Reviewer's Comments:

- *All the measured primary anticoagulation pharmacodynamic parameters (aPTT, anti-IIa and anti-Xa) increased significantly with administration of each of the two tinzaparin multiple dosing regimens that were investigated in the current study. In general, baring in mind the limited sampling scheme, maximum levels for all the pharmacodynamic markers studied were observed at 4 hrs post dose for both multiple dosing regimens.*
- *Administration of protamine sulfate was only effective in significantly reducing the aPTT and anti-IIa levels ,but not anti-Xa levels, and it did so only transiently. Based on the results of this study, at the protamine sulfate doses employed in the study, protamine sulfate does not seem to be effective in neutralizing the anticoagulant effects of tinzaparin. The Firm does contend that the short duration of protamine neutralizing effect on tinzaparin might have resulted from an inadequate protamine dose.*
- *The discontinuation of treatment in group 2 due to "unacceptable" changes in coagulation parameters indicates that the minimum toxic dose for QD dosing regimens might lie somewhere between 200 IU/kg, QD and 250 IU/kg, QD.*

NDA: 20-484/ Study 702-923 **Study Date:** Oct 1988-Jan 1989

Type of Study: Pharmacodynamic Drug Interaction of Tinzaparin with Aspirin

Introduction

Study DMP 702-923 is entitled,

"LOGIPARIN/ASPIRIN INTERACTION STUDY"

Objectives

- To determine the effect of aspirin on the pharmacodynamic properties following the concurrent administration of tinzaparin and aspirin.

Primary Review Issues:

- **Will there be a need for dose adjustment when administering aspirin concomitantly with tinzaparin in patients?**

Study Design

Open-label, non-randomized, two-period crossover study

Subjects	8 subjects
Duration of Study	3 weeks
Key Inclusion Criteria	Healthy male subjects, 18 to 45 yrs of age Subjects should have a body weight within 10% of their ideal weight Have no significant diseases or clinically-significant abnormal lab values
Treatments	Subjects were to receive treatment 1 and treatment 2 in succession separated by a washout period: • **Treatment 1: Logiparin 50 IU/kg QD, SC for 3 days** • **Treatment 2: Logiparin 50 IU/kg QD, SC for 3 days + concurrent aspirin 300 mg (enteric coated tablet)**
Interperiod Washout	2 weeks
Sampling Times	Blood samples collected at the following time points in each treatment period:

Pre-dose: at 0 hr before drug administration on days 1 & 3
Post-dose: at 4 and 24 hr on day 3

Safety — Biochemistry, haemodialysis and urinalysis screens were performed on the day prior to the first dose and 24 hrs after the final dose in each period

Pharmacodynamic Markers

The relevant pharmacodynamic parameters to be determined during the study were anti-Xa activity, anti-IIa activity, and Bleeding time (only determined in period 2). Also determined were platelet aggregation induced by collagen, adenosine diphosphate (ADP) and adrenaline.

Pharmacokinetic Analysis

No pharmacokinetic analysis of the data was performed by the Firm.

Statistical Analysis

A 2-factor (drug by time) analysis of variance was performed on the platelet aggregation data. These tests were followed by t-test comparisons of corresponding baseline values in each period. Comparisons of the difference between baseline and post-dose measurements in period 1 to the corresponding differences in period 2 were performed using the t-test.

Results and Conclusions

Table 17. Mean (SD) anti-Xa activity over the course of the study

Treatment	Prdose	4 hrs post-dose	24 hrs post-dose
Treatment 1	0.0039 (0.0052)	0.0541 (0.0173)	0.0082 (0.0139)
Treatment 2	0.03102 (0.0592)	0.0787 (0.1177)	0.0362 (0.0658)

Table 18. Mean (SD) anti-IIa activity over the course of the study

Treatment	Prdose	4 hrs post-dose	24 hrs post-dose
Treatment 1	0.0169 (0.0220)	0.0015 (0.0035)	0.0083 (0.0149)
Treatment 2	0.0205 (0.0245)	0.0056 (0.0107)	0.0207 (0.0267)

No significant differences relative to baseline were observed when tinzaparin was administered either alone or concurrently with aspirin. However, Bleeding time did increase significantly ($p = 0.001$) from a mean of 4.72 min pre-dose when tinzaparin was

administered alone, to 6.66 min when tinzaparin was administered concomitantly with aspirin.

