for different doses to estimate t_{1/2} values. Half-lives for anti-Xa activity after single s.c. dose ranged from 0.837-2.149 hour (human = 5.11±/- 2.25 hr) and 0.330-0.679 hour (human = 4.04±/- 2.46 hr) after single i.v. dose. After 7 daily i.v. doses of enoxaparin (0.85 mg/kg), plasma anti-Xa activity did not accumulate significantly and the kinetics were similar to that obtained after a single i.v. dose of 0.85 mg/kg of enoxaparin. The pharmacokinetics of radioactivity after single s.c., single i.v., or 7 daily i.v. doses of ³⁵S-enoxaparin were linear with tested doses and independent of route of administration. Furthermore, biological activity (anti-Xa activity) profile is similar to pharmacokinetic profile. In dogs, after s.c. administration, the plasma anti-Xa activity and radioactivity both

declined in biphasic manner. The C_{max} for anti-Xa activity was almost double than that for radioactivity, and the t_{1/2} alpha (2.57-3.0 hr) and t_{1/2} beta (17.67-20.35 hr) for anti-Xa activity as well as radioactivity were comparable. In rats and dogs after s.c. administration of the drug, radioactivity was distributed through out the body, with highest concentrations seen in liver and kidney. The drug is metabolized by desulphation &/or depolymerization to lower molecular weight species. Irrespective of the route of administration, in both species (rats and dogs), enoxaparin was mainly excreted in the urine (56-72%) and only less than 5% in the feces (biliary excretion ~ about 2%), and major portion of the administered radioactivity was excreted during the first 24 hours after drug administration. In dogs, about 38-60% of urinary radioactivity (0-24 hr) after i.v. dose represented unchanged drug or biologically active drug (ie having anti-Xa activity), while 34-40% of urinary radioactivity (0-24 hr) after s.c. dose represented biologically active drug.

Biological activities (antithrombotic, anti-coagulant and fibrinolytic activity) of enoxaparin were also assessed in monkeys. A dose as high as 200 anti-Xa U/kg of enoxaparin had no significant effect on platelet count and prothrombin time. Significant prolongation of TT (which return to normal by 18 hour), increase in anti-IIa activity and a dose dependent increase in anti-Xa activity were seen in treated monkeys. Enoxaparin also significantly inhibited fibrinopeptide A generation (assess the collective anti-Xa and anti-IIa activities) in treated monkeys.

TOXICOLOGY:

In the initial IND 31,532, sponsor submitted the following studies: (1) Acute toxicity studies in mice, rats and dogs, (2) 14-day s.c. dose range finding study in rats, (3) 13-Week and 6-month s.c. toxicity studies in rats, (4) 26-Week i.v. toxicity study in rats, (5) 13-Week s.c. toxicity study in dogs, (6) 26-Week s.c and i.v. toxicity studies in monkeys, (7) Segment I. s.c. fertility and general reproductive performance study in rats, (8) Segment II. s.c. and i.v. teratology studies in rats and rabbits, (9) Segment III. s.c. perinatal and postnatal study in rats, (10) Genotoxicity studies: Ames tests, double locus cell mutation assay, clastogenic activity in cultured human lymphocytes and chromosomal aberration test in rat's bone marrow, and (11) Special toxicity studies: local tolerance study in dogs, sensitization test in guinea pigs, and hemolytic and precipitating test (in vitro). All the above mentioned studies were reviewed by Dr. Sun on september 20, 1989. No additional toxicity studies are submitted in the present NDA. Dr. Sun's review of the above studies is reproduced bellow:

Acute Toxicity:

Testing laboratory:

Date of the study: Nov. 1983 to Jan. 1984

GLP requirement: A statement of compliance with GLP regulations was included.

Drug Batch No.: 812 (Potency: 57 IU/mg).

Acute toxicity of either s.c. or i.v. administration was tested in mice, rats and dogs. Observation period was 14 days. The results are summarized below.

<u>Species/ Strain</u>	<u>Route of adminis- tion</u>	<u>No/dose level/ sex</u>	<u>Dose range (mg/kg)</u>	<u>LD50</u>	<u>Time to death</u>	<u>Highest non-lethal dose</u>	<u>Toxic signs</u>
Mice/NMRI	s.c.	5	1470-21500	6700(M) 8100(F)	1-7days	2150	(1)
Mice/NMRI	i.v.	5	681-3830	2340	5 min.- 1 day	1470	(2)
Rats/S.D.	s.c.	5	14.7-6810	>46.4	6 hrs.- 2 days	14.7	(3)
Rats/S.D.	i.v.	5	215-2610	1660(M) 1810(F)	5 min.	1210	(4)
Rats/S.D.	6 hr.i.v. infusion	5	1000-21500	1000- 10000	6 hrs.- 2 days	1000	(5)
Dogs/ Beagle	i.v.	1M	1000-2150	>2150*		>2150*	(6)

*: no death occurred.

(1) body weight loss, decreases in food consumption and motility, muscular hypotonia, piloerection, pale eyes, ataxia, ptosis, cyanosis, coma, abdominal posing, bleeding and death.

(2) ataxia, decreases in food consumption, motility and body weight, dyspnea, mydriasis, pale liver and kidney, and death.

(3) hemorrhage, ataxia, dyspnea, pale eyes, muscular hypotonia, decreased motility and body weight, abdominal posing, pale liver and kidney, coma, GI tract filled with brownish masses, and death.

(4) ataxia, dyspnea, convulsion, lateral position, miosis, exophthalmus and death.

(5) decreased food consumption and motility, dyspnea, cyanosis, hypothermia, coma, posing, hemorrhage, pale liver and kidney, dark lung and death.

(6) agitation, posing, salivation, hyperventilation. No death occurred.

Comment of this Reviewer:

The signs of acute toxicity were similar in mice and rats. As a function of increasing dose, enoxaparin produced ataxia, decreased motility, dyspnea, cynosis and coma. Death frequently was preceded by convulsions. In dogs no mortality was seen at doses up to 2150 mg/kg. At the highest tested dose, enoxaparin produced mydriasis, increased salivation, transient loss of pupillary reflex, hyperventilation and tachycardia.

SUBACUTE AND CHRONIC TOXICITY:

14-day S.C. Dose Range Finding Study in Rats

Testing Laboratory:

GLP requirement: Quality assurance authentication was enclosed.

Date of the study: 9/8/81 to 10/5/81

Animals: Charles River Wistar rats weighing 100g and 5 weeks of age were used.

Methods: Three groups of animals each consisting of 5 males and 5 females were given enoxaparin (Batch No. 573, Potency: not specified) in physiological saline at dose levels of 0, 3 and 20 mg/kg/day.s.c. for 14 days. Observation period was 14 days. No histopathological examinations, blood chemistry, urinalysis and hematology were conducted or monitored.

Results: Appearance of swelling at the injection sites were observed. No changes in organ weights, body weights and food consumption were seen. Presence of an inflammatory reaction at the injection sites (females) and subcutaneous hematoma (all animals) were observed.

13-week S.C. Toxicity Study in Rats

Testing Laboratory:

Date of the study: 11/3/81-1/13/82

GLP requirement: A statement of compliance with GLP regulations was included.

Animals: Wistar rats weighing 80-100g and 4-5 weeks of age were used.

Methods: Four groups of animals each consisting of 25 males and 25 females were given enoxaparin (Batch No. 573, Potency: 52 IU/mg) in constant volume (2ml/kg) at dose levels of 0 (0.9% NaCl), 3.0, 6.5, or 15 mg/kg/day s.c. in the cervical interscapular region for 13 weeks. Blood samples were taken from and histopathological examinations were performed only in the control and the 15 mg/kg/day groups.

Results:

Mortality: There were three deaths in the animal receiving 15 mg/kg/day during the study. Two rats were found dead during week 2. No obvious cause of death was identified based on the necropsy. The third rat died at sampling during week 13.

Clinical signs: Hematoma was seen at the injection site of all drug-dosed groups. The time of appearance of these hematoma was related to the dose level received (3-6 weeks). Injection sites needed to be dispersed during the study in order to ensure continuity of dosing after week 1 in animals receiving 15mg/kg/day of the compound.

Body weight: Statistical increase (12%) in body weight was observed in the males receiving 6.5 mg/kg/day of the compound. In females, statistically significant increase in body weights were seen in both 6.5 (17%) and 15mg/kg/day (11%) groups.

Food and water consumptions: Normal.

Hematology: Decrease in Hb (9%), RBC (11%), PCV (11%) and increase in WBC (32%) were seen in the 15 mg/kg/day group.

Blood chemistry: Decrease (33%) in AP was observed in the females receiving 15 mg/kg/day in week 13.

Urinalysis: Normal.

Gross pathology: Hemorrhage and hematomas formations at and around the injection sites in animals receiving enoxaparin were seen.

Organ weight: In males, decrease in testes (8%) and brain (7%), was seen in the 6.5 mg/kg/day group. Increase in spleen (49%) was observed in the 15 mg/kg/day group. In females, adrenals were decreased (9%) in the 3 mg/kg/day group. Kidneys weights were increased in all drug-treated groups (5-6%). Heart (8%) and spleen (31%) were increased in the 15 mg/kg/day group. Liver weights were increased (14-22%) in the 6.5 and 15 mg/kg/day groups.

Histopathology: Increased extramedullary hemopoiesis in the spleen and liver and increase white pulp in the spleen were observed in the 15 mg/kg/day group. No histopathological examinations were performed in the 3 and 6.5 mg/kg/day groups.

In conclusion, blood chemistry, hematology and histopathology were performed in the control and 15 mg/kg/day groups. Lethal dose was 15 mg/kg/day. Hemorrhage and hematoma were present in all drug-treated groups. Hematological parameters were typical of animals undergoing compensation for loss of blood in that polychromasia and anisocytosis were increased while hemoglobin concentration, RBC and PCV were decreased in the 15 mg/kg/day. Histologically, increased hemopoiesis in liver and spleen, and increased white splenic pulp and splenic activity were seen in the 15 mg/kg/day group. Since complete toxicological evaluations (blood chemistry, hematology and histopathology) were not conducted in all dose levels, a no effect dose was not established in the study.

Six-Month Subcutaneous Toxicity Study in Rats

Testing Laboratory:

Date of the study: 3/8/84 - 10/14/84

GLP requirement: A statement of compliance with GLP regulation was included.

Animals: Sprague-Dawley rats weighing 134-233g and 43 days of age were used.

Methods: Four groups of rats each consisting of 30 animals per sex were given enoxaparin (Batch No. 3214/01, Potency: 12.25 IU/ml) dissolved in saline at dose levels of 0, 3, 10, 30 mg/kg/day subcutaneously for 6 months. The last 5/sex/group remained on test for a 6-week untreated recovery period. Histopathological evaluations were conducted for all animals in the control and 30 mg/kg/day groups and from animals died or killed during the study.

Results:

Mortality:

	Males	Females
Control	1	0
3mg/kg/day	1	1
10	0	2
30	12	9

Clinical signs: Swelling at the injection sites was observed in 10 and 30 mg/kg/day groups.

Body weight, food consumption and ophthalmoscopy: Normal.

Hematology: Hemoglobin, hematocrit and red blood cell counts of the 30 mg/kg/day animals were lower than the controls. Higher platelet counts were seen in all drug-treated males and the 30 mg/kg/day females. They returned to normal after 6-week recovery period. There were no significant differences between anti-factor Xa of all drug treated groups and that of the controls.

Blood chemistry: Cholesterol levels of all drug-treated males (23-80%) and the 30 mg/kg/day females (43%) were significantly greater than that of the controls at termination and at end of the recovery period.

Urinalysis: Normal.

Organ Weights: Liver and spleen weights were higher in all drug-treated males and the females receiving 10 or 30 mg/kg/day. They were still higher in the 30 mg/kg/day animal after recovery period.

Pathology: Acinar cell atrophy and interstitial fibrosis of the pancreas occurred in animals of both sexes and in both control and 30 mg/kg/day groups; however, more prominent in 30 mg/kg/day. The relationships with the dose of the compound can't be determined since histopathological evaluations were conducted only in control and 30 mg/kg/day groups.

In conclusion, the compound produced mortality at all dose levels including the control group. The cause of death was determined to be secondary to the hemorrhage and bleeding at the injection sites. Lesions

in the pancreas were evident. At dose level of 3 mg/kg/day, elevated cholesterol level, increased liver and spleen weights and deaths were observed although they were reversible after 6-week recovery period. A no effect dose was not established.

26-Week Intravenous Toxicity Study in Rats

Testing Laboratory:

Date of the study: 10/6/83 - 5/10/84

GLP requirement: A statement of compliance with GLP regulations was included.

Animals: Sprague-Dawley rats weighing 57-72g and 5 weeks of age were used.

Methods: Four groups of rats each consisting of 25-30 males or 25-30 females were given enoxaparin (Batch No. 781, Potency: 50 IU/mg) dissolved 0.9% NaCl at dose levels of 0, 10, 30, or 90 mg/kg/day intravenously into the tail vein (1ml/kg) for 26 weeks. Five rats per sex of the 90 mg/kg/day and the control groups were selected for a recovery period of 4 weeks. From the 4th week, 30 or 90 mg/kg/day were decreased to 20 or 40 mg/kg/day because of toxic effects in both groups. Hematology was performed in blood samples collected within 24 hrs after dosing. Complete histopathological examinations were conducted only in both control, 90/40 mg/kg groups and the rats killed during the study.

Results:

Mortality: Deaths occurred in all drug-treated groups.

Dose group	Males	Females
Control	0/30	0/30
10mg/kg/day	0/25	1/25
30/20	1/25	1/25
90/40	7/30	7/30

Deaths occurred between weeks 3 and 11. Cause of death: internal bleeding.

Clinical signs: Hematoma was seen in the 90/40 mg/kg/day group. No death or clinical signs were reported in the recovery groups.

Food and water consumption: Normal.

Body weight: Normal.

Hematology: At 30/20 mg/kg/day dose level, number of erythrocytes (13%) was decreased. At 90/40 mg/kg/day dose level, decreases in hemoglobin (13%), erythrocytes (15%) and hematocrit (7.5%) and increase in reticulocytes (227%) were reported. They returned to normal after 4-week recovery period. At week 13, platelets were increased (23-29%) in both 30/20 and 90/40 mg/kg/day groups.

Clinical chemistry: Increases (20%) in blood urea were observed in serum of females receiving 30/20 or 90/40 mg/kg/day of enoxaparin.

Urinalysis: Lower urine specific gravities were observed in both 30/20 and 90/40 mg/kg/day groups. They returned to normal after 4 week of recovery period.

Ophthalmoscopy: Normal.

Macroscopic examination: At 30/20 and 90/40 mg/kg/day, rats showed adhesion in the regions of liver or kidney. Severe bleeding in the abdominal cavity was seen.

Organ weight: Increased weights were found for spleen, heart, liver and kidney at 30/20 and 90/40 mg/kg/day.

Histopathological examination: At the injection sites, inflammation, hemorrhage and necrosis were found in all drug-treated groups. Thrombosis in liver and adrenal were seen in the animals receiving 90/40 mg/kg/day of enoxaparin. Interstitial nephritis was seen in the 30/20mg/kg/day group. No gross pathological inspection, nor organ weight changes and histological examination revealed any systemic effects in the animals of a 4-week recovery period.

In conclusion, mortalities were found in all drug-treated groups. The cause of death appears to be hemorrhage. Other target organs of toxicity are liver and kidney. A non-effect dose was not established.

13-Week Subcutaneous Toxicity Study in Dogs

Testing Laboratory:

Date of start and completion of the study: 10/15/81 - 1/15/82

GLP requirement: A statement of compliance with GLP regulations was included.

Animals: Beagle dogs weighing 6.9-8.4 kg and 3 1/2-4 1/2 months of age were used.

Methods: Four groups of animals each consisting of 3 males and 3 females were given enoxaparin (batch No. 573, Potency: 52 IU/mg) in physiological saline in constant volume of 0.2 ml/kg at dose levels of 0, 3, 6.5 or 15 mg/kg/day subcutaneously for 13 weeks.

Results:

Clinical signs: There were no mortalities in the study. Dermal thickness and swelling were observed in 6.5 and 15 mg/kg/day groups. Hematoma or bruising formation was evident in 15 mg/kg/day group. Animals of 3 mg/kg/day group observed less than a week of dermal thickening.

Body weight, food consumption and ophthalmoscopy: Normal.

EKG: Shortening of PR interval was seen in the 15 mg/kg/day group.

Hematology: Normal

Blood chemistry: Normal.

Urinalysis: A reduction of calcium concentrations and an increase in phosphate concentration were seen in animals receiving 15 mg/kg/day.

Parathormone levels: Normal.

Organ weight: Normal.

Gross pathology and histopathological finding: Bones were normal. The presence of local hemorrhage in the injection sites were found in all drug-treated groups. Severe inflammation was present in dogs receiving 15 mg/kg/day. Animals receiving 15 mg/kg/day showed hyperplasia in parathyroid. Eosinophilic leukocytosis of cervical lymph nodes appeared in all drug-treated groups.

In conclusion, the major treatment related finding was hemorrhaging at the injection sites. This was observed in animals receiving 15 mg/kg/day. This finding was less obvious at the dose level of 6.5 mg/kg/day. At the dose level of 3 mg/kg/day, only dermal thickening of less than a week was seen. Thus, a no effect dose level was estimated to be 3 mg/kg/day. The study did not reveal the complete toxicity profile of the compound. Higher dose levels should be incorporated to explore any target organs of toxicity.

26-Week Subcutaneous Toxicity in Monkeys

Testing laboratory:

Date of the study: 9/19/83-8/23/84.

GLP requirement: A statement of compliance with GLP regulations was included.

Animals: Cynomolgus monkeys weighing 1.8-2.5 kg and 1 year of age were used.

Methods: Four groups of animals each consisting of 7 males and 7 females were given enoxaparin (Batch No. 3214/01, Potency: 12.25 IU/ml) in 0.9% NaCl at constant volume subcutaneously at dose levels of 0, 3, 10, or 30 mg/kg/day around thigh region for 26 weeks. Dose selection was based on a range-finding study (Project No. 83-2751). Two animals per sex in each dosing group were selected for a 4-week recovery period of drug-free. Complete histopathological examinations were conducted in the control and 30 mg/kg/day groups.

Results:

Mortality: Four males and three females of the 30 mg/kg/day groups died (days 10-172) or killed in extremis (days 119-176) during the study.

Clinical signs: Reddened area on the skin, wounds, hematomas, abrasions, lacerations, lethargy and pale gums were seen in both 10 and 30 mg/kg/day groups. Treated animals exhibited dose-related increases in incidence of edema, redness, bruising, scab formation, swelling and scarring at the injection sites. These observations disappeared by the end of recovery period.

Ophthalmoscopy, body weight, food consumption and EKG: Normal.

Hematology: Reductions in hemoglobin, hematocrit and red blood cell counts were seen in both 10 and 30 mg/kg/day groups.

Clinical chemistry: Normal.

Urinalysis: Normal.

Organ weight: Higher organ weights of the kidney, livers and spleens were seen in the 30 mg/kg/day group. The spleens of the 10 mg/kg/day group were higher than that of the controls. Increased organ weights of kidneys, livers, and spleens were still evident in the 30 mg/kg/day group after 4 week recovery period.

Gross pathology: Lesions at the injection sites were reported in all drug-treated groups.

Histopathology: Microscopic examinations confirmed the lesions at the injection sites.

In conclusion, monkeys received Enoxaparin exhibited lesions at injection sites at all dose levels. Mortality due to excess hemorrhage were reported at 30 mg/kg/day. A no effect dose was not established. However, at 3 mg/kg/day dose level, only hemorrhage at injection sites were seen.

26-Week Intravenous Toxicity Study in Monkeys

Testing laboratory:

Date of the study: Aug. 1, 1983 - Sept. 1984

GLP requirement: A statement of compliance with GLP regulation was included.

Animals: Cynomolgus monkeys 3-5 years of age were used.

Methods: Four groups of animals each consisting of 4-5 monkeys per sex were given Enoxaparin (Batch No. 781, Potency: 50 IU/mg) in 0.9% NaCl at constant volume (1 ml/kg) at dose levels of 0, 5, 10, 20 mg/kg/day i.v. into a leg for 26 weeks. One monkey per sex at the 20 mg/kg/day and control groups was selected for a 4-week recovery period.

Results:

Mortality: One monkey in the 20 mg/kg/day group died.

Clinical signs: Single vomiting was found in one monkey each of 10 and 20 mg/kg groups. Swellings at the injection sites were seen in all drug-treated groups. They were not observed at the end of experiments.

There were no abnormal findings in food and water consumptions, body weight, hematology, clinical chemistry, urinalysis, EKG, blood pressure, and ophthalmoscopy.

Histopathology: There were no drug-related systemic finding in all drug-treated groups.