Reviewer's Comments:

- *The Firm investigated tinzaparin/aspirin pharmacodynamic interaction using a tinzaparin dose (50 IU/kg QD) that was significantly lower than that proposed for therapeutic use (75 IU/kg QD & 175 IU/kg QD). This complicates the interpretation of the results since simple extrapolation of the data to higher doses is not possible. In addition, the anti-Xa and anti-IIa activity levels during the study were very low that they may well be under the LOQ of the analytical assay, which casts doubt into the reliability of the data. However, this can't be verified since no analytical assay validation report is included in the study.*

Comments to the Firm

It is recommended that the Firm conduct a repeat study to investigate tinzaparin/aspirin pharmacodynamic interaction. However, please incorporate the following modification to the study protocol:

1. *Employ tinzaparin doses proposed for clinical use (75 IU/kg QD & 175 IU/kg QD) in the study. It may be adequate to only use the higher tinzaparin dose in the study.*
2. *Utilize a validated analytical assay for quantification of the pharmacodynamic parameters.*

APPEARS THIS WAY
ON ORIGINAL

NDA: 20-484/ Study 702-924 **Study Date:** Aug-Oct 1991

Type of Study: Neutralization of Tinzaparin by Protamine Sulfate

Introduction

Study DMP 702-924 is entitled,

"NEUTRALIZATION OF LOGIPARIN WITH PROTAMINE SULFATE. A SINGLE DOSE STUDY IN NON-PATIENT VOLUNTEERS GIVEN INTRAVENOUS OR SUBCUTANEOUS INJECTIONS"

Objectives

- To determine the level of neutralization of anti-Xa and anti-IIa activities with protamine sulfate after IV infusion or a SC injection of either tinzaparin or heparin.

Primary Review Issues:

- **How much of tinzaparin's anticoagulant activity is neutralized with administration of protamine sulfate?**

Study Design

Open-label, single dose, parallel group, placebo controlled study

Subjects	50 subjects; 25 males and 25 females
Duration of Study	4-6 hrs
Key Inclusion Criteria	Healthy male subjects, 18 to 45 yrs of age Subjects should have a body weight within 10% of their ideal weight Have no significant diseases or clinically-significant abnormal lab values
Treatments	Subjects were divided into 5 groups. Each group was to receive one of five treatments: • **Group 1: A single dose of IV heparin 50 IU/kg followed by a 10 min IV infusion of 1 mg protamine sulfate/100 IU heparin beginning 45 min after heparin infusion** • **Group 2: A single dose of IV tinzaparin 50 IU/kg followed by a 10 min IV infusion of 1 mg protamine sulfate/100 IU tinzaparin beginning 45 min after tinzaparin**

infusion

- **Group 3: A single dose of SC tinzaparin 75 IU/kg followed by a 10 min IV infusion of 1 mg protamine sulfate/100 IU tinzaparin beginning 3 hrs after tinzaparin infusion**
- **Group 4: A single dose of SC tinzaparin 175 IU/kg followed by a 10 min IV infusion of 1 mg protamine sulfate/100 IU tinzaparin beginning 3 hrs after tinzaparin infusion**
- **Group 5: A single dose of SC sodium chloride (placebo) 0.9% followed by a 10 min IV infusion of 0.5 mg/kg protamine sulfate beginning 3 hrs after injection of placebo**

Sampling Times — Blood samples collected at the following time points in each treatment period:

Pre-dose: at 0 hr before drug administration on days 1 & 3
Post-dose: at 4 and 24 hr on day 3

Safety — Biochemistry, haemodialysis and urinalysis screens were performed on the day prior to the first dose and 24 hrs after the final dose in each period

Pharmacodynamic Markers

The relevant pharmacodynamic parameters to be determined during the study were anti-Xa activity, anti-IIa activity, and aPTT.

Pharmacokinetic Analysis

No pharmacokinetic analysis of the data was performed by the Firm.

Statistical Analysis

Anti-Xa and anti-IIa activities before infusion/injection were compared to the levels 5 min after the end of the infusion of protamine sulfate using a paired t-test (95% CI) and Hotelling's T-square for one sample (to test the combined hypothesis of full neutralization of both anti-IIa and ant-Xa activity). An adjustment was made to the level of significance for the anti-Xa and anti-IIa tests ($p = 0.0125$) to account for the number of statistical tests performed.

Results and Conclusions

Table 19. Mean change (%) in the geometric mean of anti-Xa and anti-IIa activities

Treatment	Anti-Xa activity	Anti-IIa activity

IV heparin (50 IU/kg)	93.4 [redacted]	73.7 [redacted]
IV tinzaparin (50 IU/kg)	79.1 [redacted]	99.4 [redacted]
SC tinzaparin (75 IU/kg)	57.7 [redacted]	93.0 [redacted]
SC tinzaparin (175 IU/kg)	55.0 [redacted]	92.6 [redacted]

* Range

Administration of protamine sulfate seems to effectively neutralize the anticoagulant activity of IV heparin and tinzaparin formulations, as evidenced by reductions in anti-Xa and anti-IIa activities by 73.7-99.4%. As for SC tinzaparin formulations, administration of protamine sulfate still resulted in an effective reduction in anti-IIa activity (93%), but not anti-Xa activity (55-57.7%).
In all treatment groups, aPTT, anti-Xa and anti-II a activities relapsed after the protamine sulfate infusion, which indicates the neutralizing effects of protamine on the anticoagulant activity of heparins are transient.