In conclusion, monkeys given enoxaparin up to 10 mg/kg/day did not exhibit any signs of toxicities except swelling at the injection sites and single vomiting were observed. At 20 mg/kg/day, one animal died preceded by vomiting. However, cause of death could not be determined and was not due to hemorrhaging. Thus, a no effect dose for i.v. administration is 5 mg/kg/day.

SPECIAL STUDIES:

Local Tolerance Studies in Dogs

Testing Laboratory:

Date of the study: 9/12/83 - 10/29/83

GLP requirement: A statement of compliance with GLP regulations was included.

Animals: Beagle dogs (3 males and 3 females) were used.

Methods: 0.6 ml of injection solution each were administered into the muscular system of hind limbs (I.M.), into the vena saphena parva (IV), and beside it (para venous), under the skin of the chest (S.C.) and into the arteria femoralis (i.a.). The local reactions was inspected 2, 24, 48 and 96 hrs after the administration.

Results:

Intraarterial administration: Perivascular hematoma was seen.
Intramuscular administration: Hematoma and inflammatory infiltrate and necrosis were observed.

Intravenous administration: hematoma and inflammatory infiltrates were seen.

Paravenous administration: Hematoma was reported both in drug-treated and control sites.

Subcutaneous administration: Normal.

In conclusion, the subcutaneous route was tolerated without any local reaction.

Sensitization test in Guinea Pigs

Testing Laboratory:

Date of the study: Aug. 11 - Sept. 16, 1983

GLP requirement: A statement of compliance with GLP regulations was included.

Animals: Male Pirbright white guinea pigs weighing 250g and 40 days of age were used.

Methods: Forty guinea pigs were given placebo, enoxaparin or positive control intracutaneously at neck region. Seven days later, the animals were treated topically with 2 ml of the test compound preparation by the patch-test-technique (exposure time: 48 hrs). Two weeks after the topical application, the animals again were challenged and topical

examinations by patch-test-technique in the flank region (exposure time 24 hrs) were performed. Testing compounds were 50% of enoxaparin (Batch No. 812, Potency: 57 IU/mg). Positive controls were penicillin g. 4500 IU/animal and 40000 IU/animal in intracutaneous and epicutaneous injections, respectively.

Results: Penicillin G. caused a positive result in the study. No sensitizing properties of 50% Enoxaparin could be demonstrated.

Hemolytic and Precipitating Properties

Testing Laboratory:

Date of the study: Sept. 1983.

GLP requirement: A statement of compliance with GLP regulation was included.

Methods: Enoxaparin (Batch No. 812, Potency: 57 IU/mg) was dissolved in 0.9% NaCl solution and was mixed with 0.05 ml citrated blood. Eight concentrations (0.0316-100 mg/ml) were examined. The final volume of the preparation amounted to 2 ml. Saponin (0.0033% in water) was used as a positive control.

Results: Enoxaparin at concentrations up to 100 mg/ml did not exhibit any hemolytic potential or protein precipitating properties in human blood.

MUTAGENICITY STUDIES

Ames Test

Testing laboratory:

Date of the study: Feb. 1982.

Methods: Enoxaparin (Batch No. 573, Potency: 52 IU/mg) was examined at concentrations of 8-5000 ug/plate for mutagenic activity in five histidine-dependent auxotrophs of Salmonella typhimurium, strains TA 1535, 1537, 1538, 98 and 100. The studies were conducted in the absence and presence of an activating system derived from rat liver (S-9 mix). Benzopyrene, 2-nitrofluorene, 2-aminoanthracene, 9-aminoacridine and N-methyl-N'-nitro-N-nitrosoguanidine were used as positive controls.

Results: No increase in reversion to prototrophy were obtained with any of the five strains at the concentrations tested. Significant increases in the number of revertant colonies were induced by the positive controls.

It was concluded that enoxaparin was devoid of mutagenic activity in the Ames test.

Double Locus Cell Mutation Assay

Date of the study: March, 1982.

Methods: The compound (Batch No. 573, Potency: 52 IU/mg) was examined at concentrations of 5, 15, 20, 25 and 30 mg/ml for mutagenic potential by measuring its ability to induce mutation in mouse lymphoma cells at the two genetic foci conferring ouabain and 6-thioguanine resistances. The studies were conducted in the absence and presence of a rat-liver derived metabolic activating systems. Ethylmethane sulphonate and 7,12 dimethylbenzanthracene were used as positive controls.

Results and conclusion: No evidence of mutagenic activity was found. Positive controls produced significant increases in the incidence of mutant colonies. In conclusion, enoxaparin did not induced mutagenic activity in mouse lymphoma cells at concentrations up to 30 mg/ml.

Clastogenic Activity in Cultured Human Lymphocytes

Date of the study: March, 1982.

Methods: The effect of enoxaparin (Batch No. 573, Potency: 52 IU/mg) on chromosomal structure was investigated in human cultured lymphocytes exposed to concentrations of 100, 500 or 2500 ug/ml for 24 hours. The studies were conducted in the absence and present of a metabolic activation (S-9). Distilled water was used as negative control. Cyclophosphamide was employed as a positive control.

Results and conclusion: No significant increases in aberrations over controls were seen for enoxaparin treatment. The highest tested concentration (2500 ug/ml) caused reduction of mitotic indices. No toxic effect was observed in cultures exposed to lower concentrations. Positive control induced increases in chromosomal damage only when S-9 mix was included in the treatment. In conclusion, enoxaparin induced no damage to the chromosomal structure of human lymphocytes.

In vivo Study of Rat Bone Marrow Chromosome Aberration Test

Date of the study: March-July, 1982.

Animals: Charles River CD rats weighing 62-87 g were used.

Methods: Five groups of animals each consisting of 5 males and 5 females were given enoxaparin (Batch No. 573, Potency: 52 IU/mg) subcutaneously at dose levels of 0, 1, 4, and 20 mg/kg/day for five days. Chlorambucil (15 mg/kg/day) was used as a positive control. Bone marrow cells were sampled six hours after the final treatment.

Results:

Body weight: A reduction in body weight gain (21.5%) was seen in the females receiving 20 mg/kg/day.

Mitotic index: Normal.

Chromosomal aberrations: All treated groups had the same or lower percentages of aberrant metaphases than controls. Positive control demonstrated chromosomal damage in the study.

In conclusion, enoxaparin at subcutaneous dosage up to 20 mg/kg/day for five days produced no significant damage to chromosomal structure in rat bone marrow cells.

REPRODUCTIVE STUDIES.

Segment I: Fertility and Reproductive Performance

Testing Laboratory:

Date of the study: April 1982 - Jan. 1983

GLP requirement: A statement of compliance with GLP regulations was included.

Animals: Sprague-Dawley rats weighing 187-249g were used.

Methods: Four groups of rats each consisting of 26 males and 26 females were given enoxaparin (Batch No. 573R, Potency: 52 IU/mg) subcutaneously at dose levels of 0, 3, 10, or 20 mg/kg/day. Dose selection was based on a dose-range finding study (LSR report No. 82/PHA069/293). Males were given 71 day prior to mating and throughout mating period and until necropsy at week 14. Females were given for 15 days prior to mating and throughout the gestation period and until necropsy (1/2) at either day 21 post coitum or following weaning of the offspring (day 25 post partum). Offspring (F₁) were examined for their reproductive performance and fertility. Dose selection was based upon their preliminary dose range-finding study (Rept. No. 82/PHA 069/293).

Results:

F₀ generation: Palpable hematomas were formed and hemorrhages were detected at injection sites. Body weight gain of males was not affected. Increased body weight gain was seen in females. One male receiving 20 mg/kg/day died of bleeding. Food and water intakes were normal. The duration of estrus, precoital interval, mating performance, conception rate, fertility index and gestation index were similar in all groups. Gestation length and parturition were unaffected. Litter size, offspring survival, birth weight and growth rates were comparable in all groups. Organ weights of male reproductive organs were normal.

F₁ generation: Male body weight gain was reduced in animals derived from F₀ parents that received 3 or 20 mg/kg/day. Female body weight gain was slightly elevated during lactation in animals derived from those that received 10 mg/kg/day. Estrous cycles, mating performance, fertility and conception rate were similar in all groups. No intergroup differences in fetal development was detected. Gestation length and parturition were normal. Survival, growth or development of the F₂ generation was comparable.

In conclusion, the study showed that subcutaneous administration of enoxaparin at dose levels of up to 20 mg/kg/day to rats had no adverse effect upon reproductive performance of treated F₀ animals and F₁ progeny. Although maximum tolerated dose was not used in the study, all dose levels did cause some toxicities in the rats (hematoma at the injection site) and 20 mg/kg/day is equivalent to 16 times the proposed human dose.

Segment II. Subcutaneous Teratological Study In Rats

Testing Laboratory:

Date of the study: April-May, 1982.

GLP requirement: A statement of compliance with GLP regulations was included.

Animals: Pregnant Sprague-Dawley female rats weighing 202 to 25g were used.

Methods: Four groups of animals each consisting of 20 pregnant female rats were given enoxaparin (Batch No. 573, 52 IU/mg) dissolved in 0.9% NaCl at constant volume of 1 ml/kg at dose levels of 0, 3, 10, or 30 mg/kg/day subcutaneously from day 6 to day 15 of gestation period. On day 21 of gestation, the dams were sacrificed and maternal and fetal examinations were performed. The neck, thoracic, and abdominal cavities of two-thirds of fetuses were examined first and the eviscerated fetuses were processed for skeletal examination. The remaining one-third of fetuses were examined by the Wilson's free-hand serial section technique. Dose selection was based on a dose-range finding study (Rept. No. 13, Batch No. 573, Potency: 114 anti-Xa U/mg or 52 USP units/mg).

Results:

Clinical signs: Subcutaneous swellings at the injection sites were seen in the females receiving 10 or 30 mg/kg/day. One 30 mg/kg/day was killed in extremis following extensive bleeding at injection site.

Body weight, food consumption and water consumption: Normal.

Terminal study:

Maternal observation: Subcutaneous hemorrhage was seen in all drug-treated groups.

Litter response: The number of implantation and viable young, the extent of pre and postimplantation losses and fetal weight were comparable in all groups. Placental weight was increased (8%) in the 30 mg/kg/day group.

Fetal examination: The incidence of hydronephrosis (2-5%) and unilateral hydroureter (10%) were also increased in the 30 mg/kg/day group as compared with historical controls of 0-1.5% and 1.7-10.4%, respectively. Lower fetal weight and high incidence of slight dilation of brain ventricle were reported in the 30 mg/kg/day group. The incidence of slight dilation of brain ventricle following free-hand serial sectioning are given below:

Group	% fetus (no. of litters)				Historical control range(727 fetuses)
	0	3	10	30 mg/kg	
No. of fetuses (litters) examined	96(20)	97(20)	93(20)	82(19)	
	1(1)	2.1(2)	1.1(1)	7.3(4)	0-4.7

In conclusion, enoxaparin given subcutaneously from day 6 to day 15 of gestation period at dose level of 30 mg/kg/day (25 times the proposed clinical dose) induced lower fetal weight, hydronephrosis and slight dilation of brain ventricle. Sponsor considered these being retardations and variations but not malformations. Although MTD was not employed, all dose levels produced pharmacological effect (hemorrhage at injection sites).

Segment II. Intravenous Teratology Study in Rats

Testing laboratory:

Date of the study: Nov. 15, 1983 to Feb. 8, 1984.

GLP requirement: A statement of compliance with GLP regulations was included.

Animals: Pregnant female Sprague-Dawley Rats weighing 180-190 g and 46 days of age were used.

Methods: Four groups of animals each consisting of 24 pregnant female rats were given enoxaparin (Batch No. 812, Potency: 57 IU/mg) intravenously into tail vein from the 6th to 15th day of pregnancy at dose levels of 0 (0.9% NaCl), 10, 40 and 160 mg/kg/day. On the 20th day of gestation, the dams were sacrificed for maternal and fetal examinations. Two-third of fetuses were prepared for determination of location, size and condition of internal organs first and later for skeletal examination. The remaining one-third of fetuses were examined by the Wilson's free-hand serial section technique.

Results:

Toxic signs: At 160 mg/kg/day, it caused bleeding at the injection sites for a duration of 2 to 6 hours. One dam died of extensive loss of blood from the injection site. Piloerection, decreased motor activity and pale eyes were observed.

Body weight, food and water consumptions: Normal.

Fetal examination: The fertility results did not show any influence on the development of embryos and fetuses. There were no major skeletal malformations or visceral anomalies in the examinations.

In conclusion, enoxaparin at dose up to 160 mg/kg/day i.v. did not induce any teratogenic effects in the rat. Although MTD was not employed in the study, all dose levels produced pharmacological effects. At 160 mg/kg/day, it produced lethality.

Segment II. Subcutaneous Teratology Study in Rabbits

Testing Laboratory:

Date of the study: April 5, 1982 to May 12, 1982

GLP requirement: A statement of compliance with GLP regulations was included.

Animals: Pregnant female New Zealand White rabbits weighing 3.66-4.58 kg and 18-24 weeks of age were used.

Methods: Four groups of animals each consisting of 14 pregnant females were given enoxaparin (Batch No. 573, Potency: 52 IU/mg) dissolved in physiological saline subcutaneously from day 6 to day 18 of gestation

period at dose levels of 0.3, 10 and 30 mg/kg/day. Dose selection was based upon a dosage range-finding study (821PHA065/256). On day 29 of gestation, the dams were killed. Visceral and skeletal examinations were conducted in all fetuses.

Results:

Clinical signs and mortality: Two females in the 10 mg/kg/day and one female in the 30 mg/kg/day were killed in extremis. Necropsy revealed evidence of gastrointestinal tract disorder or respiratory tract infection. Pale creamy material was found subcutaneous to injection sites of the 10 and 30 mg/kg/day groups.

Maternal weight, food intake and maternal necropsy findings: Normal.

Litter responses: Normal.

Fetal examinations: There were spontaneous incidence of visceral and skeletal anomalies found in the study.

In conclusion, enoxaparin at dosage up to 30 mg/kg/day s.c. did not induce any teratologic effect.

Segment II. Intravenous Teratology Study in Rabbits

Testing Laboratory:

Date of the Study: Nov. 14, 1983 to Feb. 20, 1984

GLP requirement: A statement of compliance with GLP regulations was included.

Animals: Pregnant female white Russian rabbits weighing 2-2.78 kg and 4-5 months of age were used.

Methods: Four groups of animals each consisting of 12 pregnant female rabbits were given enoxaparin (Batch No. 930, Potency: 53.5 IU/mg) intravenously into the marginal ear vein (1 ml/kg) at dose levels of 0 (0.9% NaCl), 10, 40 and 160 mg/kg/day from day 6 to day 18 of gestation period. Dams were sacrificed on day 29 of gestation. All fetuses were undergoing visceral and skeletal examinations.

Results:

Clinical signs: At 160 mg/kg/day, it produced bleeding at the injection sites for a duration of 5 to 10 minutes. Pale eyes and mortality at 40 mg/kg/day were observed.

Body weight, food and water consumptions: Normal.

Fetal observation: There were no differences in the number of implantations, fetuses, placenta as well as of fetal and placental weight between control and drug treated groups. No drug related visceral and skeletal malformations were found.

In conclusion, enoxaparin at dose up to 160 mg/kg/day induced no fetal changes and teratogenic effects in the rabbit.

Segment III. Peri and Postnatal Development in Rats

Testing laboratory:

Date of the study: May 11, 1982 to June 28, 1982

GLP requirement: A statement of compliance with GLP regulations was included.

Animals: Pregnant female Sprague-Dawley rats weighing 196 to 255 g were used.

Methods: Four groups of animals each consisting of 20 pregnant female rats were given enoxaparin (Batch No. R 573, Potency: 130 Anti-Xa U/mg or 52 IU/mg) subcutaneously from day 15 postcoitum until day 21 postpartum at a constant volume of 1 ml/kg at dose levels of 0 (0.9% NaCl), 3, 10 and 20 mg/kg/day. All litters were killed after weaning on day 21 postpartum and subjected to a macroscopic necropsy examination.

Results:

Maternal observations:

Clinical signs and mortality: Subcutaneous swellings were seen in all drug treated groups. One dam in the 10 mg/kg/day group died due to prolonged bleeding from an injection site.

Body weight and gestation length: Normal.

Litter observations:

Clinical signs and litter size and viability were similar in all groups.

Body weight: Body weight was significantly reduced (11%) in the 20 mg/kg/day group.

Sex ratio: Normal

Physical development: In the 20 mg/kg/day group, onset and completion of tooth eruption and commencement of eye opening were delayed.

Auditory and visual function: Normal.

Terminal examination:

Dams: Subcutaneous hematoma was found in all drug treated groups.

Fetuses: No macroscopic change were seen that could be related to treatment.

In conclusion, subcutaneous administration of enoxaparin to female rats from day 15 of gestation until day 21 of lactation had no adverse effect upon peri and postnatal development at dose levels of up to 10 mg/kg/day. At 20 mg/kg/day, body weights of offspring were depressed, tooth eruption and eye opening were delayed.

Proposed Text of the Labeling for Enoxaparin

The label (see Appendix I) is according to 21 CFR, 201.50, Subpart B (April 1, 1991). However following changes should be incorporated:

1. Carcinogenesis, Mutagenesis, Impairment of Fertility:

Sponsor's Version: No long-term studies in animals have been performed to evaluate the carcinogenic potential of Tradename~~t~~ Injection. However, Tradename~~t~~ Injection was uniformly negative in a battery of short-term genetic toxicity tests, including a bacterial and a mammalian cell in vitro mutagenicity assay as well as in vitro and in vivo tests for chromosomal damage. Also, Tradename~~t~~ Injection was shown to have no effects on fertility and reproductive performance in rats.

Evaluation:

The text is not according to 21CFR, 201.50, Subpart B (April 1, 1991)

Proposed Version:

No long-term studies in animals have been performed to evaluate carcinogenic potential of enoxaparin. No evidence of mutagenicity was observed in in vitro Ames test, mouse lymphoma cell forward mutation test, human lymphocyte chromosomal aberration test and in vivo rat bone marrow cell chromosomal aberration test. No effects on fertility or reproductive performance were observed in male or female rats at s.c. doses up to 20 mg/kg/day.

2. Pregnancy:

Sponsor's Version:

Pregnancy Category B: Enoxaparin had no effect on embryo/fetal development in rats and rabbits or on postnatal development in rats. Rabbits that received potentially lethal doses of enoxaparin had an increased frequency of abortions and fetal resorptions but no effect on the number of corpora lutea or implantations. Thus, enoxaparin was shown to have no reproductive toxicity potential in animals. There are no adequate and well controlled studies in humans. Enoxaparin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Evaluation:

In the Segment II teratology study in rats, pregnant rats were treated from day 6 through 15 of gestation with either s.c. doses of 3, 10, and 30 mg/kg/day or i.v. doses of 10, 40 and 160 mg/kg/day of enoxaparin. No teratogenic effects at dosage up to 30 mg/kg/day (s.c.) or 160 mg/kg/day (i.v.) was observed. In Segment II teratology study in rabbits, pregnant rabbits were treated from day 6 through 18 of gestation with either s.c. doses of 3, 10, and 30 mg/kg/day or i.v. doses of 10, 40 and 160 mg/kg/day of enoxaparin. No teratogenic effects at dosage up to 30 mg/kg/day (s.c.) or 160 mg/kg/day (i.v.) was observed. The mode of administration of the drug in humans is via subcutaneous route, therefore only s.c. segment II teratology studies in rats and rabbits are relevant.

Proposed Version:

Pregnancy: Teratogenic effects. Pregnancy category B. Reproduction studies have been performed in pregnant rats and rabbits at subcutaneous doses up to 30 mg/kg/day have revealed no evidence of impaired fertility or harm to the fetus due enoxaparin. There are, however, no well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

3. Nursing Mothers:

Sponsor's Version:

There is no experience with the use of enoxaparin during human lactation. A late lactation/postnatal toxicity study conducted in rats with enoxaparin given by the subcutaneous route did not reveal any effect on the survival and growth of offspring, suggesting no effect on the lactational process nor on nurturing of the newborn. As a precaution, however, lactating mothers receiving Tradename[®] Injection should be advised to avoid breast-feeding.

Evaluation:

The text is not according to 21CFR, 201.50 Subpart B (April 1, 1991)

Proposed Version:

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when enoxaparin is administered to nursing women.

OVERDOSAGE:

Sensor's Version:

Symptoms/Treatment:

Accidental overdose following administration of Tradename[®] Injection may lead to hemorrhagic complications. This may be largely neutralized by the slow intravenous injection of protamine sulfate (1% solution). The dose of protamine sulfate should be equal to the dose of Tradename[®] Injection injected: 1 mg protamine sulfate should be administered to neutralize 1 mg Tradename[®] Injection. A second infusion of 0.5 mg/mg protamine sulfate may be administered if the APTT measured 2 to 4 hours after the first infusion remains prolonged. However, even with higher doses of protamine, the APTT may remain more prolonged than under normal conditions found following administration of conventional heparin. In all cases, the anti-Factor Xa activity is never completely neutralized (maximum about 60%). Particular care should be taken to avoid overdose with protamine sulfate. Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported, the drug should be given only when resuscitation techniques and treatment of anaphylactoxic shock are readily available. For additional information consult the labeling of Protamine Sulfate Injection, USP, products.

Evaluation:

Sponsor did not provide any clinical or preclinical overdose data. A single dose of 46.4 mg/kg was lethal to rats. The symptoms of acute toxicity were ataxia, decreased motility, dyspnea, cyanosis and coma.

Proposed Version:

The following sentences should be added to the sponsor's version:

A single dose of 46.4 mg/kg was lethal to rats. The symptoms of acute toxicity were ataxia, decreased motility, dyspnea, cyanosis and coma.

SUMMARY AND EVALUATION:

Enoxaparin is a low-molecular weight heparin fragment (average M.W. = 4500 daltons). Enoxaparin and heparin both are antithrombotic in various animal models, and both prolonged APTT and TT and inhibited factor IIa and factor Xa activities. One important distinction between the two drugs is that enoxaparin markedly inhibited factor Xa activity and slightly inhibited factor IIa activity, while heparin inhibited both factors equally. Furthermore, heparin had greater anticoagulant activity and produced greater inhibition of platelet aggregation induced by various agents than enoxaparin at similar dose levels. Hence the antithrombotic activity of enoxaparin may be related to its relative specific inhibition of factor Xa and drug may cause less bleeding and/or thrombocytopenia compared to heparin at similar biologically active dose.

Sponsor submitted a new Drug Application for enoxaparin for marketing it for prevention of deep vein thrombosis which may lead to pulmonary embolism in patients undergoing hip replacement surgery. The drug comes in prefilled syringes containing 30 mg of enoxaparin sodium salt in 0.3 ml of sterile water. The recommended dose of enoxaparin is 30 mg b.i.d. subcutaneously for 7-10 days (1.2 mg/kg, 50 kg body weight assumed).

In support of the new drug application for enoxaparin, sponsor has submitted preclinical pharmacology studies; absorption, distribution, metabolism and excretion (ADME) studies in rats, dogs and monkeys; acute toxicity studies in mice, rats and dogs; 13-Week and 6-month s.c. toxicity studies in rats; 26-Week i.v. toxicity study in rats; 13-Week s.c. toxicity study in dogs; 26-Week s.c. and i.v. toxicity studies in monkeys; Segment I. s.c. fertility and general reproductive performance study in rats; Segment II. s.c. and i.v. teratology studies in rats and rabbits; Segment III. s.c. perinatal and postnatal study in rats; Genotoxicity studies: Ames tests, mouse lymphoma cell forward mutation test, clastogenic activity in cultured human lymphocytes and chromosomal aberration test in rat bone marrow cells; and Special toxicity studies: local tolerance study in dogs, sensitization test in guinea pigs, and hemolytic and precipitating test (in vitro). All the above mentioned studies were reviewed by Dr. Sun on September 20, 1989 under IND 31,532. I have consulted Dr. Sun's review of toxicity studies for my summary and evaluation.

Absorption, distribution, metabolism, and excretion studies were conducted in rats and dogs. The drug is absorbed rapidly and completely in both rats and dogs following s.c. administration of ³⁵S-enoxaparin. The T_{max} of radioactivity for rat was 0.45-0.7 hr and for dog was 1-2 hr. In rats, plasma mean maximum anti-Xa activity over the tested s.c. or i.v. dose range increased linearly with dose. Due to a secondary rise in plasma anti-Xa activity as well as in whole blood radioactivity it was difficult to assess

the $t_{1/2}$ values. Variable sampling time durations were used for different doses to estimate $t_{1/2}$ values. Half-lives for anti-Xa activity after single s.c. dose ranged from 0.837-2.149 hour (human = 5.11+/- 2.25 hr) and 0.330-0.679 hour (human = 4.04+/- 2.46 hr) after single i.v. dose. After 7 daily i.v. doses of enoxaparin (0.85 mg/kg), plasma anti-Xa activity did not accumulate significantly and the kinetics were similar to that obtained after a single i.v. dose of 0.85 mg/kg of enoxaparin. The pharmacokinetics of radioactivity after single s.c., single i.v., or 7 daily i.v. doses of ³⁵S-enoxaparin were linear with tested doses and independent of route of administration. Furthermore, biological activity (anti-Xa activity) profile is similar to pharmacokinetic profile. In dogs, after s.c. administration, the plasma anti-Xa activity and radioactivity both declined in biphasic manner. The C_{max} for anti-Xa activity was almost double than that for radioactivity, and the $t_{1/2}$ alpha (2.57-3.0 hr) and $t_{1/2}$ beta (17.67-20.35 hr) for anti-Xa activity as well as radioactivity were comparable. In rats and dogs after s.c. administration of the drug, radioactivity was distributed through out the body, with highest concentrations seen in liver and kidney. Furthermore, in multiple dose study in rats, radioactivity in all tissue accumulated and the levels were 3-5 fold greater than the initial values (24-hr after first dose), and this radioactivity correspond to inactive drug and/or metabolite(s). The drug is metabolized by desulphation &/or depolymerization to lower molecular weight species. Irrespective of the route of administration, in both species (rats and dogs), enoxaparin was mainly excreted in the urine (56-72%) and only less than 5% in the feces (biliary excretion = about 2%), and major portion of the administered radioactivity was excreted during the first 24 hours after drug administration. In dogs, about 38-60% of urinary radioactivity (0-24 hr) after i.v. dose represented unchanged drug or biologically active drug (ie having anti-Xa activity), while 34-40% of urinary radioactivity (0-24 hr) after s.c. dose represented biologically active drug.

Biological activities (antithrombotic, anti-coagulant and fibrinolytic activity) of enoxaparin were also assessed in monkeys. A dose as high as 200 anti-Xa U/kg of enoxaparin had no significant effect on platelet count and prothrombin time. Significant prolongation of TT (which return to normal by 18 hour), increase in anti-IIa activity and a dose dependent increase in anti-Xa activity were seen in treated monkeys. Enoxaparin also significantly inhibited fibrinopeptide A generation (assess the collective anti-Xa and anti-IIa activities) in treated monkeys.

In acute toxicity studies, the highest nonlethal doses for mice were 2150 mg/kg and 1470 mg/kg when given s.c. and i.v. respectively (LD_{50} : s.c. = 6700 mg/kg for male and 8100 mg/kg for female mice; ID_{50} : i.v. = 2340 mg/kg for both male and female). The highest nonlethal doses for rats were 14.7 mg/kg and 1210 mg/kg when given s.c. and i.v. respectively (LD_{50} : s.c. = could not be calculated in either sex; LD_{50} : i.v. = 1660 mg/kg for male and 1810 mg/kg for female rats). The lowest s.c. lethal doses for NMRI mice and SD rats were 3160 (report # 002: for unknown strain of mice = 37.5 mg/kg) and 46.4 mg/kg respectively. Mice and rats, treated with enoxaparin showed similar toxic signs. These signs were ataxia, decreased motility, dyspnea, cyanosis, coma and convulsions.

In the 13-week s.c. toxicity study in rats, doses of 3, 6.5 and 15 mg/kg/day were used. Hemorrhage and hematoma were seen in all treated animals. Lethality was observed at 15 mg/kg/day dose level. Blood chemistry and hematology tests and histopathological examinations were performed on only control and high dose treated animals. Extramedullary hematopoiesis in spleen and liver, increased white pulp in the spleen, and increased megakaryocytes in bone marrow were seen in high dose treated rats. Only hematoma at the

injection sites, and slight increases in kidneys (both sexes) and adrenals (only females) weights were seen at 3 mg/kg/day, therefore this dose level can be considered as tolerated dose.

In the 6-month s.c. toxicity study in rats, doses of 3, 10 and 30 mg/kg/day were used. The drug produced mortality at all dose levels including the control group. Hemorrhage at the injection sites were seen in all treated animals and severe bleeding at the injection sites were the main cause of deaths. The serum cholesterol levels were increased by 28-80% in all treated males and by 43% in high dose treated females when compared to their respective control values, and cholesterol levels remain elevated even after 6 weeks of recovery period. Histopathological examinations were performed on only control and high dose treated animals. Acinar cell atrophy and pancreatic interstitial fibrosis were seen in high dose treated animals.

In the 26-week i.v. toxicity study in rats, doses of 10, 30/20 and 90/40 mg/kg/day were used. The drug produced mortality at all doses. Hemorrhage, inflammation and necrosis at the injection sites were seen in all treated animals. Thrombosis and thrombosis related infarcts in livers and adrenal glands, and renal tubular nephrosis were seen at 30/20 mg/kg/day and higher doses. No drug related histopathological changes were evident at the end of 4 weeks of recovery period.

In the 13-week s.c. toxicity study in dogs, doses of 3, 6.5 and 15 mg/kg/day were used. Dermal thickening, swelling and hemorrhage at the injection sites were seen in all treated animals. Mild parathyroid hyperplasia was seen in some high dose treated dogs. Sponsor did not use sufficient high doses to elicit clear toxicity. At 3 mg/kg/day only dermal thickening was observed for less than a week, therefore, this dose level can be considered a no effect dose in this study.

In the 26-week s.c. toxicity study in monkeys, doses of 3, 10 and 30 mg/kg/day were used. Dose related edema, redness, bruising, scab formation, swelling, s.c. hemorrhage and hematoma were seen in treated animals. Increased kidney, liver, and spleen weights were seen at 30 mg/kg/day and these increases were still present at the end of 4 weeks of recovery period. Increased spleen weights were also seen in 10 mg/kg/day dose group. At 3 mg/kg/day only hemorrhage was observed at the injection sites, therefore, this dose level can be considered a no effect dose in this study.

In the 26-week i.v. toxicity study in monkeys, doses of 5, 10 and 20 mg/kg/day were used. Mortality was seen at 20 mg/kg/day. Swelling at the injection sites were seen in all treated animals. Mid and high dose levels produced vomiting. No target organ of toxicity was identified in this study. The no effect dose was 5 mg/kg/day in this study.

In Segment I fertility and general reproductive performance study in rats, s.c. doses of 0, 3, 10, and 20 mg/kg/day were used. There were no abnormal effects on the fertility and mating performance of the treated male and female rats at doses up to and including 20 mg/kg/day (16.6 times the proposed clinical dose) of enoxaparin.

In the first Segment II teratology study in rats, s.c. doses of 0, 3, 10 and 30 mg/kg/day were used. Pregnant rats were treated from day 6 through 15 of gestation. No teratogenic effects at dosage upto 30 mg/kg/day (25 times the proposed clinical dose) was observed.

In the second Segment II teratology study in rats, i.v. doses of 0, 10, 40 and 160 mg/kg/day were used. Pregnant rats were treated from day 6 through 15 of

gestation. No teratogenic effects at dosage upto 160 mg/kg/day was observed.

In the first Segment II teratology study in rabbits, s.c. doses of 0, 3, 10 and 30 mg/kg/day were used. Pregnant rabbits were treated from day 6 through 18 of gestation. All pregnant rabbits were sacrificed on day 29 of gestation. Visceral and skeletal examinations were conducted in all fetuses. No teratogenic effects at dosage upto 30 mg/kg/day (25 times the proposed clinical dose) was observed.

In the second Segment II teratology study in rabbits, i.v. doses of 0, 10, 40 and 160 mg/kg/day were used. Pregnant rabbits were treated from day 6 through 18 of gestation. All pregnant rabbits were sacrificed on day 29 of gestation. All pregnant rabbits were sacrificed on day 29 of gestation. Visceral and skeletal examinations were conducted in all fetuses. No teratogenic effects at dosage upto 160 mg/kg/day was observed.

In Segment III prenatal and postnatal study, pregnant rats were given s.c. doses of 0, 3, 10, and 20 mg/kg from day 15 of gestation to day 21 after parturition. No adverse effect were seen in rats following s.c. administration of up to 20 mg/kg/day of enoxaparin during perinatal and postnatal period except the body weight gains of the F₁ pups during lactation period were retarded in dose dependent manner but the results were statistically significant only at high dose. In high dose group tooth eruption and eye opening were also delayed.

No mutagenic potential was demonstrated when enoxaparin was tested in 4 different tests: Ames test, mouse lymphoma cell forward mutation test, chromosomal aberration tests in cultured human lymphocytes (in vitro) and rat's bone marrow (in vivo).

In the special toxicity studies, the s.c. route was tolerated well without any local reaction in dogs, while intra-arterial, intramuscular, intravenous, and paravenous injections of enoxaparin produced hematomas and inflammatory infiltrates at the injection sites. Furthermore, local hematomas and inflammatory reactions were also seen after multiple s.c. injections of the drug to rabbits and dogs. Enoxaparin produced no sensitization in guinea pigs. In vitro, Enoxaparin at concentrations up to 100 mg/ml did not cause hemolysis in human blood.

In humans the proposed route of administration is subcutaneous. Sponsor has adequately characterized enoxaparin and conducted sufficient preclinical s.c. toxicity studies in different species. A subcutaneous dose of 3.0 mg/kg/day of enoxaparin can be considered as no effect dose in rats (13-week), dogs (13-week) and monkeys (26-week), since the drug only produced hemorrhage at the injection sites in rats and monkeys and only dermal thickening for less than a week in dogs. In addition to extramedullary hemopoiesis in spleen and liver, increased white pulp in the spleen and increased megakaryocytes in bone marrow were seen in treated rats. These effects are consequences of anti-coagulant activity of enoxaparin (exaggerated pharmacological effects). In rats, liver (increased cholesterol levels), Acinar cell of exocrine pancreas (atrophy) and kidneys (nephrosis) are the target organs of toxicity. In dogs, parathyroid (hyperplasia, cell unspecified) is the target organ of toxicity. No target organ of toxicity was identified in monkeys. Thus from a preclinical standpoint the application is approvable.

The label is according to 21 CFR, 201.50 Subpart B (April 1, 1991), however, it needs minor changes in the text as outlined in the review portion.

RECOMMENDATIONS:

From a preclinical standpoint the application is approvable. Sponsor should be asked to change the labeling as outlined in the review portion.

Tanveer Ahmad 2/21/92

Tanveer Ahmad, Ph.D.
Pharmacologist, HFD-180

cc:
Orig. NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Ahmad
HFD-180/Dr. Choudary
HFD-180/Dr. Fredd
HFD-345/Dr. James
HFD-502/Dr. Weissinger
TA/10/24/91/w2082c
c:\wp51\pharm\n\20164201.0ta

Concur

A handwritten signature, possibly of a reviewer, written in dark ink. The signature is stylized and appears to be a name followed by a surname or initials.

PHARMACOLOGY/TOXICOLOGY REVIEW

HFD-180

NDA # 20-164
IND # _____

DRUG NAME: ENOXAPARIN
OTHER NAMES: PK 10169

INDICATIONS: Prevention of DVT

SPONSOR: Rhone-Poulenc Rorer Pharma. Inc.
Fort Washington, PA

STEREISOISOMER? yes ___ no x
DELIVERY SYSTEM? yes ___ no x

Toxicology Studies Included in this Review

	<u>Mouse</u>	<u>Rat</u>	<u>Dog</u>	<u>Monkey</u>	<u>Rabbit</u>
Single Dose					
intravenous	<u>x</u>	<u>x</u>	<u>x</u>	_____	_____
s.c.	<u>x</u>	<u>x</u>	_____	_____	_____
Repeat Dose					
13-week, s.c.	_____	<u>x</u>	<u>x</u>	_____	_____
13-week, i.v.	_____	_____	_____	_____	_____
26-week, s.c.	_____	_____	_____	<u>x</u>	_____
26-week, i.v.	_____	<u>x</u>	_____	<u>x</u>	_____
6-month, s.c.	_____	<u>x</u>	_____	_____	_____
Carcinogenicity	_____	_____	_____	_____	_____
Reproductive Tox	_____	_____	_____	_____	_____
Segment I (s.c.)	_____	<u>x</u>	_____	_____	_____
Segment II (i.v. & s.c.)	_____	<u>x</u>	_____	_____	<u>x</u>
Segment III (s.c.)	_____	<u>x</u>	_____	_____	_____
Dermal Toxicity	_____	_____	_____	_____	_____
Ocular Toxicity	_____	_____	_____	_____	_____
Genotoxicity					

1. Ames Test
2. Mouse Lymphoma Cell Forward Mutation test
3. Chromosomal Aberration test in Human Lymphocytes
4. Chromosomal Aberration test in Rat's Bone Marrow cells

Pharmacology Studies Included in this Review:

	<u>Mouse</u>	<u>Rat</u>	<u>dogs</u>	<u>Pig</u>	<u>Monkey</u>	<u>Human</u>
Pharmacokinetics	_____	<u>x</u>	<u>x</u>	_____	_____	_____
Pharmacologic Effects	_____	<u>Hamster</u>	<u>Rabbit</u>	<u>Dog</u>	<u>Monkey</u>	<u>Sheep</u>
1. Anti-thrombotic		<u>x</u>	<u>x</u>	<u>x</u>	<u>x</u>	
2. Anti-coagulant			<u>x</u>		<u>x</u>	<u>x</u>
3. Fibrinolytic			<u>x</u>		<u>x</u>	

Conclusions

1. IND: No objection _____ Objection _____
NDA: No objection x Objection _____
2. Tumorigen? yes ___ no ___ Neurotoxic? yes ___ no x Immunotoxic? yes ___ no ___
3. Put an asterisk by the studies that were conducted using the final formulation!
4. Inactive ingredient or metabolite concerns? None

Reviewer Tanveer Ahmad, Ph.D.

Date 2/21/91

PHARMACOLOGIST'S REVIEW OF NDA 20-164
(Amendments dated June 19, 1992)

OCT - 7 1992

Reviewer: Tanveer Ahmad, Ph.D.
Pharmacologist, HFD-180

Sponsor & Address: Rhone-Poulenc Rorer Pharmaceuticals Inc.
Fort Washington, PA 19034

Drug: Enoxaparin (injection)/ RP 54563/ PK 10169 (low M.W. heparin)

Category: Antithrombotic agent

Date of Review: 9/29/90

Date of HFD-180 Receipt: 6/22/92

Submission Contents: Safety test, pyrogen test, and depressor substance test for enoxaparin.

All the above mentioned tests were conducted at Institute of Biopharmacy, Rhone-Poulenc Rorer, Antony, France.

Safety Test

Methods: Test was performed according to USP procedures.

Results: The test results indicated that the drug is safe.

Pyrogen Test

Methods: Test was performed according to USP procedures.

Results: The drug is not a pyrogen.

Depressor Substance Test

Methods: Test was performed according to USP procedures.

Results: The drug was less hypotensive than histamine i.e histamine (0.1 mcg base/kg) produced a mean drop of blood pressure by 39 mmHg, while the test drug (50 mg/ml/kg) produced a mean drop of 15 mmHg. The test result was in compliance with the code of federal regulations.

SUMMARY AND EVALUATIONS:

In this submission sponsor reported the results of safety test, pyrogen test, and depressor substance test for enoxaparin. Enoxaparin is safe, non-pyrogen and less hypotensive than histamine.

NDA 20-164
Page 2

RECOMMENDATION: None.

cc:
Orig NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Ahmad
HFD-180/Dr. Sieczkowski
HFD-180/Dr. Choudary
HFD-180/Dr. Fredd
N\20164209.0TA

Tanveer Ahmad 9/29/92
Tanveer Ahmad, Ph.D.
Pharmacologist, HFD-180

Concur
[Signature] 10/7/92

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Chemistry Review # 1

MAY - 4 1992

1. DMF#
2. Date Completed: 7 April 1992
3. Type of Submission: Type I and Type II (Originals)
4. Center's Therapeutic Classification: N/A
5. Status of Application: Active
6. Name of Sponsor/Applicant: Valori 5
7. Addresses:
 - US Agent
Rhone-Poulenc Rorer Pharma. Inc
Attention: Margaret S. Masters
500 Virginia Drive
Fort Washington, PA 19034
(215) 628-6000
8. Product Names:
 - (a) Proprietary: N/A
 - (b) Established: Heparin sodium
USAN: Heparin sodium
USP: Heparin sodium
 - (c) Code Name and Number: N/A
 - (d) CAS 9041-08-1
9. Dosage Form(s), Strength/Potency, and Route of Administration: N/A
10. Proposed Marketing Status:
Commercial raw starting material for enoxaparin (drug substance).
11. Pharmacological Category and Indication(s):
anticoagulant
12. Structural Formula, Chemical Name, Empirical Formula, Molecular Weight:
See "The Merck Index," Eleventh Edition, "4571 - Heparin."
13. Structural Formulas of Related Compounds:
Enoxaparin, low molecular weight heparins.
14. Document Date(s): December 23, 1991

15. CDB Date: December 26, 1991
16. Division Date: N/A
17. Assigned Date: N/A
18. Supporting Documents: None
19. Related Documents: None

20. Remarks:

Heparin sodium (Porcine intestinal mucosa) is the raw starting material for a particular low molecular weight heparin (enoxaparin) which is manufactured by Rhone-Poulenc Rorer Pharmaceuticals, Inc. (also the U.S. Agent for DMF 9472 - Heparin sodium/Valori 5). Heparin sodium is the sodium salt of a heterogeneous mixture of sulfated polysaccharide chains composed of repeating units of D-glucosamine and either L-iduronic or D-glucuronic acids and which polysaccharides chains vary in molecular weight between 6,000-30,000 daltons. Heparin in the U.S. is isolated from beef lung or porcine intestinal mucosa, however outside the U.S., other sources of heparin are used such as beef intestinal mucosa, sheep intestinal mucosa or sheep lung. The animal source of heparin for this DMF is specified as porcine intestinal mucosa.