Reviewer's Comments:

While protamine sulfate was quite effective in inhibiting anti-IIa activity, it failed to exert a similar inhibitory effect on anti-Xa activity. Results of the study indicate that protamine sulfate has a limited and transient ability to neutralize tinzaparin activities.
The Firm suggests that the inhibitory efficacy of protamine sulfate is related to the administered dose of tinzaparin as well as the stage of pharmacokinetics in which neutralization is performed. However, protamine sulfate exerted similar inhibitory effects on anti-IIa and anti-Xa activities for both the 75 IU/kg and 175 IU/kg tinzaparin SC treatments, which suggests that the dose of tinzaparin was not the major factor in determining the effectiveness of the protamine sulfate infusion in inhibiting tinzaparin anticoagulant activities. It seems more plausible that the neutralizing effects of protamine are primarily related to the pharmacokinetic phase of tinzaparin during which protamine was administered. This is suggested by the faster reversal of protamine inhibitory effects on the SC tinzaparin formulations compared to the IV tinzaparin formulation. This might be explained by the fact that while the whole IV tinzaparin dose is immediately available in the systemic circulation for protamine to neutralize, the SC tinzaparin dose is being released slowly from the SC compartment. Thus, absorption of tinzaparin from the SC compartment is likely continuing as protamine is dissipating from the systemic circulation.

NDA: 20-484/ Study 702-925 Study Date: Jun-Jul 1990

Type of Study: Pharmacokinetics of tinzaparin in Renally Impaired Patients on Haemodialysis

Introduction

Study DMP 702-925 is entitled,

"COMPARATIVE PHARMACOKINETIC/PHARMACODYNAMIC STUDY OF LOGIPARIN, A LOW MOLECULAR WEIGHT HEPARIN, AND UNFRACTIONATED HEPARIN IN PATIENTS WITH CHRONIC RENAL FAILURE IN REGULAR DIALYSIS"

Objectives

- To compare the pharmacokinetics and systemic tolerability of tinzaparin and heparin in patients undergoing regular dialysis because of chronic renal insufficiency.

Primary Review Issues:

- **How different is the pharmacokinetics of tinzaparin in renally impaired patients on haemodialysis compared to that of heparin?**

Study Design

Open-label, single dose, randomized, two-period crossover study

Subjects	6 subjects; 5 males and one female
Duration of Study	9 days
Key Inclusion Criteria	Patients undergoing regular haemodialysis due to chronic renal insufficiency, 18 to 70 yrs of age Subjects should have a body weight within 20% of their ideal weight
Treatments	Subjects were randomized to receive one of the two treatments in each period: • **Treatment A: Tinzaparin 75 anti-Xa IU/kg, IV** • **Treatment B: Heparin 75 anti-Xa IU/kg, IV**

Assay Validation	Precision (anti-Xa activity): [redacted] Precision (anti-Xa activity): [redacted] LOD and LOQ were not provided
Interperiod – Washout	7 days
Sampling Times	Blood samples collected at the following time points in each treatment period: **Pre-dose**: at 0 hr before drug administration **Post-dose:** at 0.5, 1, 4, 8, 16, 24, 30 and 36 hrs
Safety	Subjects monitored for incidence of any adverse events

Pharmacodynamic Markers

The pharmacodynamic parameters determined during the study were anti-Xa activity, anti-IIa activity, and aPTT.

Pharmacokinetic Analysis

The following baseline-corrected pharmacokinetic parameters were determined using non-compartmental analysis: C_{max}, t_{max}, $t_{1/2}$, Ke, V_d[1], CL[2], $AUC_{0\rightarrow t}$ and $AUC_{0\rightarrow\infty}$

Results and Conclusions

Table 20. Mean pharmacokinetic parameters for primary pharmacodynamic markers after administration of treatments A & B

	Anti-Xa activity		Anti-IIa activity		aPTT Activity		Hep-Test	
Parameter	**Tinzaparin**	**Heparin**	**Tinzaparin**	**Heparin**	**Tinzaparin**	**Heparin**	**Tinzaparin**	**Heparin**
$AUC_{0\rightarrow 8}$ (IU·hr/ml)	2.8 (1.2)[3]	1.4 (0.3)	---	---	262 (75)	366 (99)	---	---
$AUC_{0\rightarrow 24}$ (IU·hr/ml)	---	---	1.3 (0.55)	0.73 (0.32)	---	---	---	---
$AUC_{0\rightarrow 36}$ (IU·hr/ml)	---	---	---	---	---	---	6.8 (1.0)	1.8 (0.27)
$AUC_{0\rightarrow\infty}$ (IU·hr/ml)	3.5 (1.8)	1.9 (0.2)	1.4 (0.5)	0.73 (0.36)	333 (105)	407 (121)	6.9 (0.99)	1.7 (0.16)
C_{max} (IU/ml)	0.96 (0.22)	0.76 (0.12)	0.35 (0.15)	0.49 (0.24)	95 (28)	213 (76)	1.9 (0.56)	1.0 (0.10)
$t_{1/2}$ (hr)	5.2 (1.8)	5.9 (1.3)	2.7 (0.63)	0.98 (0.32)	5.3 (3.1)	4.2 (2.1)	5.3 (1.4)	1.0 (0.061)
CL (L/hr·kg)	0.028 (0.020)	0.039 (0.004)	---	---	---	---	0.011 (0.0015)	0.044 (0.004)
V_d (L/kg)	0.17 (0.037)	0.32 (0.10)	---	---	---	---	0.086 (0.029)	0.065 (0.004)

[2] CL and V_d were only determined for anti-Xa activity and Hep-Test
[3] S.D.

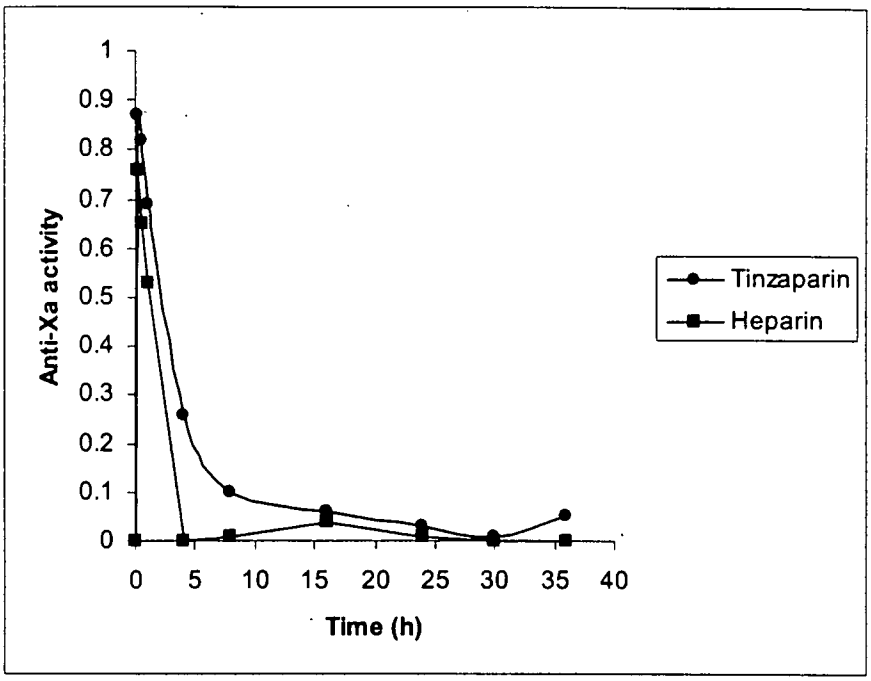


Fig.4. Anti-Xa activity profile over time after administration of a dose of 75 anti-Xa IU/kg, IV of each, heparin and tinzaparin.

Reviewer's Comments:

These comments will primarily focus on anti-IIa and anti-Xa activities as they are the primary pharmacodynamic markers of interest.
Overall, tinzaparin treatment resulted in pharmacokinetic parameters (C_{max}, $t_{1/2}$ and CL) that were comparable in value to those observed with heparin treatment. However AUCs on anti-IIa and anti-Xa activities were 2-fold higher with tinzaparin treatment relative to those with heparin treatment (Table 20). Thus, indicating higher exposure would be expected with tinzaparin compared to heparin in renally impaired patients on haemodialysis. Half-life on anti-IIa activity was also more than 2.7-fold higher with tinzaparin treatment relative to that with heparin treatment.
A comparison of the pharmacokinetic parameters of tinzaparin in this current study with those of a comparable tinzaparin dose (4500 anti-Xa IU, IV) in healthy subjects (See study DMP 702-918) indicates that most of the calculated pharmacokinetic parameters including CL, V_d, and AUC (corrected for dose) were similar. However, half-life of tinzaparin was more than 3-fold higher in renally impaired patients on haemodialysis. In conclusion, adjustment of the therapeutic dose is likely to be needed in renally impaired patients on haemodialysis who might be receiving multiple doses of tinzaparin.