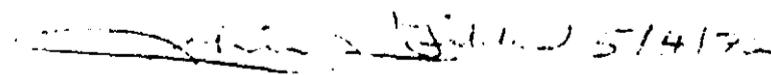
21. Conclusion and Recommendations (Include Consulting Review Status)

I recommend additional information be requested by letter from the DMF holder. See attached letter.

22.


Joseph Sieczkowski, Ph.D. 5-1-92
Chemist, HFD-180

23.


John J. Gibbs, Ph.D.
Supervisory Chemist, HFD-180

24. Review Notes:

(a) Drug Substance:

1. Description, Including Physical and Chemical Characteristics and Stability:

A natural source material for heparin is porcine intestinal mucosa. Heparin is a biosynthesized molecule which is stored in the mast cells of various animal tissues from which it can be isolated by proteolysis (in this case protease A₃). The sulfated mucopolysaccharides (Heparin) can be reproducibly isolated according to the tissue, animal species, method of extraction and purification. The resultant heparin is never a crystalline powder and is never a singly defined chemical molecule. Since the heterogeneity of heparin prevents structure elucidation as for a similarly synthesized molecule, heparin manufacturers have not elucidated the structure of the heparin manufactured but tested it for its biological activity through "Anti-Factor Xa activity" and "Assay" (sheep plasma coagulation) testing. The USP XXII Heparin Sodium monograph provides a short descriptive paragraph concerning the nature of heparin sodium and its biological activity. The commonly used methods, for degrading the animal tissue and for isolation, have not been known to degrade heparin. Future changes to the USP Heparin Sodium monograph may require that other specifications be met (i.e., molecular weight range, Anti-Xa/Anti-II ratio), however this is not the present situation and the best means of characterizing the isolated heparin is through its biological activity (Anti-Factor Xa activity and assay).

No structure proof for heparin is required at this time due to the nature of heparin and the fact that consistent manufacturing processes have been worked out to isolate heparin, in spite of its heterogeneous nature, on the basis of its biological activity.

DMF Description of Heparin Sodium

H - DESCRIPTION OF HEPARIN SODIUM

a) Chemical and biological information

Heparin sodium is the sodium salt of forms of a sulfated glycosaminoglycan of mixed mucopolysaccharide nature varying in molecular weights. The VALORI 5 Heparin Sodium is exclusively obtained from porcine intestinal mucosa.

Heparin sodium has the characteristic property of delaying the clotting of freshly shed blood.

b) CAS registry number

9041 - 08 - 1

c) Physical characteristics

A white or almost white, odorless or almost odorless, moderately hygroscopic powder.

Solubility and pH :

- One gram dissolves in 20 ml water.

- A 1% solution has a pH of 5.0 to 7.5

d) Stability

The Heparin sodium, USP monograph does not specify any particular conditions except for the preservation in tight containers. Nevertheless, in order to conform with GMP, a stability testing program shall be initiated with re-analysis of three batches which have been stored for 1, 2 and 3 years respectively. Furthermore, one batch per year shall be stored at room temperature for up to 5 years and examined each year during this period using current USP procedures.

COMMENT:

Adequate except that stability considerations are commented on further in this review under "2. Stability."

2. Manufacturer(s):

A - ADMINISTRATIVE DATA

a - Addresses

• DMF holder / administrative address:

VALORI 5
ZI de GOURHEL

56 800 PLOERMEL
FRANCE

• Manufacturing Facility

• Contact for FDA correspondence
Official U.S. Agent

Mrs MARGARET MASTERS

Associate Director, Regulatory Control

RHONE POULENC RORER INC.

500 Virginia Dr
FORT WASHINGTON, PA 19034

b) Drug Establishment Registration

as a foreign manufacturer, has no registration number in the U.S.A.

Type I, DMF information is on the following pages:

- A. Administrative Data (page 4).
- B. Statement of Commitment (page 5).
- C. Location and Description of Equipment (page 6-12).
- D. Organization and Personnel (pages 13-14).

3. Method(s) of Manufacture:

- I. Manufacture of Heparin Sodium (pages 25-46).

1) Extraction Workshop on
page 10 of DMF.

2) Purification workshop on
page 11 of DMF.

b) Manufacturing procedure

Introduction

COMMENT:

- should provide:
1. The detailed method of

 2. The method of tracking or identifying

 3. The written procedures for recycling of batches which do not comply with the standards given in the specifications (statement on page 19 and specifications on page 47).

 4. Process Controls:

I. (Page 30).

c - Control of raw materials

1 - List of raw materials

;

II. Identification/receipt testing methods for materials (page 31-33).

III. (Page 34).

III - Assurances or statements of quality from suppliers.

has obtained assurances or statements of quality from suppliers with respect to the following raw materials delivered.

Raw material	Supplier

(Pages 35-44).

III Reliability of the suppliers quality assurances through quality control

At least once a year, raw materials are checked by the quality control laboratory of the

(Pages 45-46)/USP method Ja) (page 47).

COMMENT:
Adequate in-process controls.

N20-164

6 of 7

5. Specifications and Analytical Methods:
(Section J)

"a) Specifications and test methods for
acceptance and release" (pages 47-50).

Page 47

Current USP Specifications
NOTES:

1. Anti-Factor Xa activity standard is not available and the test was not performed.
2. Dermatan sulfate content is an additional internal specification.

Page 48-49

"USP Monograph of Heparin Sodium."

Page 50

Letter of commitment by
to analyze heparin sodium prior
to release according to USP
requirements.

Page 51

 **RHÔNE-POULENC RORER**

NOM DU PRODUIT HEPARIN SODIUM USP
Name of the Product
(Source : Porcine intestinal Mucosa)

NOM DU CLIENT
Customer's name

ADRESSE
Address

N° D'ORDRE
Order n°

POIDS
Weight

CERTIFICAT D'ANALYSE
Certificate of analysis

LOT N° 91 284 62
Batch

DETERMINATIONS
Determinations

RESULTATS
Results

USINE DE VILLENEUVE LA GARENNE le December, 19th, 1991. GE.

LE CHEF DU SERVICE ANALYTIQUE
Analytical Services Manager

Patrick PESCHER

COMMENT:

Because heparin sodium manufacture is for the purpose of producing an acceptable raw starting material for the manufacture of enoxaparin (a new drug substance), it will be recommended that the "Dermatan sulfate" and "Anti-Factor Xa" specifications be adopted as part of the finished heparin sodium specifications

(page 47). In this situation, heparin sodium as a raw starting material, Anti-Factor Xa testing may be conducted with international standards. The specification test results should be reported on the heparin sodium "Certificate of Analysis" (page 51).

Some evidence of the specialty of Heparin Sodium:

(Page 20)

Label tied to the bag

Envoi de Héparine Sodique de Porc Spéciale Enoxaparine
lot EV 230

M TARE 0.180 kg

BRUT 18.360 kg

NET 18.160 kg

Remis le 25/11/91

label
stuck on the drum

HEPARINE SODIQUE DE PORC
Spéciale Enoxaparine
Lot EV 230
tare 3.080 Kg
brut 21.240 Kg
net 18.160 Kg

6. Container-Closure System: (page 29)
 - A. See under "Chemical Purification" above which is to put Heparin sodium in double polyethylene sacks and seal.
 - B. (Page 19)

Packaging

Heparin Sodium USP is packed in quantities, ie. around 20 kg, in two plastic bags which are placed in 60 litre plastic drums. The drums and bags comply with the French legislation regarding public health and safety. The bags are closed with metal bands coated with plastic, and the drums are sealed before dispatch.

COMMENT:

1. Please provide a more detailed description of the bulk packaging and identify the bulk packaging suppliers.
2. Please provide the

7. Microbiology:

COMMENT:

Heparin Sodium conforms to the USP Pyrogen testing as provided under the USP Heparin Sodium monograph and the USP pyrogen specification is adequate for heparin sodium.

8. Stability:

COMMENT:

No stability data was provided. The heparin sodium produced under this DMF is as a raw material for Rhone-Poulenc Rorer in the manufacture of enoxaparin and therefore the stability of the heparin sodium is of some concern.

Therefore, we should request of

1. Storage conditions for heparin sodium prior to shipment.
2. Specification testing of heparin sodium just prior to shipment.
3. Submission, if available, of short term stability data on

heparin sodium Lots under the storage conditions at
If no stability data is available, please submit a
stability protocol for testing future heparin sodium
production Lots.

(b) Drug Product:
N/A

(c) Investigational Formulations: N/A

(d) Environmental Assessment: (pages 52-56)

Page 52 certifies that the DMF conforms
to French current regulations concerning
environment protection and notes that two
documents are appended.

Page 53 "Document No. 1" in French.

Page 54 "Document No. 1" (English translation)
from the Regional Department of Industry,
Research and Environment of Brittany.

Page 55 "Document No. 2" in French.

Page 56 "Document No. 2" (English translation)
from the Department Office of Health and
Social Sciences.

COMMENT:

Both documents appear to be satisfactory to meet the
environmental assessment requirements. Phillip G. Vincent,
Ph.D., Environmental Assessment Officer, CDER, HFD-102 was
consulted on the adequacy of the two documents for a E.A.

(e) Methods Validation: N/A

(f) Labeling: (Page 19-20.)

COMMENT:

Adequate labeling.

(g) Other Contractors, Fabricators: None

(h) Establishment Inspection:

COMMENT:

The inspection of the facility is to be conducted in

conjunction with the Rhone-Poulenc Rorer (RPR) facility prior to the approval of RPR's NDA for Enoxaparin Injection.

25. Samples and FDA Laboratory Results: N/A
26. Summary:
See #27, Draft of Reviewer's Part; Letter to the Drug Master File Holder.
27. Draft of Reviewer's Part; Letter to Master File Holder:
See attached draft letter to

CC:

DMF 9472

DIVISION FILE FOR 20-164

HFD-180

HFD-181/CSO

HFD-180/Fred

HFD-82/Lipov

HFD-180/JSieczkowski/

R/D init JGibbs/4-7-92

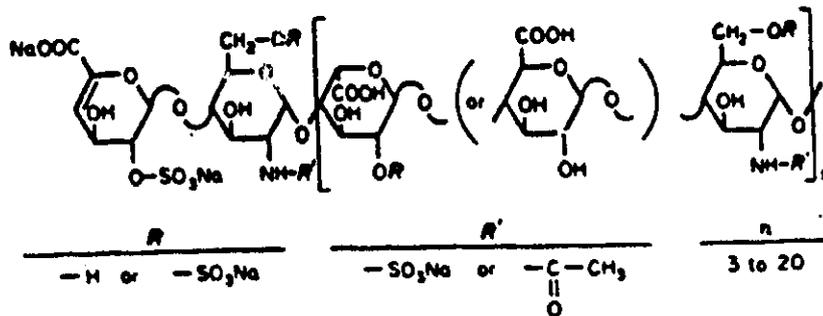
dob/DRAFT 4-28-92/F/T 5-1-92/wp/chem/d/09472204.1JS

020
12/92

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Chemistry Review # 1

MAY 12 1992

1. NDA 20-164
2. Date Completed: March 31, 1992
3. Type of Submission: Original (RS)
4. Center's Therapeutic Classification: 1-P
5. Status of Application: Active
6. Name of Sponsor/Applicant: Rhone-Poulenc Rorer
Pharmaceuticals Incorporated
7. Addresses: 500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107
8. Product Names:
 - (a) Proprietary: (to be established)
 - (b) Established: Enoxaparin Injection
USAN: Enoxaparin
USP: -
 - (c) Code Name and Number: RP54563, PK10169
 - (d) Other Registered Names: Clexan, Clexane, Lovenox
9. Dosage Form(s), Strength/Potency, and Route of Administration: Injection; 100 mg/mL, 30 mg and 40 mg prefilled syringes; subcutaneous injection
10. Proposed Marketing Status: Rx.
11. Pharmacological Category and Indication(s):
Prevention of deep vein thrombosis.
12. Structural Formula, Chemical Name, Empirical Formula, Molecular Weight:



13. Structural Formulas of Related Compounds:
RD Heparin, Fragmin (Both LMW Heparins)

14. Document Date(s): December 30, 1991

15. CDB Date: -

16. Division Date: January 3, 1992

17. Assigned Date: January 9, 1992

18. Supporting Documents:

DMF

DMF

IND 31,532

19. Related Documents:

IND

IND

IND

IND

IND

20. Remarks:

I. Outstanding Consults and Requests:

- A. Stability consult to HFD-715 for a statistical evaluation of drug product stability data.
- B. Microbiology consult to HFD-160 for a microbiological evaluation of the drug product sterile fill into Hypak syringes.
- C. EER Memo to DMPQ (HFN-320) for the evaluation of the manufacturing facilities.
- D. Environmental Assessment (E.A.) to the E.A. Officer Phil Vincent, Ph.D. (HFD-102).

II. Uncompleted reviews:

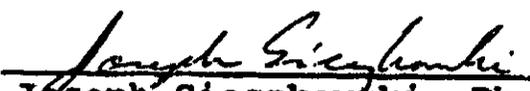
A. DMF

B. DMF

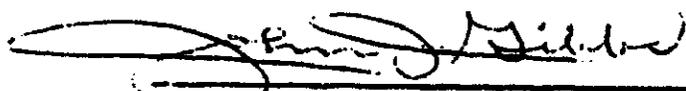
21. Conclusion and Recommendations (Include Consulting Review Status)

The chemistry, manufacturing, controls and stability for the drug substance and drug product have not been adequately established. The application should not be approved and the applicant notified of this by letter.

22.


Joseph Sieczkowski, Ph.D. 5-12-52
Review Chemist, HFD-180

23.


John J. Gibbs, Ph.D.
Supervisory Chemist, HFD-180

JUL 27 1992

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #20-164 CHEM REVIEW #2 REVIEW DATE: 1 JUL 92

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
AMENDMENTS: [AZ]	26 MAR 1992	31 MAR 1992	02 APR 1992
[AC]	19 JUN 1992	22 JUN 1992	24 JUN 1992

NAME & ADDRESS OF APPLICANT : Rhone-Poulenc Rorer
500 Arcola Road, P.O. Box 1200
Collegeville, PA 19426-0107

DRUG PRODUCT NAME

Proprietary: None
Nonproprietary/USAN: enoxaparin injection
Code Name/#: RP54563, PK10169
Chem.Type/Ther.Class: 1-P

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION:

Prevention of deep vein thrombosis

DOSAGE FORM: Injection

STRENGTH: 100 mg/mL, 30 mg in a prefilled syringe

ROUTE OF ADMINISTRATION: subcutaneous injection

HOW DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

See Chemistry Review #1

SUPPORTING DOCUMENTS: None

RELATED DOCUMENTS (if applicable): None

CONSULTS:

Microbiology: Carol Vincent, Microbiologist, HFD-160
Consult request date: 24 JUN 1992

Pharmacology: Dr. Tanveer Ahmad, Pharmacologist, HFD-180
Consult request date: 24 JUN 1992

The two consult reviews are in progress; neither consult request has been completed.

REMARKS/COMMENTS:

As noted in the cover letter to the March 26, 1992 amendment, Rhone-Poulenc Rorer is responding by Amendment to:

- a) the HFD-180 letter of February 24, 1992,
- b) a telephone information request by the CSO, Bronwyn Collier, for the chemist Dr. Joseph Sieczkowski, and
- c) a request, for English language translations of the approved package inserts used in France and Germany, by Dr. Stephen B. Fredd, Division Director of HFD-180.

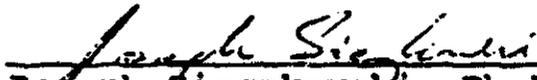
However, the response to the letter of February 24, 1992 in the March 26, 1992 amendment was partial and the completed response to the letter was received in the amendment of June 19, 1992.

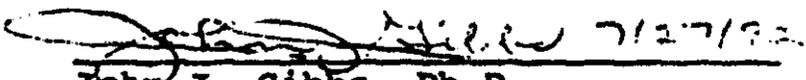
The information from both amendments was handled in the following manner:

- A. The amendment of March 26, 1992 (Appendix II) and the amendment of June 19, 1992 were consulted to the HFD-180 pharmacologist, Dr. Tanveer Ahmad, and to the microbiologist, Carol Vincent, Microbiologist, HFD-160.
- B. The information from the March 26, 1992 amendment (Appendix I and III) was received by this reviewer and it appears adequate. The information provided in Appendix I and III was requested from Rhone-Poulenc Rorer as an additional help to the review process rather than a deficiency in the application.
- C. The information from the March 26, 1992 amendment (Appendix IV) was distributed to Dr. S. Fredd. The information provided in Appendix IV concerning the English language translation of the French and German package inserts was requested by Dr. Fredd at the meeting on November 13, 1991 to discuss the NDA Refusal to File letter with Rhone-Poulenc Rorer.

CONCLUSIONS & RECOMMENDATIONS:

There are no issues concerning chemistry with respect to Rhone-Poulenc Rorer's amendments, AZ (March 26, 1992) and AC (June 19, 1992). Information from both amendments were sent for consult reviews to the microbiologist (HFD-160) and pharmacologist (HFD-180), and any deficiencies noted in the consult reviews will be sent to Rhone-Poulenc Rorer. No other issues are noted and no letters issued with respect to the information submitted in these amendments.


Joseph Sieczkowski, Ph.D. 07-27-92
Review Chemist, HFD-180


John J. Gibbs, Ph.D. 7/27/92
Supervisory Chemist, HFD-180

cc:

- ✓ NDA 20-164
 - ✓ HFD-180/SFredd
 - HFD-82/Lipov
 - ✓ HFD-180/Division File
 - ✓ HFD-181/CSO
 - HFD-180/JGibbs
 - HFD-102/CKumkumian [#1 only]
 - ✓ HFD-180/JSieczkowski
- R/D Init by: JGibbs/7-2-92 filename: Wp chem/N\20164207.2JS
dob/DRAFT 7-16-92/F/T 7-23-92

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

COO
4/2

DMF 9472

CHEM REVIEW #2

REVIEW DATE: 6 JAN 1993

JAN 14 1993

SUBMISSION TYPE

DATES

	<u>DOCUMENT</u>	<u>CDER</u>	<u>REVIEW</u>	<u>LETTER</u>
ORIGINAL	23 DEC 91	26 DEC 91	4 MAY 92	4 May 92
AMENDMENT	20 JUL 92	24 JUL 92	Rev. #2	None

NAME & ADDRESS OF HOLDER AND US REPRESENTATIVE (IF FOREIGN):

Holder:

L

(Representative): US Agent
Rhone-Poulenc Rorer Pharma. Inc.
Attention: Margaret S. Masters
500 Virginia Drive
Fort Washington, Pennsylvania 19034
(215) 628-6000

PRODUCT NAME

Proprietary: N/A
Nonproprietary/USAN: Heparin Sodium
Code Name/#: N/A
Chem. Type/Ther. Class: Derived from a natural product,
porcine intestinal mucosa

PHARMACOLOGICAL CATEGORY Anticoagulant

INDICATION: N/A

DOSE FORM: N/A

STRENGTH: N/A

ROUTE OF ADMINISTRATION: N/A

SPONSOR FOR WHICH DMF IS IN SUPPORT:

NDA 20-164

CONTACT PERSON AT APPLICANT: Judith R. Plon of
Rhone-Poulenc Rorer Inc.

DATE OF LETTER OF AUTHORIZATION: 18 December 1991

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

See "The Merck Index", Eleventh Edition, "4571 Heparin".

SUPPORTING DOCUMENTS: None

RELATED DOCUMENTS (if applicable): None

CONSULTS: None

REMARKS/COMMENTS:

The DMF updated replacement pages, which were the result of responding to the information request questions in the letter of May 4, 1992, are the following:

CONCLUSIONS & RECOMMENDATIONS:

has responded satisfactorily to the information request letter of May 4, 1992. No other issues are pending. should be allowed as a supplier of bulk heparin sodium to Rhone-Poulenc Rorer Inc. for the manufacture of enoxaparin.