NDA: 20-484/ Study 702-926 **Study Date:** Apr 1986-Mar 1988

Type of Study: Distribution of Tinzaparin in Pregnancy (I)

Introduction

Study DMP 702-926 is entitled,

"THE DISTRIBUTION OF LOW MOLECULAR WEIGHT HEPARIN [redacted] (lhn-1) OVER THE PLACENTAL BARRIER DURING WEEK 15-23 OF PREGNANCY"

Objectives

- To determine if tinzaparin crosses the placental barrier.

Primary Review Issues:

- **Does tinzaparin distribute into the fetus during pregnancy?**

Study Design

Single dose, randomized, controlled, parallel-group study

Subjects	21 subjects. An additional group of 14 subjects were enrolled in a control group a year later
Duration of Study	3 hrs
Key Inclusion Criteria	Women undergoing an abortion by caesarian section during week 15 to 23 of pregnancy Subjects should have a body weight within 20% of their ideal weight
Treatments	Subjects were randomized to receive either of the two treatments: • **Treatment A: Tinzaparin 40 anti-Xa IU/kg, IV, 120 min before anesthesia** • **Treatment B: Heparin 70 anti-Xa IU/kg, IV, 120 min before anesthesia**
Assay Validation	Precision (anti-Xa activity): [redacted] Precision (anti-Xa activity): Not provided LOD and LOQ were not provided

Sampling Times	Blood samples collected at the following time points in each treatment group: **Pre-dose**: at 0 hr before drug administration **Post-dose:** at 10 min, 2 hrs, and when the fetus was removed, a sample was obtained from the umbilical cord of the fetus
Safety	Subjects monitored for incidence of any adverse events

Pharmacodynamic Markers

The pharmacodynamic parameters determined during the study were anti-Xa activity, anti-IIa activity, and aPTT.

Pharmacokinetic Analysis

A pharmacokinetic analysis was not conducted probably due to the limited data available from the study.

Results

Only anti-Xa activity was detectable throughout the study.
10 min after injection, anti-Xa activity levels with heparin treatment were twice as high as with tinzaparin treatment. At 2 hrs post-dose, anti-Xa activity levels were hardly detectable. However, low levels of anti-Xa activity were detectable in the fetal blood in both groups (0.04 and 0.05 anti-Xa IU/ml, respectively).

Reviewer's Comments:

It was interesting to note that anti-Xa activity levels were significantly higher with heparin treatment compared to those with tinzaparin treatment. This points to disappearance of tinzaparin from the systemic circulation at a faster rate than heparin, which might be due to either increased elimination of tinzaparin in pregnant women or to increased distribution, probably to the fetus. The later theory is more plausible. However, the results of the current study do not provide a conclusive answer as to whether tinzaparin crosses the placenta.

NDA: 20-484/ Study 702-927 **Study Date:** Apr 1986-1989

Type of Study: Distribution of Tinzaparin in Pregnancy (II)

Introduction

Study DMP 702-926 is entitled,

"THE DISTRIBUTION OF LOW MOLECULAR WEIGHT HEPARIN [redacted] (lhn-1) OVER THE PLACENTAL BARRIER DURING SECOND TRIMESTER OF PREGNANCY"

Objectives

- To determine if tinzaparin crosses the placental barrier.

Primary Review Issues:

- **Does tinzaparin distribute into the fetus during pregnancy?**

Study Design

Open-label, non-randomized, single dose study

Subjects	17 subjects. Control samples were drawn from 10 women that were not entered into the study.
Duration of Study	3-7 hrs
Key Inclusion Criteria	Women undergoing an abortion by caesarian section during week the second trimester of pregnancy, age 15-36 Subjects should have a body weight within 20% of their ideal weight
Treatments	Subjects were to receive: **Tinzaparin 35 anti-Xa IU/kg, SC, 3-7 hrs before the abortion procedure**
Assay Validation	Precision (anti-Xa activity): Not provided Precision (anti-Xa activity): Not provided LOQ was [redacted] for anti-IIa and anti-Xa activities
Sampling Times	Blood samples collected at predose and at various time points 3-7 hrs post-dose in the women and fetuses

Safety Subjects monitored for incidence of any adverse events

Pharmacodynamic Markers

The pharmacodynamic parameters determined during the study were anti-Xa activity and anti-IIa activity.

Pharmacokinetic Analysis

A pharmacokinetic analysis was not conducted probably due to limited data available from the study.

Results

Table 21. Summary of the mean anti-Xa activity levels in women and fetuses

	Tinzaparin	Control
Predose in women	0.02 ± 0.01	0.02 ± 0.01
After removal of fetus in women	0.17 ± 0.07	0.02 ± 0.01
Fetuses	0.02 ± 0.01	0.02 ± 0.01

Reviewer's Comments:

In the current study, no significant changes were notable in anti-Xa or anti-IIa activity levels in the fetus. However, the results do not explain the low anti-Xa activity levels observed in study DMP 702-926 after administration of an IV dose of tinzaparin. The discrepancy between the two studies might be related to different routes of administration employed in those studies. In conclusion, further studies might be needed to investigate the pharmacokinetic profile of tinzaparin in pregnant women.

NDA: 20-484/ Studies 702-900 & 702-903 **Study Date**: Dec 1988-Apr 1992 & Mar 1994-Oct 1994

Type of Study: Population PK Analysis

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

Division of Pharmaceutical Evaluation II

NDA:	**20-484**
Generic	**Tinzaparin Sodium Injection**
(Brand®)	**Innohep®**
Submission Date:	**July 1, 1999**
Sponsor:	**Dupont Pharma**
Consult:	**Population Pharmacokinetics Analysis**
Pharmacometrics Scientist:	**Sam H. Haidar**

Background

NDA 20-484 for tinzaparin subcutaneous (s.c.) injection (Innohep®) was submitted by Dupont on July 1, 1999. The proposed indication for tinzaparin is initial treatment of acute symptomatic deep vein thrombosis (DVT) with or without pulmonary embolism when administered in conjunction with warfarin sodium.

Tinzaparin is a low molecular weight heparin with anti-thrombotic properties. According to the sponsor, it acts as a potent co-inhibitor of several activated coagulation factors, especially factor Xa and IIa (thrombin). Low molecular weight heparins, including tinzaparin, are polydisperse polysaccharides, which include biologically inactive species. This has made it difficult to measure blood levels following administration of the drug. Currently, anti-Xa activity is used as a clinically relevant pharmacokinetic/ pharmacodynamic (PK/PD) biomarker to characterize drug exposure (pharmacokinetic parameters).

This pharmacometric consult evaluated the population pharmacokinetic analysis performed on data from two Phase III Clinical trials (DMP 702-900 Study designs and results are given below.

Title: Population pharmacokinetic modeling of tinzaparin sodium

Objectives:

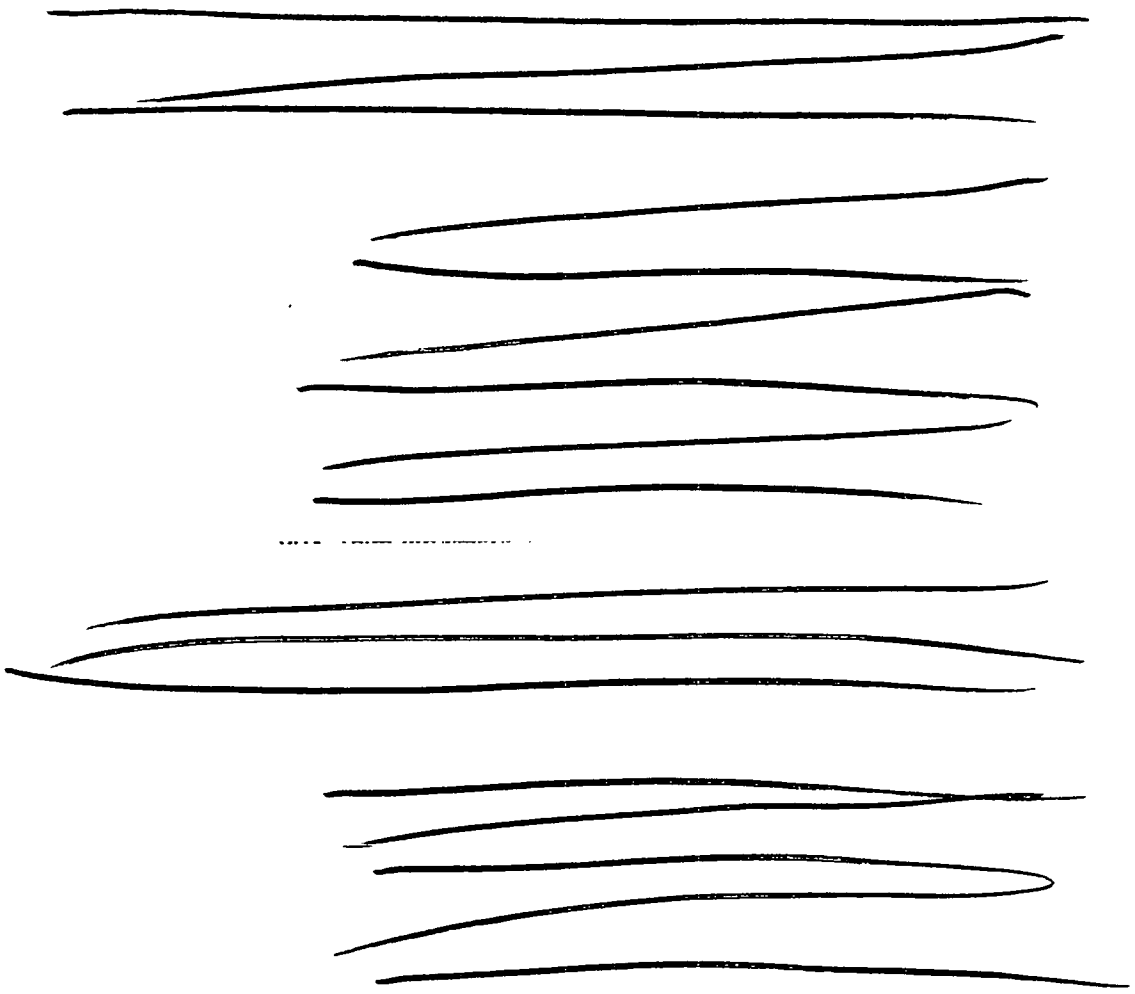
1. Perform a retrospective population analysis of anti-Xa data collected from Phase III clinical trials
2. Evaluate the effect of patient covariates on the anti-Xa effect of tinzaparin