Joseph Sieczkowski, Ph.D. *Jan 14, 1993*
Review Chemist, HFD-180


John J. Gibbs, Ph.D. *11/14/93*
Supervisory Chemist, HFD-180

CC:

DMF 9472

HFD-180/Division File/NDA 20-164

HFD-180/SFredd

~~HFD-82/Lipov~~

HFD-181/CSO

HFD-180/JSieczkowski

R/D Init by:JGibbs/1-12-93

dob DRAFT 1-12-93/ F/T 1-14-93

filename: Wp c:\chem\D\09472301.2JS

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA 20-164 CHEM.REVIEW #3 REVIEW DATE: 11 Jan 1993

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
AMENDMENT [AZ]	26 MAR 1992	31 MAR 1992	2 APR 1992
[AC]	19 JUN 1992	22 JUN 1992	24 JUN 1992
[BC]	29 JUN 1992	30 JUN 1992	6 JUL 1992
[BC]	11 AUG 1992	13 AUG 1992	18 AUG 1992
[BC]	17 DEC 1992	18 DEC 1992	22 DEC 1992
[BC]	24 DEC 1992	29 DEC 1992	30 DEC 1992
[AI]	13 AUG 1992	19 AUG 1992	-
[BL]	8 DEC 1992	10 DEC 1992	-
ADDENDUM [AZ]	8 JAN 1993	11 JAN 1993	13 JAN 1993

NAME & ADDRESS OF APPLICANT: Rhone-Poulenc Rorer
500 Arcola Road, P.O. Box 1200
Collegeville, PA 19426-0107

DRUG PRODUCT NAME
Proprietary: Lovenox Injection
Nonproprietary/USAN: enoxaparin injection
Code Name/#: RP54563, PK10169
Chem.Type/Ther.Class: 1-P

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION:
Prevention of deep vein thrombosis.

DOSAGE FORM: Injection

STRENGTHS: 100 mg/mL, 30 mg in a prefilled syringe

ROUTE OF ADMINISTRATION: subcutaneous injection

DISPENSED: X Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
See Chemistry Review #1.

SUPPORTING DOCUMENTS:

DMF

DMF

RELATED DOCUMENTS (if applicable): None

CONSULTS:

MICROBIOLOGY: Carol Vincent, Microbiologist, HFD-160.
CONSULT REQUEST DATE: 24 JUN 1992

PHARMACOLOGY: Dr. Tanveer Ahmad, Pharmacologist, HFD-180.
CONSULT REQUEST DATE: 24 JUN 1992

The amendment of March 26, 1992 (Appendix II) and the amendment of June 19, 1992, were consulted to the HFD-180 pharmacologist, Dr. Tanveer Ahmad, and to the HFD-160 microbiologist, Carol Vincent.

CONSULTS RETURNED:

Pharmacologist's Review of NDA 20-164.
REVIEW DATE: 29 SEP 1990
(The year should be 1992)
STAMP DATE: 7 OCT 1992

Microbiologist's Review of NDA 20-164.
Micro. Rev. #2: **REVIEW DATE:** 6 JAN 1993
Micro. Rev. #3: **REVIEW DATE:** 7 JAN 1993

REMARKS/COMMENTS:

- 1) The AZ (March 26, 1992), and AC (June 19, 1992), amendments were consulted to pharmacology (HFD-180) for a recommendation concerning the adequacy or inadequacy of the safety test, the pyrogen test, and the depressor substance test for enoxaparin. The information was reviewed and no recommendations were made. Therefore these tests will remain for enoxaparin in the NDA.
- 2) The AZ (March 26, 1992), and AC (June 19, 1992), amendments were consulted to microbiology (HFD-160) for a review concerning enoxaparin injection sterility testing, pyrogen testing, and validation information for sterility assurance of the fill manufacturing process

The microbiologist's review determined that the microbiological tests (drug substance pyrogen test and microbial limit; drug product pyrogen, and sterility) performed in the NDA were acceptable. The application remained not recommended for approval on the basis of microbiological quality and sterility assurance.

Pending Items: Microbiologist's review concludes, "Recommend not approval for sterility assurance."

NOTE: Items 1) and 2) above complete Chemistry Review #2 (Review date: July 1, 1992). No chemistry issues are pending for the two amendments under Chemistry Review #2, AZ/March 26, 1992, and AC/June 19, 1992.

- 3) BC/June 29, 1992 - Deficiencies in this amendment were conveyed to Rhone-Poulenc Rorer by the CSO (Memo by Kati Johnson, December 23, 1992). Responses to the deficiencies were received in the BC amendment of December 24, 1992. The additional comments on this Amendment (BC/June 29, 1992) are in the form of recommendations to and requests for commitments from Rhone-Poulenc Rorer.

Pending Items: Recommendations and Requests

- 4) BC/August 11, 1993 - This amendment contains the corrected versions of Appendices XIV, XV, and XVI which are a part of the June 29, 1992, Amendment. The revised appendices are:
- a. Appendix XIV/Engineering Drawing of Complete Syringe System.
 - b. Appendix XV/Statistical Evaluation of Enoxaparin Stability Data for the Anti-Xa and Anti-coagulant Activity.
 - c. Appendix XVI/Anti-IIa Activity Statistical Analysis (Bioavailability parameters).

Review Comments:

- a. Appendix XIV was found satisfactory in this review (Chemistry Review #3).
- b. Appendix XV was sent for a statistical review to Biometrics (HFD-715).

Status (Appendix XV):

See the Statistical Review and Evaluation of the enoxaparin injection stability data submitted in the August 11, and December 17, 1992, amendments by Daphne Lin, Ph.D. dated January 4, 1993. See chemist's comments in this review under Item 13.f) (BC/12-17-92).

- c. The Appendix XVI information is in response to a Biopharmaceutics request.

Pending Items: None (as concerns chemistry).

- 5) BC/December 17, 1992 - This amendment completes the responses to the May 6, 1992 Agency letter which was initially responded to by the June 29, 1992 amendment. The following was provided in this amendment (December 17, 1992) as modified by the June 1, 1992, telephone conference (Dr. Gibbs and Rhone-Poulenc Rorer):
- a. Additional information in response to request #8 of the June 29, 1992 letter.
 - b. Additional information in response to request #11(c) of the June 29, 1992, letter.
 - c. Additional information in response to request #13, (a) through (g), of the June 29, 1992, letter.

Status (Request #13):

See the Statistical Review and Evaluation of the enoxaparin injection stability data submitted in the August 11, and December 17, 1992, amendments by Daphne Lin, Ph.D., dated January 4, 1993.

Pending Items: Recommendation and Requests

- 6) BC/December 24, 1992 - This amendment was submitted in response to the telephone conference of December 23, 1992 between Kati Johnson, CSO, HFD-180, and Judith Plon, Director of Regulatory Affairs, Rhone-Poulenc Rorer concerning Rhone-Poulenc Rorer's deficient responses to Items 3.D.(4), 3.D.(5), and 5.B. in the Agency letter of May 6, 1992, to Rhone-Poulenc Rorer.

Review Comment:

- a. Item 3.D.(4)/NOT ADEQUATE.
- b. Item 3D.(5)/Future response; NOT ADEQUATE.
- c. Item 5.B./ADEQUATE.

Pending Items: Deficiencies for Items 3.D.(4) and 3.D.(5), Item H.

- 7) AI/August 13, 1992 - This amendment was submitted in response to the June 16, 1992, HFD-180, Information Request Letter which conveyed questions concerning fill validation and other microbiological issues from the microbiologist's consult review, Microbiologist Review #1 (May 7, 1992), of the original NDA. Microbiologist's Review #3 (January 7, 1993) of this amendment concludes, "Recommend not approval for sterility assurance."

Pending Items: Attached to Microbiologist Review #3 is a "Draft of Letter to Applicant" (pages 12 - 16 and

pages 1 - 4) which contains all the microbiology deficiencies.

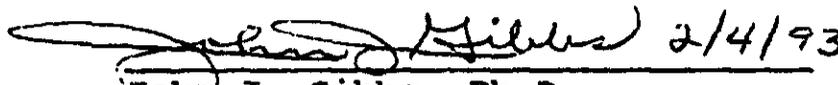
- 8) BL/December 8, 1992 - This amendment was submitted in response to the FDA Approvable Letter of November 20, 1992, which requested FPL. This amendment was reviewed in this chemistry amendment under F. Labeling. The CSO has reviewed this amendment in the "Consumer Safety Officer Review" dated December 16, 1992.

Pending Items: Recommendations, requests, and 21 CFR requirements, Item H.

CONCLUSIONS & RECOMMENDATIONS:

The chemistry, manufacturing, controls, and stability for the drug substance and drug product have been adequately established. Two chemistry issues remain pending and a number of chemistry recommendations and requests should be forwarded to Rhone-Poulenc Rorer. With respect to microbiology; the application should not be approved and the applicant notified of this by letter.


Joseph Sieczkowski, Ph.D. *Feb 4, 1993*
Review Chemist, HFD-180
(January 11, 1993)


John J. Gibbs, Ph.D. *2/4/93*
Supervisory Chemist, HFD-180

cc:
Orig. NDA 20-164
HFD-180/Division File
HFD-181/CSO
HFD-180/JSieczkowski/1-11-93
R/D Init by:JGibbs/1-12-93 filename: WP: c:\chem\N\20164301.3JS
dob DRAFT 1-19-93/F/T 2-3-93

FEB 5 1993

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA 20-164 CHEM. REVIEW #4 REVIEW DATE: 3 FEB 1993

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
AMENDMENT [AC]	29 JAN 1993	1 FEB 1993	2 FEB 1993

NAME & ADDRESS OF APPLICANT: Rhone-Poulenc Rorer
500 Arcola Road, P.O. Box 1200
Collegeville, PA 19426-0107

DRUG PRODUCT NAME

<u>Proprietary:</u>	Lovenox Injection
<u>Nonproprietary/USAN:</u>	enoxaparin injection
<u>Code Name/#:</u>	RP54563, PK10169
<u>Chem. Type/Ther. Class:</u>	1-P

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL. CATEGORY/INDICATION: Prevention of deep vein thrombosis

<u>DOSAGE FORM:</u>	Injection
<u>STRENGTHS:</u>	100 mg/mL; 30 mg in a prefilled syringe
<u>ROUTE OF ADMINISTRATION:</u>	subcutaneous injection
<u>DISPENSED:</u>	<input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
See Chemistry Review #1.

SUPPORTING DOCUMENTS:

DMF
DMF

RELATED DOCUMENTS (if applicable): None

CONSULTS:

Pharmacology (HFD-180):	"Pharmacologist's Review of NDA 20-164"; Stamp Date 7 Oct 1992. No recommendations were made; no information requests were made to Rhone-Poulenc Rorer; no issues pending.
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Statistics (HFD-715):	"Statistical Review and Evaluation" of enoxaparin injection stability data; Review Date 4 Jan 1993. Recommends two year expiry dating
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for the 20 mg and 40 mg prefilled syringes; no issues pending.

Microbiology (HFD-160):

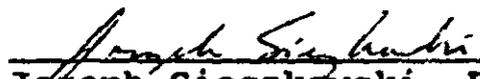
"Microbiologist's Review #3" (7 January 1993) of fill validation and other microbiological issues (AI amendment of 13 August 1992) concluded: "Recommend not approval for sterility assurance." Issues conveyed to Rhone-Poulenc Rorer in the Information Request letter of 15 January 1993. Response to that letter received in this Amendment and Consulted to the microbiologist for review.

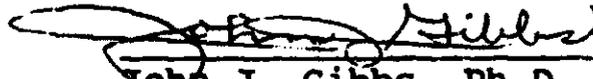
REMARKS/COMMENTS:

1. With respect to chemistry, there are no remaining issues.
2. With respect to microbiology, the consult review of their amendment, AC/29-01-93, is pending.
3. A CGMP Facilities Update Request was submitted to Compliance (2 February 1992). No response to date.

CONCLUSIONS & RECOMMENDATIONS:

No chemistry issues remain pending and the application should be approved with respect to chemistry. Microbiology issues [Information Request #2, 15 January 1993 Agency letter] are under review. If the microbiologist's review finds the responses adequate, then the application should be approved with respect to microbiology. With respect to Methods Validation, we should request the assistance of Rhone-Poulenc Rorer in drug substance and drug product methods validation.


Joseph Sieczkowski, Ph.D. Feb. 5, 1983
Review Chemist, HFD-180


John J. Gibbs, Ph.D. 2/5/73
Supervisory Chemist, HFD-180

CC:
Orig. NDA 20-164
HFD-180/Division File
HFD-180/JSieczkowski
HFD-181/CSO
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**ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT
FOR**

Lovenox (enoxaparin)

Injection

NDA 20-164

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-164

Lovenox (enoxaparin)

Injection

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application, the Rhone-Poulenc Rorer has conducted a number of environmental studies and prepared an abbreviated environmental assessment (21 CFR 25.31a(b)(5) (attached) which evaluates the potential environmental impacts of the manufacture and use of the product. Enoxaparin is a depolymerized heparin obtained by alkaline degradation of heparin benzyl ester from porcine mucosa. Enoxaparin is indicated for prevention of deep vein thrombosis, which may lead to pulmonary embolism, following hip replacement surgery.

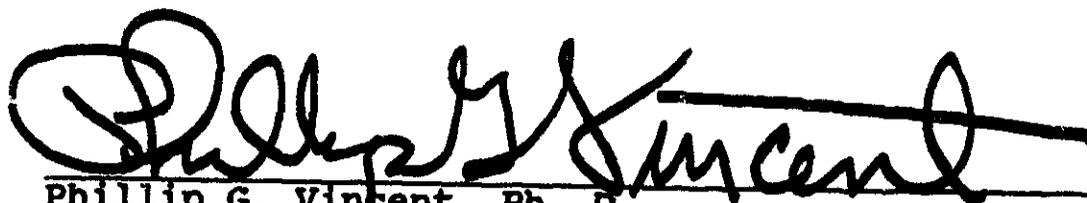
The drug substance and drug product is manufactured and packaged in France. The firm has provided documentation from the French authorities that they are in compliance with French environmental law. The will be used in hospital settings for in-patients. Disposal is by hospitals as medical waste and returned or damage product as infectious waste.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected

adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Any residues of enoxaparin or its major metabolites entering the environment as a result of administering the drug to humans are expected to rapidly degrade.

JAN 13 1993

DATE



Phillip G. Vincent, Ph. D.
Environmental Assessment Officer
Center for Drug Evaluation and Research

1/13/93
DATE



Charles S. Kumkumian, Ph. D.
Assistant Director (Chemistry)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment: Environmental assessment
MSDS
FPL

Lovenox® (enoxaparin) Injection
NDA #20-164

Environmental Assessment

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COLLEGEVILLE, PA 19426-0107
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NDA NO.: 20-164
FORM: FDA 356h
SECTION: (d)(1)
ITEM: (iii)

ENOXAPARIN INJECTION

TITLE: Environmental Assessment

1. **DATE:** November 23, 1992
2. **APPLICANT:** Rhône-Poulenc Rorer Pharmaceuticals Inc.
3. **ADDRESS:** 500 Arcola Road
Collegeville, PA 19426-0107

4. **Description of the Proposed Action:**

a) Requested Action

Rhône-Poulenc Rorer has filed a new drug application, NDA 20-164 for Lovenox® (enoxaparin) Injection.

The drug substance, enoxaparin, is a depolymerized heparin obtained by alkaline degradation of heparin benzyl ester from porcine mucosa. The starting material is Heparin Sodium USP (porcine intestinal mucosa). Additional information as well as physical and chemical characteristics of enoxaparin have been provided in Appendix II.

Enoxaparin, a low molecular weight heparin categorized as an anticoagulant, is a novel antithrombin whose mode of action resembles that of heparin in that it binds reversibly to antithrombin-III and catalyzes its inhibition of activated clotting factors, in particular, factors Xa and IIa (thrombin). Enoxaparin's mode of action differs from that of heparin in that its anti-Xa: anti-IIa ratio is greater than that of heparin. Partial loss of the original catalytic activity of heparin occurs during enoxaparin's preparative alkaline depolymerization process with its ability to catalyze thrombin inhibition decreasing to a much greater extent than its ability to catalyze the inhibition of factor Xa.

The drug product will be provided as a prefilled syringe containing only enoxaparin at a strength of 30 mg enoxaparin and Water for

Injection. The drug product contains enoxaparin at a concentration of 100 mg/mL and is filled at a volume of 0.3 mL. The drug product is packaged in syringes supplied by Becton-Dickenson as follows:

**Syringes HYPAK SCF 0.5 mL, 26 G, 1/2" Needle
Stoppers PH 701/50 C black**

b) Need for the Action

Enoxaparin is a low molecular weight heparin which has antithrombotic properties. Clinical studies have demonstrated that enoxaparin offers a safe and effective prophylactic therapy for deep vein thrombosis when administered postoperatively to patients undergoing hip replacement surgery. Approval of this action would make this therapy, already in use in other parts of the world, available to patients in the U.S.

c) Location Where the Product Will Be Produced and the Types of Environments Adjacent to Those Locations.

The drug substance and drug product will be manufactured and packaged in RPR facilities in France. Please note that enoxaparin drug products have been produced at these plants, on a commercial basis, since their approval in that country in 1987.

Drug Substance - Production Facility

**Rhône-Poulenc Rorer
Villeneuve-La-Garenne Plant
35, Avenue Jean Jaures
92390 VILLENEUVE-LA-GARENNE
FRANCE**

Drug Product - Production Facility

**Rhône-Poulenc Rorer
Propharm
Maisons-Alfort
180, rue Jean Jaures
94700 MAISONS-ALFORT
FRANCE**

The types of environments present at the locations noted above are as follows:

The Rhône-Poulenc Rorer Villeneuve-La-Garenne Plant is located in an industrially zoned area some 5 km northwest of Paris in the "Department des Hauts de Seine.

The Rhône-Poulenc Rorer Maisons-Alfort plant is located on 23,000 square meters in an urban residential area surrounded by private houses and apartment buildings.

Both locations have soil that is free draining with good structure.

Both facilities are provided with appropriate potable water sources and sewage connection per local requirement.

d) To the Extent Possible, Locations Where the Products Will Be Used and Disposed of:

Enoxaparin injection will be used in hospitals for in-patient use throughout the United States.

Disposal of empty syringes (Use of the product results in an empty syringe with no drug residue) by the hospitals using the product is, to the best knowledge of Rhône-Poulenc Rorer, through incineration of the used syringes by a licensed infectious waste disposer similar to that described below for the returned goods to Rhône-Poulenc Rorer.

Return of Lovenox® (enoxaparin) Injection will be made to one of two Rhône-Poulenc Rorer facilities located in Fort Washington, Pa. or Kankakee, Il. Both facilities are located in an industrially zoned area. In order to prevent release to the environment at these facilities, the following precautions will be taken in handling/disposing of returned goods:

- 1) Returned or Damaged Goods (syringes) still in the original container must be placed into an Infectious Waste disposal box. The box must be lined with two (2) 1.5 mil thick plastic bags which must be labeled with the words "Infectious Waste:." These bags and boxes are provided by a state licensed hazardous waste transporter.

If a syringe is not in its original container, it must be placed into a "Sharps" disposal container. The "Sharps" disposal container will be placed into an Infectious Waste disposal box.

- 2) Each bag must be individually tied.
- 3) Each box must be sealed and indicate the following information on the outer container:
 - a) The words "Infectious Waste" and the universal "Biohazard" symbol;
 - b) The name, address and telephone number of the generator of the waste, and the date the waste was generated;
 - c) The name of the approved state licensed hazardous waste transporter.
- 4) Prior to removal and transportation by a licensed transporter, a State Infectious Waste Manifest must be completed. The manifest is supplied by the licensed transporter.
- 5) The waste will be transported by a state licensed hazardous waste transporter to a licensed infectious waste disposal facility, where the waste will be destroyed in accordance with federal, state and local regulations.
- 6) Upon completion of the destruction, the manifest will be signed and dated by an authorized hazardous waste facility employee and returned.
- 7) The generator's copy and returned copies of the manifest will be maintained for at least five (5) years after the date of shipment by the appropriate safety department at the two Rhône-Poulenc Rorer sites.

The state licensed infectious waste transporter used by Rhône-Poulenc Rorer is:

Fort Washington, PA Site

There is no disposal at the _____ site. _____ transports the material through a related company, _____ to the following licensed infectious waste disposal facility:

Kankakee, IL Site

There is no disposal at the _____ transports the material to the following licensed infectious waste disposal facility:

_____ destroy the material by incineration. Appendix I contains applicable permits for both transporters plus a description of the disposal method used by the disposers.

5. Identification of Chemical Substances That are Subject to This Proposed Action

Appendix II contains a description of the chemical and physical properties of the drug substance, enoxaparin used in the manufacture of Lovenox[®] Injection. Also included are Material Safety Data Sheets for the drug substance, enoxaparin, and for the drug product Lovenox[®] Injection.

6. Introduction of Substance into the Environment

Villeneuve-La-Garenne

Appendix III contains a list of material used in the manufacture of enoxaparin drug substance at Villeneuve-La-Garenne.

The controls in place at the facility for the expected emissions are as follows:

Air Controls

Synthesis of intermediates are manufactured in a closed reaction vessel linked to the atmosphere through vents fitted with filters.

The manufacturing area is supplied with filtered air. The efficiency of the incoming air filtration system is 99.99%. The system is capable of retaining particles over 0.3 microns. The air discharged from the area is also filtered. The preparation area is also supplied with filtered air, 90% of the air is recycled.

Liquid Controls

Hazardous waste associated with the manufacturing process is stored in tanks specially intended for this purpose, then sent to a company which is authorized for waste disposal.

Currently, these companies are:

For non-chlorinated solvent liquid waste

1.

2.

For chlorinated solvent liquid waste

1.

Solid Controls

General trash and paper at the site are collected, then sent out to a company who disposes of it in compliance with local rules and regulations.

Currently, this company is:

Solid hazardous waste is collected, kept in a special storage area, then sent to a company who is authorized to dispose of the material for disposal and destruction.

Currently, this company is:

Maisons-Alfort

Appendix III contains a list of materials used in the manufacture of Enoxaparin Injection at Maisons-Alfort.

The controls in place at the facility for the expected emissions are as follows:

Air Controls

As this is a product labeled as sterile, class 100 conditions are maintained in the areas of solution filtration and syringe filling and class 10,000 conditions are maintained in the solution preparation area by means of absolute HEPA filters.

The filtered air leaving the manufacturing area is 90% recycled back to the manufacturing area filtration system. The remaining 10% is vented to the outside. The efficiency of the filtering system for in-coming air is 99.999% and retains all particles larger than 0.2 micron diameter.

Liquid Controls

All fluid wastes are treated through a liquid waste treatment station before being discharged to the exterior sewage network.

Solid Controls

General trash and paper are collected by

Solid hazardous waste is collected by

Certification

An official statement from the French Ministry which certifies that both facilities are in compliance with local French environmental regulations and that the manufacturing processes of both the drug substance and drug product also comply with the environmental regulations in France has been provided in Appendix IV. It should be noted that this letter refers to the product as "Clexane" which is the trade name used in France for enoxaparin injection. For the U.S. market, the trade name will be Lovenox[®] Injection.

The product is currently produced at the two sites for marketing in other parts of the world. Approval for the U.S. market would result in approximately _____ year additional enoxaparin production at the Villeneuve-La-Garenne site and approximately _____ additional 30 mg syringes per year at the Maisons-Alfort site. This figure is based on the fifth production year estimate following approval.

Standard clinical practice for the administration of the disposal of empty syringes by the hospitals using the product is, to the best knowledge of Rhône-Poulenc Rorer, through incineration of the used syringes by a licensed infectious waste disposer similar to that _____ described for the returned goods to Rhône-Poulenc Rorer.

7. Fate of Emitted Substances in the Environment

Due to the measures taken at the two manufacturing sites, there is no expected emission to the environment from the production of Lovenox[®] Injection.

For U.S. production, a maximum expected emitted concentration (MEEC) from use of the product, would be as follows:

Disposal of any returned filled syringes is through incineration and since incineration is considered final disposal, there is no emission to the environment.

6. Environmental Effects of Released Substances

From the information given in the above section concerning the lack of any expected release to the environment from the production, use, and disposal of this product, there is no environmental effect expected.

However, information concerning the low toxic effect of enoxaparin in several mammalian species (mouse, rat, and dog) determined through preclinical studies is included in Item 15, Appendix V.

9. Use of Resources and Energy

The manufacture of Enoxaparin Injection for distribution in the U. S. will require the use of less than 2% of the plant capacity at Villeneuve-La-Garenne and less than 2% of the plant capacity at Maisons-Alfort.

The use and disposal of the product in the U.S. will not affect any endangered species or any site listed in the U.S. National Register of Historic Places.

10. Mitigation Measure

Since the information given in the preceding sections has indicated that no environmental effect is expected, Rhône-Poulenc Rorer sees no necessity for any mitigation measures.

11. Alternatives to the Proposed Action

Due to the controls in place at the manufacturing sites, the low waste stream levels which result from the use of the product, the incineration of any returned product, and the low level toxic effect of Enoxaparin Injection,

Rhône-Poulenc Rorer
Environmental Assessment
Enoxsarin Injection
Page - 10 -

Rhône-Poulenc Rorer does not consider it necessary to formulate any alternatives to this action. The overall effect of this action will be to the positive, i.e., a new treatment for prevention of deep vein thrombosis following hip replacement surgery.

12. List of Preparers

The following individuals participated in the preparation of this EA

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**Mr. A. Grimal
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**Dr. R. P. Gural
Director, World Wide Regulatory Affairs Operations
Rhône-Poulenc Rorer
Antony, France**

**J. C. Crubezy
Rhône-Poulenc Rorer
Villeneuve-la-Garenne, France**

13. Certification

Appendix IV contains the certification as to the veracity of this document.

14. References

There are no references to report. For the reasons given above, this drug is not considered environmentally controversial.

15. Appendices

The following is a list of appendices referenced in this report and contained in this item.

- | | | |
|----------------------|--|------------------|
| Appendix I: | Permits for disposal for Fact sheet for | Method of |
| Appendix II: | Enoxaparin Drug Substance: Physical and Chemical Characteristics
Material Safety Data Sheet: enoxaparin
Material Safety Data Sheet: Lovenox® Injection
Packaging Specifications | |
| Appendix III: | Materials List: Enoxaparin Drug Substance and Product | |
| Appendix IV: | Certification: Rhône-Poulenc Rorer
Certification: Ministère de L'environnement, République Française | |
| Appendix V: | Drug Safety Studies: Enoxaparin | |

As indicated in the previous items no additional testing was required to support the proposed action because Enoxaparin Injection is not environmentally controversial.

Appendix VI: Environmental Impact Assessment from

Appendix VII: French Regulations and Decrees

1. Circular and Directive Dated June 6, 1953.
2. Law No. 76-663 Dated July 19, 1976.
3. Decree No. 77-1133 Dated September 21, 1977.
4. Authorization Decree from the Prefect of Morbihan Dated July 13, 1982.
5. Authorization Decree from the Prefecture Du Val De Marne Dated December 18, 1986.
6. Authorization Decree from the Prefect of Morbihan Dated October 7, 1988.
7. Authorization Decree from the Prefect of the Hauts De Seine Dated May 29, 1991.

Appendix I

Appendix I

This attachment contains the following permits and procedures pertaining to the disposal of returned stocks of Lovenox[®] Injection by the two licensed infectious waste transporters indicated in Item 4, entitled "Description of the Proposed Action".

1.

2.

13 Pages

Redacted

Appendix II

**Enoxaparin Drug Substance:
Physical and Chemical Characteristics**

**Material Safety Data Sheets:
Enoxaparin
Lovenox® Injection**

Packaging Specifications

15 Pages

Redacted

PAGES 47-54 OMITTED

Appendix III

**Materials List:
Enoxaparin Drug Substance
and
Loventor® Injection**

PAGE 56 OMMITTED CBI

Appendix IV

**Certification:
Rhône-Poulenc Rorer**

**Ministere de L'environnement
Republique Française**

CERTIFICATION

The undersigned certify that the information contained in this Environmental Assessment Report is true, accurate, and complete to the best of our knowledge and that of Rhône-Poulenc Rorer Pharmaceuticals Inc.

24-Nov-92

Date

Donald F. Dwyer

Donald F. Dwyer
Manager
Regulatory Affairs

11-24-92

Date

Mark Adelsberger

Mark Adelsberger
Manager
Regulatory Control

24. XI. 1992

Date

Philippe Jospin

Philippe Jospin
Senior Director
Quality Assurance

November 26, 1992

Date

Jean-Pierre Bravard

Jean-Pierre Bravard
Manager
Quality Assurance Active Ingredients

DIRECTION DE L'EAU
ET DE LA PREVENTION DES POLLUTIONS
ET DES RISQUES

Neuilly, le 08 AVR. 1991

SERVICE DE L'ENVIRONNEMENT INDUSTRIEL

Poste : 26.23
N.REF. : DEPPR/SEI/AG/MF N°
(A Rappeler)

**O B J E T : Production d'ENOXAPARINE et de CLEXANE sur les sites
RHONE-POULENC-RORER en France -**

Les productions d'ENOXAPARINE (matière active) et de CLEXANE (médicament) s'effectuent sur les sites RHONE-POULENC-RORER respectivement de VILLENEUVE-la-GARENNE et MAISONS-ALFORT. Ces deux usines respectent les lois et règles françaises concernant l'environnement. Les procédés de production d'ENOXAPARINE et de CLEXANE répondent également aux lois et règlements français en vigueur, en matière d'environnement.

The manufacture of ENOXAPARIN (drug substance) and CLEXANE (drug product) occur at the sites of RHONE-POULENC-RORER in VILLENEUVE-la-GARENNE and MAISONS-ALFORT respectively. The two facilities comply with local french environmental regulations. The manufacturing processes of ENOXAPARIN and CLEXANE are also in accordance with local french environmental regulations.

Le Directeur Adjoint de l'Eau
et de la Prévention des Pollutions et des Risques

François DEMARCO

Appendix V
Drug Safety Studies

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Appendix VI

Types I and II DMF

Environmental Assessment

From

5 Pages

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PAGES 84-257 OMITTED

Lovenox® (enoxaparin) Injection

IN-1107

Rev. 1/93

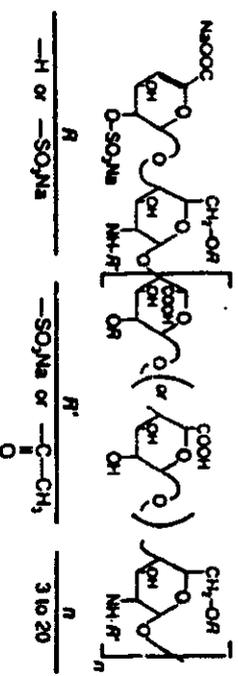
Lovenox® (enoxaparin) Injection

DESCRIPTION
Enoxaparin is a sterile, low molecular weight heparin for injection. Each syringe contains 30 mg enoxaparin in 0.3 mL Water for Injection. The approximate anti-factor Xa activity per syringe is 3000 IU (with reference to the V.H.O. First International Low Molecular Weight Heparin Reference Standard). Heparin is used in the heparin to make oxidation. The pH of the injection is 5.7-7. The solution is preservative free and intended for use only as a single dose injection.

Enoxaparin is obtained by alkaline degradation of heparin heparin ester derived from porcine intestinal mucosa. Its structure is characterized by a 2-O-sulfo-4-epoxyheptanoic acid group at the non-reducing end and a 2-N,6-O-desulfo-D-glucosamine at the reducing end of the chain. The substance is the sodium salt. The average molecular weight is about 4500. The molecular weight distribution is:

<2000 daltons 5.20%
2000 to 8000 daltons 2.85%
>8000 daltons 5.95%

STRUCTURAL FORMULA



CLINICAL PHARMACOLOGY

Enoxaparin is a low molecular weight heparin which has antithrombotic properties. In man enoxaparin is characterized by a higher ratio of anti-factor Xa to anti-factor IIa activity (1.25 ± 0.28) than unfractionated heparin (1.22 ± 0.13). Following the administration of a single subcutaneous dose of up to 80 mg of enoxaparin to healthy subjects, no appreciable change was observed in fibrinogen level and other parameters of hemostasis. At the recommended dose, single injections of enoxaparin do not significantly influence platelet aggregation or direct global clotting tests (i.e. prothrombin time [PT] or activated partial thromboplastin time [APTT]).

Pharmacodynamics

Maximum anti-factor Xa and antithrombin (anti-factor IIa) activities occur 3 to 5 hours after subcutaneous injection of enoxaparin. Mean peak anti-factor Xa activity was 0.16 IU/mL (1.68 IU/mL) and 0.26 IU/mL (2.63 IU/mL) after the 20 mg and the 40 mg clinically tested doses, respectively. Mean absolute bioavailability of enoxaparin based on anti-factor Xa activity is 87% in healthy volunteers. The volume of distribution of anti-factor Xa activity is about 6 L. Following i.v. dosing, the total body clearance of enoxaparin is 25 mL/min. Elimination half life based on anti-factor Xa activity was about 4.5 hours after subcutaneous administration. Following a 40 mg dose significant anti-factor Xa activity persists in plasma for about 12 hours. There appears to be no appreciable increase in anti-factor Xa activity after dosing for 3 days in young healthy subjects. Clearance, C_{max}, and AUC for anti-factor Xa activity following single and multiple s.c. dosing in elderly subjects with renal failure were close to those observed in normal subjects. An increase of 25% in the area under anti-factor Xa activity versus time curve was observed following once daily dosing in healthy elderly subjects for 30 days. The kinetics of anti-factor Xa activity in acute patients under long daily dosing are similar to those in normal subjects following i.v. dosing.

The kinetics of anti-factor Xa activity with time was parallel to the decay curve of plasma total radioactivity (¹²⁵I) in healthy volunteers. Following neovascular dosing of enoxaparin labeled with the gamma emitter, ¹²⁵I, 40% of radioactivity and 80% of anti-factor Xa activity were recovered in urine in 24 hours.

CLINICAL TRIALS

Lovenox has been shown to prevent postoperative deep vein thromboses (DVT) following hip replacement surgery. The data from two controlled clinical trials are summarized in the following table. In all studies, efficacy is based on all treated patients' analysis. In a double blind study, Lovenox 30 mg q12h sc was compared to placebo. Treatment was initiated within 12-24 hours post surgery and was continued for 10-14 days post operatively.

Treatment Group	Treatment Group	
	Lovenox 30 mg q12h n (%)	Placebo q12h n (%)
All Treated Patients Deep Vein Thromboses (DVT) (%)	50 (100%)	50 (100%)
Proximal DVT (%)	5 (10%)	23 (46%)
Distal DVT (%)	1 (2%)	11 (22%)
*p value versus placebo = 0.0002		
**p value versus placebo = 0.0134		

A double blind, multicenter study compared three dosing regimens of Lovenox. Treatment was initiated within two days post surgery and was continued for up to 7 days post operatively.

Dose	Treatment Group		
	Lovenox 30 mg QD n (%)	Lovenox 20 mg QD n (%)	Placebo n (%)
All Treated Patients Treatment Failures	191 (100%)	208 (100%)	199 (100%)
Total DVT (%)	40 (21%)	22 (11%)	27 (14%)
*p value versus Lovenox 30 mg QD = 0.0008			
**p value versus Lovenox 30 mg QD = 0.0188			

There was no significant difference between the 30 mg BID and 40 mg QD regimens. **INDICATION AND USAGE**
Lovenox (enoxaparin) injection is indicated for the prevention of deep vein thromboses and pulmonary embolism following hip replacement surgery.

CONTRAINDICATIONS

Lovenox injection is contraindicated in patients with active major bleeding, in patients with thrombocytopenia associated with a positive or vitro test for anti-platelet antibody in the presence of Lovenox injection, or in patients with hypersensitivity to Lovenox injection. Patients with known hypersensitivity to heparin or pork products should not be treated with enoxaparin.

WARNINGS

Lovenox injection is not intended for intramuscular administration. Lovenox cannot be used interchangeably (unit for unit) with unfractionated heparin or other low molecular weight heparins.

Lovenox should be used with extreme caution in patients with history of heparin-induced thrombocytopenia (Heparin/Heparin).

Lovenox injection like other anticoagulants should be used with extreme caution in conditions with increased risk of hemorrhage, such as bacterial meningitis, congenital or acquired bleeding disorders, active ulceration and angiodysplastic gastrointestinal disease, hemorrhagic stroke or shortly after brain, spinal or ophthalmological surgery. Bleeding can occur at any site during therapy with enoxaparin. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

Thrombocytopenia

Moderate platelet thrombocytopenia (platelet counts <100,000/mm³ and >50,000/mm³) occurred at a rate of about 2% in patients given Lovenox. 3% in patients given heparin, and 0% in patients receiving placebo in clinical trials. Thrombocytopenia of any degree should be monitored closely.

PRECAUTIONS

General
Lovenox injection should not be mixed with other injections or infusions. Lovenox injection should be used with care in patients with a bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration and hemorrhage. Elderly patients and patients with renal insufficiency may show delayed elimination of enoxaparin. Enoxaparin should be used with care in these patients.

Thrombotic events

If thrombotic events occur despite enoxaparin prophylaxis, Lovenox should be discontinued and appropriate therapy initiated.

Laboratory Tests

Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with Lovenox injection.

Drug Interactions

Lovenox injection should be used with care in patients receiving oral anticoagulants, and/or platelet inhibitors.

Loventox® (enoxaparin) Injection

IN-1107

Rev. 1/83

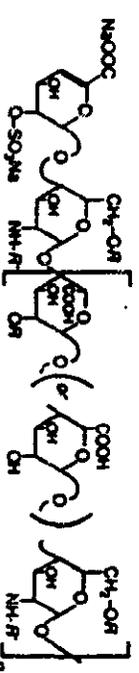
DESCRIPTION

Enoxaparin is a sterile, low molecular weight heparin for injection. Each syringe contains 30 mg enoxaparin in 0.3 mL of water for injection. The approximate anti-factor Xa activity per syringe is 2000 IU (with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard). Nitrogen is used in the heparin to inhibit oxidation. The pH of the injection is 5.5-7.5. The solution is preservative-free and intended for use only as a single dose injection.

Enoxaparin is obtained by selective degradation of heparin; heparin ester derived from porcine intestinal mucosa. Its structure is characterized by a 2-O-sulfo-4-O-methylsulfonic acid group at the non-reducing end and a 2-N,S-O-desulfo-D-glucosamine at the reducing end of the chain. The substance is the sodium salt. The average molecular weight is about 4500. The molecular weight distribution is:

<2000 daltons 5.20%
2000 to 3000 daltons 2.80%
>3000 daltons 5.10%

STRUCTURAL FORMULA



CHEMICAL PHARMACOLOGY

Enoxaparin is a low molecular weight heparin which has antithrombotic properties. In man enoxaparin is characterized by a higher ratio of anti-factor Xa activity (1.25 ± 0.05 IU/ml) than unfractionated heparin (1.22 ± 0.13). Following the administration of a single subcutaneous injection of 30 mg of enoxaparin to healthy subjects, no appreciable changes were observed in thromboplatelet count and other parameters of hemostasis. At the recommended doses, single injections of enoxaparin do not significantly influence platelet aggregation or fibrin gelatin clotting tests (i.e. prothrombin time [PT] or activated partial thromboplastin time [APTT]).

Pharmacokinetics
Maximum anti-factor Xa and antithrombin (anti-factor III) activities occur 3 to 5 hours after subcutaneous injection of enoxaparin. Mean peak anti-factor Xa activity was 0.16 IU/ml (1.60 μg/ml) and 0.26 IU/ml (2.63 μg/ml) after the 20 mg and the 40 mg enoxaparin doses, respectively. Mean absolute bioavailability of enoxaparin, based on anti-factor Xa activity is 82% in healthy volunteers. The volume of distribution of anti-factor Xa activity is about 5 L. Following i.v. dosing, the total body clearance of enoxaparin is 25 ml/min. Elimination half-life based on anti-factor Xa activity was about 4.5 hours after subcutaneous administration. Following a 40 mg dose significant anti-factor Xa activity persisting in plasma for about 12 hours. There appears to be no appreciable increase in anti-factor Xa activity after dosing for 3 days in young healthy subjects. Clearance, C_{max}, and AUC for anti-factor Xa activity following subcutaneous administration of 30 mg enoxaparin and 40 mg enoxaparin were similar to those observed in normal subjects. At a dose of 25 mg, in the same subjects, anti-factor Xa activity was observed following once daily dosing in healthy elderly subjects for 10 days. The kinetics and factor Xa activity in other patients undergoing surgery are similar to those in normal subjects following i.v. dosing.

The inactive anti-factor Xa activity with time was parallel to the decay curve of plasma total radioactivity (³⁵S-³⁵S) in healthy volunteers following subcutaneous dosing of enoxaparin labeled with the gamma emitter, ¹²⁵I. 40% of radioactivity and 8.20% of anti-factor Xa activity were recovered in urine in 24 hours.

Enoxaparin has been shown to prevent postoperative deep vein thrombosis (DVT) following hip replacement surgery. The data from two controlled clinical trials are summarized in the following tables in all studies, efficacy is based on all treated patients analyzed.

Treatment Group	Treatment Group	
	Enoxaparin	Placebo
Enoxaparin	30 mg q12h n (%)	30 mg q12h n (%)
All Treated Patients	50 (100%)	50 (100%)
Prevalent DVT (%)	5 (10%)	23 (46%)
Postoperative DVT (%)	1 (2%)	11 (22%)
*p value versus placebo = 0.0007		
**p value versus placebo = 0.0134		

A double blind, multicenter study compared three dosing regimens of Loventox. Treatment was initiated within two days post surgery and was continued for up to 7 days post-operatively.