Methods:

Data from two Phase III studies (listed below) which evaluated the efficacy and safety of tinzaparin in the treatment and prevention of DVT were used to develop a population pharmacokinetic model. According to the sponsor, model validation was performed by evaluating the predictive performance of the model on the Validation set. The Index set model with fixed parameters was used to predict individual anti Xa activity in the Validation set. Anti Xa activity was used for the determination of pharmacokinetic parameters.

Study DMP 702-900:

A multi-center, randomized trial of subcutaneous low molecular weight heparin (tinzaparin) versus continuous intravenous unfractionalted heparin for the initial treatment of proximal-vein thrombosis.



Results:

The pharmacokinetics of anti-Xa activity following s.c. injection of tinzaparin were described by a two-compartment model with first order absorption, first order elimination, and endogenous levels of anti-Xa activity. Figure 1 shows anti-Xa activity over time for Study DMP 702-900. Two covariates were found to have a significant effect on clearance: serum creatinine and percent above ideal body weight. The evaluation of individual clearance estimates showed that in severe renal function impairment (creatinine clearance of < 30mL/min), clearance was reduced by 24% compared to normal. Additionally, obese patients (BMI > 30kg/m^2) had clearance that was 22% lower compared to normal. The relationship between clearance and body weight and clearance and serum creatinine, are illustrated in Figures 2 and 3, respectively. The pharmacokinetic

parameters of anti-Xa activity for Study DMP 702-900 and Study [redacted] are listed in Table 1 [redacted] respectively.

Table 1. Parameter estimates of the population model evaluating the Full Data Set of Study DMP 702-900.

Parameter	Estimate	%RSE[a]	95% Confidence Interval		CV[b]
			Low	High	
CL	0.0176	17%	0.012	0.023	NA
V2	0.0981	5.4%	0.088	0.109	NA
KA	0.206	6.2%	0.181	0.231	NA
Q	0.007	44%	0.001	0.013	NA
V3	0.864	81%	-0.512	2.24[c]	NA
ENDO	0.098	9.1%	0.081	0.116	NA
CL_{CREA}	-0.213	37%	-0.366	-0.060	NA
CL_{PIBW}	-0.006	40%	-0.104	-0.001	NA
Inter-individual variability					
ω^2_{CL}	0.125	26%	0.060	0.19	35.4%
ω^2_{KA}	0.182	22%	0.105	0.259	43%
ω^2_{Q}	0.785	80%	-0.45	2.02[c]	89%
ω^2_{V3}	4.69	70%	-1.7	11.08[c]	217%
ω^2_{ENDO}	0.455	37%	0.128	0.782	68%
Residual (intra-individual) variability					
σ^2_{ADD}	0.0103	25%	0.005	0.015	SD = 0.101
σ^2_{PROP}	0.042	22%	0.024	0.060	20.4%