Dose	Treatment Group		
	Enoxaparin	Enoxaparin	Enoxaparin
All Treated Patients	18 (90%)	20 (100%)	40 (100%)
Zenithal Embolus	161 (100%)	208 (100%)	109 (100%)
Total DVT (%)	40 (22%)	22 (11%)	27 (14%)*
*p value versus placebo = 0.0008			
**p value versus Enoxaparin 30 mg OD = 0.0788			
†p value versus Enoxaparin 40 mg OD = 0.0788			

Loventox (enoxaparin) injection is indicated for the prevention of deep vein thrombosis and pulmonary embolism following hip replacement surgery.

CONTRAINDICATIONS

Enoxaparin injection is contraindicated in patients with active major bleeding, in patients with thrombocytopenia associated with a positive in vitro test for anti-heparin antibody in the presence of Loventox injection, or in patients with hypersensitivity to Loventox injection.

WARNINGS

Enoxaparin injection is not intended for intramuscular administration. Enoxaparin cannot be used interchangeably (oral for oral) with unfractionated heparin or other low molecular weight heparins.

Precautions

Enoxaparin should be used with extreme caution in patients with history of heparin induced thrombocytopenia. Hemorrhage: Enoxaparin injection like other anticoagulants should be used with extreme caution in conditions with increased risk of hemorrhage, such as bacterial endocarditis, congenital or acquired bleeding disorders, active ulceration and angiodysplastic gastrointestinal disease, hemorrhagic stroke or shortly after brain, spinal or ophthalmological surgery. Bleeding can occur at any site during therapy with enoxaparin. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

Thrombocytopenia

Moderate thrombocytopenia (platelet counts < 100,000/mm³ and > 50,000/mm³) occurred at a rate of about 2% in patients given Loventox. 3% in patients given heparin, and 0% in patients receiving placebo in clinical trials. Thrombocytopenia of any degree should be monitored closely.

PRECAUTIONS

General
Enoxaparin injection should not be mixed with other injections or infusions. Loventox injection should be used with care in patients with a bleeding diathesis, uncorrected arterial hypertension or a history of recent gastrointestinal ulceration and hemorrhage. Elderly patients and patients with renal insufficiency may show delayed elimination of enoxaparin. Enoxaparin should be used with care in these patients.

Interactions

If thrombotic events occur despite enoxaparin prophylaxis, Loventox should be discontinued and appropriate therapy initiated.

Labelling Tests

Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with Loventox injection.

Drug Interactions

Enoxaparin injection should be used with care in patients receiving oral anticoagulants, and/or platelet inhibitors.

Drug/Laboratory Test Interactions:

Elevenfold at Serum Transaminases
Asymptomatic increases in transaminase levels (SGOT (AST) and SGPT (ALT) greater than three times the upper limit of normal) of the laboratory reference range have been reported in 2 of 30 normal subjects and in up to 5% of patients during treatment with Lovonox Injection. Similar significant increases in transaminase levels have also been observed in patients and normal volunteers treated with heparin and other low molecular weight heparins. Such elevations are likely reversible and are rarely associated with increases in bilirubin. Since transaminase elevations are important in the differential diagnosis of myocardial infarction, liver disease and pulmonary embolus, elevations that might be caused by drugs like Lovonox should be interpreted with caution.

Cardiovascular Management, Importance of Caution:
No long term studies in animals have been performed to evaluate cardiotoxic potential of enoxaparin. Enoxaparin was not mutagenic in *in vitro* tests, including the Ames test, mouse lymphoma cell forward mutation test, and human lymphocyte chromosomal aberration test and the *in vivo* rat bone marrow chromosomal aberration test. Enoxaparin was found to have no effect on quality or reproductive performance of male and female rats at subcutaneous doses up to 20 mg/kg/day or 141 mg/kg/day. The maximum received human dose in clinical trials was 1.5 mg/kg/day or 48.6 mg/kg/day.

Pregnancy: Teratogenic Effects:
Pregnancy category B: Teratology studies have been conducted in rats and rabbits at subcutaneous doses of enoxaparin up to 20 mg/kg/day or 211 mg/kg/day and 18 mg/kg/day, respectively. The maximum received human dose in clinical trials was 1.5 mg/kg/day or 48.6 mg/kg/day. There was no evidence of teratogenic effects or fetotoxicity (as measured by resorptions, stillbirths, or abortions) in either species. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers:
It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when enoxaparin is administered to nursing women.

Pediatric Use:
Safety and effectiveness of enoxaparin in children has not been established.

ADVERSE REACTIONS
Hemorrhage:
The incidence of hemorrhagic complications during Lovonox® Injection treatment has been low. The following rates of major bleeding events have been reported during clinical trials with Lovonox Injection and heparin and placebo in patients undergoing hip replacement surgery:

Enoxaparin 30 mg Q12h	Heparin 5000 U/24h	Placebo
n = 768	n = 541	n = 50
31 (4%)	32 (6%)	2 (4%)

Bleeding complication considered major if accompanied by a significant clinical event or if hemoglobin decreased by 2 g/dL or transfusion of 2 or more units of blood products was required.

Thrombocytopenia:
During clinical trials with Lovonox Injection, moderate thrombocytopenia, defined as a platelet count less than 300,000/mm³, was reported in 2% of patients given Lovonox, 3% in patients given heparin and 0% in patients receiving placebo (see WARNINGS).

Local Irritation:
Mild local irritation, pain, numbness and erythema may follow subcutaneous injection of Lovonox Injection.

Other:
Other adverse effects that were thought to be possibly or probably related to treatment with Lovonox Injection, heparin or placebo in clinical trials, and that occurred at a rate of at least 2% in the enoxaparin group, are shown below.

Adverse Event	Enoxaparin 30 mg Q12h n = 768		Heparin 5000 U/24h n = 541		Placebo n = 50	
	Events	Total	Events	Total	Events	Total
Fever	<1%	4%	<1%	3%	0%	4%
Pain	<1%	2%	1%	3%	0%	8%
Hemorrhage	<1%	9%	<1%	5%	0%	2%
Nausea	<1%	3%	<1%	2%	0%	2%
Echymosis	<1%	2%	<1%	2%	0%	2%
Hypochloric anemia	1%	3%	3%	7%	2%	10%
Edema	1%	3%	<1%	2%	0%	4%
Peripheral edema	1%	3%	1%	2%	0%	0%
Constipation	<1%	2%	<1%	1%	0%	0%

OVERDOSE/TREATMENT:
Accidental overdose following administration of Lovonox Injection may lead to hemorrhagic complications. This

may be largely neutralized by the slow intravenous injection of protamine sulfate (1% solution). The dose of protamine sulfate should be equal to the dose of Lovonox Injection injected: 1 mg protamine sulfate should be administered if the APTT measured 2 to 4 hours after the first injection remains prolonged. However, even with higher doses of protamine, the APTT may remain more prolonged than under normal conditions found following administration of conventional heparin. In all cases, the end factor Xa activity is never completely neutralized (maximum about 60%). Particular care should be taken to avoid overdosage with protamine sulfate. Administration of protamine sulfate can cause severe hypotensive and anaphylactic reactions. Because local reactions, often resembling erythema, have been reported with protamine sulfate, it should be given only when resuscitation techniques and treatment of anaphylactic shock are readily available. For additional information consult the labeling of Protamine Sulfate Injection, USP, products.

A single subcutaneous dose of 48.6 mg/kg enoxaparin was lethal to rats. The symptoms of acute toxicity were anemia, decreased motility, dyspnea, cyanosis and coma.

DOSEAGE AND ADMINISTRATION
Adult Dosage:
In patients undergoing hip replacement, the recommended dose of Lovonox Injection is 30 mg twice daily administered by subcutaneous injection with the initial dose given as soon as possible after surgery, but not more than 24 hours post-operatively. Treatment should be continued throughout the period of post-operative care until the risk of deep vein thrombosis has diminished. Up to 14 days administration has been well tolerated in controlled clinical trials. The average duration of administration is 7 to 10 days.

All patients should be screened prior to prophylactic administration of Lovonox to rule out a bleeding disorder. There is usually no need for daily monitoring of the effect of Lovonox in patients with normal pre-surgical coagulation parameters.

Administration:
Lovonox Injection is administered by subcutaneous injection. It must not be administered by intramuscular injection.

Subcutaneous Injection technique: Patients should be lying down and Lovonox Injection administered by deep subcutaneous injection. Administration should be alternated between the left and right anterolateral and left and right posterolateral abdominal wall. The whole length of the needle should be introduced into a skin fold held between the thumb and forefinger; the skin fold should be held throughout the injection.

Enoxaparin Injection is a clear colorless to pale yellow sterile solution and as with other parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

HOW SUPPLIED
Lovonox Injection is available in packs of 10 prefilled syringes. Each Lovonox (tenoxaparin) prefilled syringe is affixed with a 28 gauge x 1/2 inch needle.

Lovonox contains 30 mg enoxaparin in 0.3 mL of Water for Injection. Lovonox has an anti-factor Xa activity of approximately 3000 IU (with reference to the WHO First International Low Molecular Weight Heparin Reference Standard).

Lovonox Injection should be stored at or below 25°C.

Made in France
Rev. 1/93
IN 1307

RHÔNE-POUL ENC ROBER PHARMACEUTICALS INC.
COLLEGEVILLE, PA 19426

CC: Original NDA 20-164 HFD-180
Phil Chao HFD-362
FONSI File 20162
P. Vincent HFD-102
B. Collier HFD-180

F/T 01-13-93

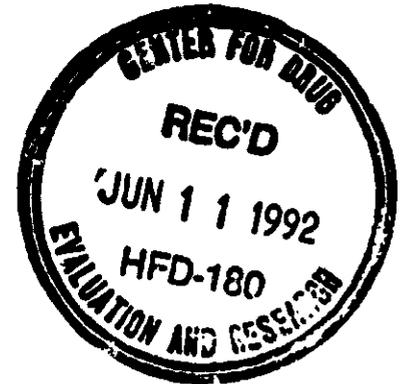
MAY 22 1992

CONSULTATIVE REVIEW TO HFD-180
DIVISION OF MEDICAL IMAGING, SURGICAL, AND DENTAL DRUG PRODUCTS
MICROBIOLOGIST'S REVIEW NO. 1
May 7, 1992

A. 1. NDA No.: 20-164

Product Name: Enoxaparin Injection

APPLICANT: Rhone-Poulenc Rorer
PROPHARM
Maisons-Alfort
180, rue Jean Jaures
94700 Maisons-Alfort
France



2. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Sterile liquid for injection in pre-filled syringe.

3. METHOD(S) OF STERILIZATION:

4. PHARMACOLOGICAL CATEGORY AND / OR PRINCIPAL INDICATION:
For prevention of deep vein thrombosis following hip replacement surgery.

5. DRUG PRIORITY CLASSIFICATION: 1 P

B. 1. INITIAL APPLICATION DATE: 12-31-91

2. RECEIVED FOR REVIEW: 03-17-92

C. REMARKS: The drug substance is a depolymerized heparin derived from heparin benzyl ester (source is porcine intestinal mucosa) by alkaline degradation, and is a new molecular entity because of the low molecular weight and altered chemical bond structure.

Inspection of the facilities has already been requested by HFD-180. The applicant needs to clearly identify whether the information in this submission applies to a pilot or production manufacturing facility.

D. CONCLUSION: Do not recommend approval for sterility assurance because of insufficient validation information for the fill manufacturing process.

cc:
Orig. NDA 20164
HFD-180/Sieczkowski
HFD-160/Consult file/CKVincent
Drafted by: CKVincent/05-07-92
R/D Init by: PHCooney/05-22-92

Carol K. Vincent
5-22-92

Carol K. Vincent

R.K. 5/27/92

WMC 6/10/92

N20-164

7 of 7

CONSULTATIVE REVIEW TO HFD-180
DIVISION OF MEDICAL IMAGING, SURGICAL, AND DENTAL DRUG PRODUCTS
MICROBIOLOGIST'S REVIEW NO. 2
January 6, 1993

A. 1. NDA No.: 20-164

Product Name: Enoxaparin Injection

APPLICANT: Rhone-Poulenc Rorer
PROPHARM
Maisons-Alfort
180, rue Jean Jaures
94700 Maisons-Alfort
France



2. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Sterile liquid for injection in pre-filled syringe.

3. METHOD(s) OF STERILIZATION:

4. PHARMACOLOGICAL CATEGORY AND / OR PRINCIPAL INDICATION:
For prevention of deep vein thrombosis following hip replacement surgery.

5. DRUG PRIORITY CLASSIFICATION: 1 P

B. 1. INITIAL APPLICATION DATE: 12-31-91

2. AMENDMENTS:

a. March 26, 1992; part I of response to February 24, 1992 Information Request Letter from HFD-180.

b. June 19, 1992; part II of response to February 24, 1992 Information Request Letter from HFD-180.

3. RECEIVED FOR REVIEW: 08-24-92

C. REMARKS: The drug substance is a depolymerized heparin derived from heparin benzyl ester (source is porcine intestinal mucosa) by alkaline degradation, and is a new molecular entity because of the low molecular weight and altered chemical bond structure.

D. CONCLUSION: The microbiological data submitted in the two amendments dated March 26, 1992 and June 19, 1992 (subject of this Microbiological Review No. 2 dated January 6, 1992) are acceptable. However, the application remains not recommended for approval on the basis of microbiological quality and sterility assurance.

cc:
Orig. NDA 20-164
HFD-180/Sieczkowski
HFD-160/Consult file/CKVincent
Drafted by: CKVincent/11-24-92
Revised by: CKVincent/01-06-93
R/D Init by: PHCooney/01-06-93

Carol K. Vincent

Carol K. Vincent 1-6-93

PKC 1/6/93

Paula Boston MD 1/13/93

CONSULTATIVE REVIEW TO HFD-180
DIVISION OF MEDICAL IMAGING, SURGICAL, AND DENTAL DRUG PRODUCTS
MICROBIOLOGIST'S REVIEW NO. 3
January 7, 1993

A. 1. NDA No.: 20-164

Product Name: Enoxaparin Injection

APPLICANT: Rhone-Poulenc Rorer
PROPHARM
Maisons-Alfort
180 rue Jean Jaures
94700 Maisons-Alfort
France



2. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Sterile liquid for injection in pre-filled syringe.

3. METHOD(S) OF STERILIZATION:
fill manufacturing process.

4. PHARMACOLOGICAL CATEGORY AND / OR PRINCIPAL INDICATION:
For prevention of deep vein thrombosis following hip replacement surgery.

5. DRUG PRIORITY CLASSIFICATION: 1 P

B. 1. INITIAL APPLICATION DATE: 12-31-91

2. AMENDMENTS: August 13, 1992

3. RECEIVED FOR REVIEW: 08-24-92

C. REMARKS: This amendment responds to the June 16, 1992 Information Request Letter from HFD-180 conveying the questions relative to fill validation and other microbiological issues from the consult Microbiologist Review No. 1, dated May 7, 1992.

D. CONCLUSION: Recommend not approval for sterility assurance.

Carol K. Vincent 1-7-93

Carol K. Vincent

cc:
Orig. NDA 20164
HFD-180/Sieczkowski
HFD-160/Consult file/CKVincent
Drafted by: CKVincent/12-28-92
R/D Init by: PHCooney/01-07-93

7/1/93

CONSULTATIVE REVIEW TO HFD-180
DIVISION OF MEDICAL IMAGING, SURGICAL, AND DENTAL DRUG PRODUCTS
MICROBIOLOGIST'S REVIEW NO. 3
January 7, 1993

A. 1. NDA No.: 20-164

Product Name: Enoxaparin Injection

APPLICANT: Rhone-Poulenc Rorer
PROPHARM
Maisons-Alfort
180 rue Jean Jaures
94700 Maisons-Alfort
France



2. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Sterile liquid for injection in pre-filled syringe.

3. METHOD(S) OF STERILIZATION:
fill manufacturing process.

4. PHARMACOLOGICAL CATEGORY AND / OR PRINCIPAL INDICATION:
For prevention of deep vein thrombosis following hip replacement surgery.

5. DRUG PRIORITY CLASSIFICATION: 1 P

B. 1. INITIAL APPLICATION DATE: 12-31-91

2. AMENDMENTS: August 13, 1992

3. RECEIVED FOR REVIEW: 08-24-92

C. REMARKS: This amendment responds to the June 16, 1992 Information Request Letter from HFD-180 conveying the questions relative to fill validation and other microbiological issues from the consult Microbiologist Review No. 1, dated May 7, 1992.

D. CONCLUSION: Recommend not approval for sterility assurance.

Carol K. Vincent 1-7-93

Carol K. Vincent

cc:
Orig. NDA 20164
HFD-180/Sieczkowski
HFD-160/Consult file/CKVincent
Drafted by: CKVincent/12-28-92
R/D Init by: PHCooney/01-07-93

PHC 1/7/93

CONSULTATIVE REVIEW TO HFD-180
DIVISION OF MEDICAL IMAGING, SURGICAL, AND DENTAL DRUG PRODUCTS
MICROBIOLOGIST'S REVIEW NO. 4
March 11, 1993

- A. 1. NDA No.: 20-164
Product Name: Enoxaparin Injection
APPLICANT: Rhone-Poulenc Rorer
PROPHARM
Maisons-Alfort
180 rue Jean Jaures
94700 Maisons-Alfort
France
2. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Sterile liquid for injection in pre-filled syringe.
3. METHOD(s) OF STERILIZATION:
fill manufacturing process.
4. PHARMACOLOGICAL CATEGORY AND / OR PRINCIPAL INDICATION:
For prevention of deep vein thrombosis following hip replacement surgery.
5. DRUG PRIORITY CLASSIFICATION: 1 P
- B. 1. INITIAL APPLICATION DATE: December 31, 1991
2. AMENDMENT: January 29, 1993
RECEIVED FOR REVIEW: February 3, 1992
3. AMENDMENT: February 18, 1993
RECEIVED FOR REVIEW: March 1, 1992
4. AMENDMENT: February 23, 1993
RECEIVED FOR REVIEW: March 1, 1993
- C. REMARKS: These amendments respond to the January 15, 1993 Information Request Letter from HFD-180 conveying the questions relative to fill validation and other microbiological issues from the consultative Microbiologist's Review No. 3, dated January 7, 1993.
- D. CONCLUSION: Recommend approval for sterility assurance. The applicant has satisfactorily addressed and answered all questions and concerns raised in Microbiologist's Review No. 3, dated January 7, 1993 in these three amendments.

We recommend NDA 20164 for approval based on sterility assurance and microbiological quality.

cc:
Orig. NDA 20-164
Orig. NDA 20164
HFD-180/Sieczkowski
HFD-160/Consult file/CKVincent
Drafted by: CKVincent/02-17-93
Revised by: CKVincent/03-10-93
R/D Init by: PHCooney/03-11-93

Carol K. Vincent 3-11-93

Carol K. Vincent

PAZ 3/12/93

CTB

DMF
Page 10

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4

ATL

N20-164 BIO RV

NDA 20-164

1

NOA 20-164

MEDICAL OFFICER
REVIEW
(MISSING PAGES)

EVALUATION AND SCHEDULING; The study procedures and the schedule are outlined in Table I reproduced from vol 33 of the NDA.

TABLE I
STUDY SCHEDULE - OVERVIEW

Evaluation/Procedure	Prior to Surgery	Periodic Interval														End of Study ²
		Calendar/Treatment Day ¹														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Informed Consent	X															
Complete Medical History	X															
Complete Physical Examination	X															
Laboratory Tests: Hematology and Coagulation, Serum Chemistry and Urinalysis	X															
Vital Signs	X															
Impedance Plethysmography (IPG)	X					X		X		X		X	X	X		
¹²⁵ I-Fibrinogen Leg Scan	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
Lung Scan	X															
Pulmonary Angiography ⁵																
Anti-Factor Ia Activity ⁶		X	X	X	X	X	X	X	X	X		X	X	X	X	
Bleeding Assessment		X	X	X	X	X	X	X	X	X		X	X	X	X	
Hemoglobin, Hemocrit, RBC		X	X	X	X	X	X	X	X	X		X	X	X	X	
Coagulation Tests (PT, APTT)		X	X	X	X	X	X	X	X	X		X	X	X	X	
Adverse Experience Evaluation		X	X	X	X	X	X	X	X	X		X	X	X	X	
Dosing		X	X	X	X	X	X	X	X	X		X	X	X	X	
Bilateral Venography ⁷																X
Concomitant Medications																X
Assessment of Operative Site																X

¹ Day 1 was the first post-operative day; the next calendar day was Day 2.
² 0: at time of discontinuation of study medication.
³ ¹²⁵I-fibrinogen was injected immediately following surgery (study day 0); scans were performed daily post-operatively.
⁴ At entry and between days 10 and 14.
⁵ Selective pulmonary angiography performed to establish definitive diagnosis of pulmonary embolism, if necessary.
⁶ Plasma samples to be obtained 6 hours after first daily dose.
⁷ Mandatory venography was strictly enforced for the last 76 patients enrolled.

EFFICACY PROCEDURES; Because of the low incidence of DVT detected in the first 24 patients in whom surveillance of DVT had been carried out with ¹²⁵I-fibrinogen leg scanning and IPG, bilateral venograms were made mandatory in the rest of patients. The VG was obtained between day 10 and 14 of study or at the time of patient's discontinuation from the study. VGs were reviewed blindly by qualified physicians at the study site. The results were reported separately for each leg as "positive" "negative" or "inadequate". The location of the obstruction was noted in the positive VGs. A unilaterally obtained negative VG was classified as inadequate. Factors affecting the reading of the VG were recorded and their location was noted.

¹²⁵I-fibrinogen leg scans were performed at study entry and daily post-operatively. The scans were read blindly and were classified as "positive", "negative" or "inadequate". IPG was performed on day 5, 7, 9 11 and 13 post-operatively and were read blindly.

The protocol states that a lung scan would be performed at entry and between days 10 and 14 of study, and that a pulmonary angiogram would be obtained if the lung scan was positive. However, routine lung scans were not performed during the study.

Table 12
Testing of Patients Discontinued Due to an Adverse Event.
(Appendix D.10)

Patient ID#	Study Day Discontinuation	Adverse Event	Severity	Relationship to Study Medication
Inoperable				
20080	7	Cough	Severe	None
20101	9	Thrombocytopenia	Severe	Possible
20048	11	Edema	Severe	Possible
20128	2	Flaccid/diagram abnormal	Severe	None
	2	Sweating	Severe	None
	2	Tachycardia	Severe	None
31008	2	Malena	Moderate	Possible
40157	2	Hypoxia	Severe	Possible
20128	10	Dyspnea	Severe	Possible
Calcium Heparin				
20014	3	Hypochromic anemia (Hb decreased)	Severe	Definite
	3	Hemoptysis	Severe	Possible
20060	8	Thrombocytopenia	Severe	Definite
40105	10	Chest pain	Severe	Possible
30137	11	Lung disorder	Severe	Probable
	12	Embolus Pulmonary	Severe	Definite
40120	11	Pain	Severe	Definite
	11	Edema	Moderate	Possible
40183	11	Thrombocytopenia	Severe	Probable
60030 ^b	11	Thrombocytopenia	Severe	Definite
	12	Headache ^d	Moderate	Possible
60108	13	Hematuria	Moderate	Possible
30029	10	Injection site reaction	Severe	Definite

^a Patient was discontinued on post-operative day 11 and the clotting of embolus pulmonary occurred after the patient was discontinued.

^b Patient was discontinued on post-operative day 11 and the clotting of headache occurred after the patient was discontinued.

Two percent (2%) and 3% of all patients had SGOT and SGPT elevations from 3 to 6 times normal values, elevations of SGOT and AGPT above six times normal occurred only in 1% of all patients. The incidence rates of the elevated serum transaminases were similar in both groups. Elevations of AP occurred at similar rates in the two groups (5% and 8%). Four percent (4%) of all patients had clinically significant elevation of BUN, and less than 1% had creatinine values of clinical significance. The data are summarized in table 16.

Table 16
Summary of the On-Study Incidence of Patients with Clinically Significant Values for Selected Laboratory Parameters
(Appendix B.18)

	Treatment Group		p-value ^a	Overall n (%)
	ESOPHAGOLIN n (%)	CALCIUM HEPARIN n (%)		
All Treated Patients	333 (100%)	332 (100%)		665 (100%)
Hemoglobin:				
< 8 gm/dL	38 (11%)	42 (13%)	0.636	80 (12%)
> 2 gm/dL drop	74 (22%)	84 (25%)	0.363	158 (24%)
Platelets: Thrombocytopenia ^b				
mild	83 (25%)	75 (23%)	0.524	158 (24%)
moderate	8 (2%) ^d	12 (4%)	0.376	20 (3%)
severe	0	1 (<1%)	0.499	1 (<1%)
Platelets: Thrombocytosis ^c				
mild	211 (63%)	216 (65%)	0.248	427 (67%)
moderate	97 (29%)	88 (27%)	0.489	185 (28%)
severe	2 (<1%)	3 (<1%)	0.686	5 (<1%)
SGOT/ALT:				
3-6x Up-Norm	8 (2%)	10 (3%)	0.205	15 (2%)
>6x Up-Norm	0	1 (<1%)	0.499	1 (<1%)
SGPT/ALT:				
3-6x Up-Norm	9 (3%)	13 (4%)	0.397	22 (3%)
>6x Up-Norm	3 (<1%)	8 (2%)	0.505	8 (1%)
Bilirubin:				
>3 mg/dL	1 (<1%)	0	1.000	1 (<1%)
Alkaline Phosphatase:				
>2x Up-Norm	16 (5%)	28 (8%)	0.063	44 (7%)
Creatinine:				
>2 mg/dL	3 (<1%)	3 (<1%)	1.000	6 (<1%)
BUN:				
>30 mg/dL	18 (5%)	17 (5%)	0.176	37 (6%)

^a P-values from two tailed Fisher's Exact Test comparison vs the heparin dose group.

^b Platelets, thrombocytopenia:
Mild, 100,000/mm³ ≤ x < Lower limit of normal;
Moderate, 20,000/mm³ ≤ x < 100,000/mm³;
Severe, x < 20,000/mm³.

^c Platelets, thrombocytosis:
Mild, upper limit of normal ≤ x < 600,000/mm³;
Moderate, 600,000/mm³ ≤ x < 1,000,000/mm³;
Severe, x ≥ 1,000,000/mm³.

^d Up-Norm, upper limit of investigator's normal range.
A data entry error was made for the end of study platelet count for patient number 73076 in the esophageal treatment group. The erroneous value of 30,000/mm³ remains in the database and is included in the total number of patients for whom moderate thrombocytopenia was reported. The correct value from the case report form is 30,000/mm³.

Three investigators from 3 Canadian centers had participated in a previous study, study ENO 884, a pivotal efficacy study for the present NDA. Although these two studies are different in design (ENO 884 assesses the effect of enoxaparin compared to placebo and PK 523 compares enoxaparin to heparin), they fail to fulfill the requirement of independence.

Prophylaxis with low-dose heparin is an approved regimen for the prevention of DVT and PE following high risk general surgery. Although effective in orthopedic surgery, similar prophylaxis with low-dose heparin is not approved for this indication, nor it is widely accepted because of the concern about excessive perioperative bleeding caused by the anticoagulant therapy. Moreover, the post-operative administration of heparin in the attempt to reduce perioperative bleeding has not been investigated. Thus, in study PK 523, enoxaparin was compared to a non-approved, untested regimen of prophylaxis of DVT in elective orthopedic surgery with sc heparin 7500 U q12h. Protocol PK 523 was initially designed based on: 1) the hypothesis that the incidence of DVT would be 20% in the heparin group and that it would be reduced to 10% in the enoxaparin, and 2) that this hypothesis could be demonstrated by entering 195 patients in each group ($\alpha=0.05$, two-tailed, and $\beta=0.20$). In the course of the study, in order to avoid Type II error, the sample size had to be increased to 520 to have a power of 90% for true rates of DVT of 20% and 10%. Further increase of sample size become necessary to maintain the 90% power because of inadequacy of non-invasive vascular tests, rate of VG of 80% and patients exclusions.

The results of the study failed to show superiority of enoxaparin compared to heparin or the anticipated reduction of post-operative DVT. In four of the five centers participating in the study, enoxaparin was as effective as heparin in preventing DVT in patients undergoing elective hip replacement surgery. In one center, heparin appeared to be superior to enoxaparin, however, the difference was not statistically significant and the center had the smallest number of patients. There is no evidence that the enrollment of patients in this center was prematurely discontinued.

The overall results of the study show that both enoxaparin and heparin regimens effectively reduce the risk of DVT and, particularly, the risk associated with proximal deep veins thrombosis, given the reported incidence of DVT in the range of 40%-60% in patients undergoing elective hip replacement in the absence of surveillance or without prophylactic antithrombotic therapy.

Pulmonary embolization occurred in two patients treated with heparin and in none of the patients receiving enoxaparin, however, the total number of patients is not large enough to permit statistical conclusions.

Enoxaparin appeared to have some safety advantages over heparin with statistically significantly less overall bleeding. The incidence of major and minor bleeding was 5% in the enoxaparin group and 9% in the heparin group ($p=0.0375$). Study treatment had to be discontinued due to excessive bleeding in 6 patients on heparin compared to 3 on enoxaparin. However, the incidence of severe bleeding and the transfusion requirements were similar in the two treatment groups.

Skin rash was reported in 9% of patients in the enoxaparin group compared to 5% in the heparin group ($p=0.021$). The significance of this finding is unclear, as no skin rash was reported in the enoxaparin group in study ENO 884 and equal incidence of about 7% was reported for each of the three groups (heparin 5000U q8h, enoxaparin 30 mg q12h and enoxaparin 40 mg QD) in study PK 525. Severe thrombocytopenia occurred only in the heparin-treated group. At present, it is unclear whether the low molecular weight heparins are less immunogenic, thus, less likely to stimulate the production of heparin antibodies and/or less likely to cross-reacting with preformed heparin antibodies. It is possible, however, that the lower incidence of heparin-induced thrombocytopenia associated with enoxaparin administration is due mainly to the limited exposure to this new compound compared to wide-spread use of unfractionated heparin. Whether this difference will persist after repeated administration of enoxaparin remains to be seen.

to that of unfractionated heparin 500 U sc q8h (total daily dose 15,000 U) for the prevention of DVT in patients undergoing elective hip replacement.

STUDY DESIGN

This study was randomized, open-label, parallel-group, multicenter. The patients were randomized to receive either enoxaparin at the dose of 40 mg once daily, enoxaparin at the dose of 30 mg q12h, or heparin at the dose of 5000 U q8h for a period of up to 7 days starting within the first 24 hours after surgery.

The primary efficacy assessment for DVT was bilateral VG at day 7, or earlier if clinically indicated. Additional efficacy assessment was performed with non-invasive vascular procedures represented by IPG, Doppler sonography or ultrasonography obtained at day 4 and 7 or earlier if necessary, and by evaluation of clinical signs or symptoms of DVT.

Safety evaluation was obtained daily during treatment, at the end or discontinuation of the treatment and within 14 days after discontinuation of study treatment.

SELECTION OF STUDY POPULATION

ELIGIBILITY CRITERIA

Male and female patients, 40 years of age or older, scheduled for elective hip replacement (placement of prosthetic device in the intramedullary space of femur, with or without reconstruction of acetabulum), with negative noninvasive vascular examination for DVT within 14 days prior to surgery and consenting to the study were eligible for the study.

EXCLUSION CRITERIA

Female patients of child-bearing potentials, patients with presurgical diagnosis of DVT by noninvasive techniques, history of surgery of the ipsilateral hip within the preceding year, history of DVT, bleeding disorder, heparin-induced thrombocytopenia, surgery to eyes, spinal cord, or CNS within three months, active PUD, hypertension, uncontrolled asthma, allergy to heparin, allergy to fish, porcine products, sulfites, iodine or contrast media, regular use of ASA or other NSAID for four days before surgery, current drugs or alcohol abuse, treatment with investigational drugs during the previous 4 weeks,

enoxaparin 30 mg q12h ($p < 0.05$). The results in the evaluable patients showed a rate of DVT of 6% for the enoxaparin 30 mg q12h group, 15% for the heparin group and 21% for the enoxaparin 40 mg QD group. The difference among the three groups was not statistically significant.

The incidence of major and minor bleeding complications and the total transfusion requirements were comparable in all three groups.

Among the serious adverse reactions encountered during the study, there were five cases of PE: one in a patient treated with enoxaparin 40 mg QD and four in patients treated with heparin. The PE of the enoxaparin patient occurred on day 4 of therapy and was associated with the finding of a superficial femoral vein phlebitis. The episodes of PE in the heparin patients occurred at the end of the study. One patient experienced PE concomitant with calf vein thrombosis. The other three patients developed PE between 2 and 3 weeks post-study, off medication, and beyond the follow-up time.

Among the serious adverse events regarded as associated with the study medication, one case of severe thrombocytopenia and thrombosis, resulting in bilateral lower extremities gangrene, occurred in a patients treated with heparin.

The effectiveness of enoxaparin 30 mg q 12h in preventing DVT in hip surgery patients was greater in this study than that obtained with the same regimen in study ENO 884 and PK 523 (5% treatment failure versus 10% and 17% respectively).

The study design presented numerous deficiencies, therefore the interpretation of the results is subject to such limitations. The study was not double-blind; moreover, the investigators were provided with the randomization list which introduced the additional bias of patients selection. The patients were assigned the study treatment either presurgery or postsurgery. The protocol underwent various amendments; several protocol variations were allowed in the evaluation of efficacy.

The study is, therefore, unacceptable for efficacy evaluation. The study can, however, contribute to the safety evaluation of enoxaparin.

STUDY NUMBER; PK 526

TITLE: Multiple-dose, double-blind clinical trial of the safety and efficacy of enoxaparin for the prevention of post-operative Deep Vein Thrombosis (DVT) following total hip replacement surgery.

The study was initiated on January 19, 1989. A total of 572 patients were enrolled by 32 investigators in US until August 24, 1990.

NDA Volumes: 59-61; 2.18

The investigators enrolling more than 10 patients were:

<u>Investigator</u>	<u>Study location</u>	<u>Patients Enrolled</u>
J.R. Roberson, M.D.	Emory Univ. Atlanta, GA	14
R.B. Brasier, M.D.	Ann Arbor VAH Ann Arbor, MI	27
R. Bona, M.D.	St. Francis H., Hartford CT	16
F.G. Ebaugh Jr, M.D.	VAMC Palo Alto, CA	17
J.J. Flechtner, M.D.	Dakota Clinic, Fargo, MD	27
D. MacFarlane, M.D.	U.Iowa Col.Med., Iowa City, IA	30
T. Siesholtz, M.D.	Grand View H., Sellerville, PA	19
G Johnson, M.D.	VAMC, Minneapolis, MN	34
R.M. Lyons, M.D.	Humana H., San Antoni, TX	45
M.D. Tremaine, M.D.	Anderson Clinic, Anderson, VA	45
J. Ansell, M.D.	U. Massachusetts, Worcester, MA	24
R. Rodvien, M.D.	Pacific Presb.H. San Francisco, CA	18
C.G. Savory, M.D.	Hughston Sports M.H., Columbus, GA	50
M. Rader, M.D.	Nyack Hospital, Nyack, NY	11
W.K. Furman, M.D.	Sarasota Mem.H., Sarasota, FL	48
W.L. Overdyke, M.D.	Highland Clinic, Shreveport, LA	19
M. Christie, M.D.	Vanderbilt Univ.H., Nashville, TN	18
G.B. Shaver, M.D.	Asheville Med.Ctr. Asheville, NC	23
F.E. White Jr, M.D.	Presbyt. Hosp., Albuquerque, NM	15
M. Ritter, M.D.	Kendrick Mem.H., Woosville, IN	14

STUDY OBJECTIVE: The objective of the study was to determine the safety and the efficacy of enoxaparin administered subcutaneously (sc) at doses of 10 mg once daily (10 mg/qd), 40 mg once daily (40 mg/qd), and 30 mg every 12 hours (30 mg/q12h) for up to 7 days for the prevention of DVT in patients undergoing elective hip replacement.

STUDY DESIGN

The clinical trial was conducted as a Phase III randomized, double-blind, parallel-group, multicenter study. The patients were randomly assigned to receive either enoxaparin 10 mg.qd,

TABLE 2
STUDY SCHEDULE - OVERVIEW

Evaluation/Procedure	Prior to Surgery ¹	Upon Admission ²	Peridosing Interval							End of Study ⁷	Follow Up
			Calendar/Treatment Day ³	1	2	3	4	5	6		
Informed Consent	X										
Complete Medical History	X										
Complete Physical Examination	X									X	X
12-Lead ECG	X									X	
Chest X-Ray ⁴	X										
Intense History		X									
Brief Physical Examination		X									
Biochemistry and Urinalysis	X									X	X
Hematology and Coagulation	X		X	X	X	X	X	X	X	X	X
Noninvasive Vascular Examination ⁵	X				X					X	
Vital Signs ⁶	X		X	X	X	X	X	X	X	X	X
Assessment of Operative Site ³			X	X	X	X	X	X	X	X	X
Bleeding Assessment			X	X	X	X	X	X	X		
Adverse Experience Evaluation			X	X	X	X	X	X	X	X	X
Dosing			X	X	X	X	X	X	X		
Bilateral Venography										X	
Concomitant Medications											X

- ¹ Up to 30 days prior to surgery
- ² If complete history and physical examination were performed more than 48 hours prior to surgery.
- ³ Day 1 was the first dosing day; the next calendar day was Day 2.
- ⁴ Only if results of chest X-ray done within the preceding six months were not available.
- ⁵ Immediately prior to first dose of study drug on a dosing day.
- ⁶ Several techniques were permitted, but each center was to select one technique to be used for all patients.
- ⁷ Within 24 hours of the last dose of study medication

EFFICACY PROCEDURES

Bilateral venograms were scheduled within 24 hours following last dose of study medication at the end of the study or following premature discontinuation of study treatment.

Venography represented the primary assessment of DVT. At one study site, venography was performed with radionuclide imaging instead of radiocontrast imaging. This test was included among the non-invasive vascular tests.

The procedures for interpreting VG and the non-invasive evaluation of DVT were as described in protocol 525.

SAFETY PROCEDURES

The clinical and laboratory assessments of bleeding and other adverse reactions were as described in protocol 525.

CLINICAL MONITORING PROCEDURES

In addition to Rhone-Poulenc personnel, monitoring of the study was performed on a regular basis by the following contract research organizations:

PACKAGING, BLINDING, AND LABELING PROCEDURES

Study medication was supplied in identical, prefilled syringes containing either placebo or 10, 40 or 30 mg enoxaparin in a volume of 0.4 mL.

All enoxaparin syringes contained also sodium metabisulfite (<0.6 mg); the 10 mg enoxaparin syringe contained 14.4 mg of mannitol; the 30 mg enoxaparin syringe contained 4.6 mg of mannitol. Mannitol was added to maintain isotonicity.

Each enoxaparin placebo syringe contained 20 mg of mannitol and less than 0.6 mg of sodium metabisulfite.

To maintain the double-blind character of the study, all patients received an injection q12h. For the enoxaparin 10 mg qd and 40 mg qd, the enoxaparin was given for the odd doses and the placebo for the even doses. Each patient's daily supply of study medication was packaged in an individual blister pack pre-labeled with the patient's number and dose number (1,3,5,7,etc; 2,4,6,8,etc). Patients received the entire content of the syringe. No dose adjustment was allowed.

The following lot numbers were used in this trial:

Enoxaparin, 10 mg: CB 3424, CB 3965
Enoxaparin, 40 mg: CB 3427, CB3974
Enoxaparin, 30 mg: CB 3422, CB 3645, CB 4372
Enoxaparin Placebo: CB 3426P, CB 3951P, CB 4006P

Investigators were supplied with study medication for blocks of 6 or 12 patients.

All supplies of enoxaparin used in the study were tested by the sponsor.

STATISTICAL METHODS

The sample size was determined based on the reported incidence of DVT in patients treated with either 40 mg qd or 30 mg q12h, on the assumed incidence of DVT in patients treated with 10 mg of enoxaparin qd of 25%, and on an anticipated 80% rate of evaluable patients. It was calculated that approximately 200 patients in each group would give a 80% power using a two-tailed test at a significance level of 0.05.

PATIENTS RANDOMIZATION

Patients were assigned to treatment group in a 1:1:1 ratio in blocks of six using a computerized randomization schedule. The

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I. Summary

F. Environmental Assessment

a) Air Emissions Controls and Citations - Bulk Drug Substance (Con't)

regulation under Table Ia and Ib, Chapter 391-3-1-.02(2)(e), for new and existing equipment. Approval of the proposed action will not impact the facility's ability to comply with the above stated requirements. No new regulation parameters are anticipated as a result of the proposed action.

b) Liquid Emissions Controls and Citations- Bulk Drug Substance

The plant has separate sanitary, process and stormwater sewer systems. All process and sanitary wastewater from laboratory, production and administration areas are sent to the on-site wastewater treatment plant. The treatment plant consists of the following processes: equalization, neutralization, primary clarification, activated sludge, secondary settling, thickening, sludge dewatering and off-site sludge disposal.

The stormwater collection system is equipped with a deluge containment to collect any spills and allow subsequent rerouting to the wastewater treatment plant. Uncontaminated stormwater may be discharged directly to the Flint River.

Organic liquid waste streams generated from the manufacture of drug substance will be subject to on-site recovery of the organic solvents to the extent practicable. Residues from the solvent recovery operations are sent to the plant's wastewater treatment plant or, if necessary, shipped off-site to a permitted hazardous waste management facility.