[a]%RSE is percent relative standard error;
[b]Coefficient of variation (CV) for log-normally distributed random variables, standard deviation (SD) for normally distributed random variables;
[c]Indicates 95% confidence interval that includes zero;
[d]Complete variance-covariance matrix is provided in Appendix C.4..2
NA=Not applicable

where CL = clearance (L/hr/kg), V2 = volume of central compartment (L/kg), KA = absorption rate constant (hr^{-1}), Q = intercompartmental clearance (L/hr/kg), V3 = peripheral volume of distribution (L/kg), ENDO = endogenous anti-Xa levels (IU/L), CL_{CREA} = estimated effect of creatinine levels on clearance, CL_{PIBW} = estimated effect of %above ideal body weight on clearance.

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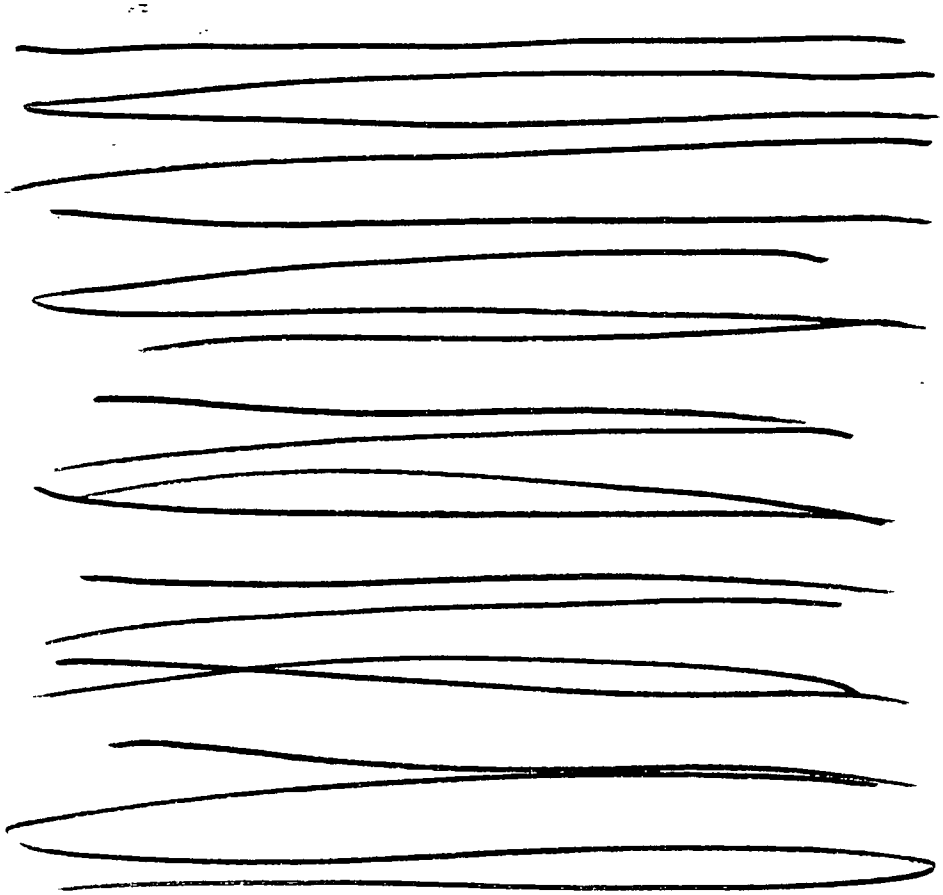

Reviewer's Comments:

The population PK model and analysis are acceptable, but only for qualitative evaluation of the effect of covariates on clearance. The rationale for this plus other comments are listed below:

1. Non-compartmental analysis with previous studies revealed a non-linearity in AUC for doses greater than 5000 IU. For example, a dose of 4500 IU had a mean AUC of 2.0 (±0.5) IU*hr/mL, while a dose of 175 IU/kg (~ 12,000 IU) yielded a mean AUC of 9.6 (±1.6) IU*hr/mL (doubling the dose increased AUC by a factor of 5). The population PK model did not account for this non-linearity: absorption and elimination were represented by 1st order processes. The non-linear response observed at higher doses may be explained by the following: if we plot concentration (tinzaparin) versus response (anti-factor Xa activity), at low doses, a change in concentration would lead to a proportional change in activity (linear part of the curve); at high doses, however, maximum effect is approached (curve levels off) and large changes in drug concentration would yield a small (non-proportional) change in effect. In other words, high doses of tinzaparin produce PD changes that are not parallel to PK changes.

2. Although we acknowledge the difficulties of determining tinzaparin blood levels, anti-Xa activity is a pharmacodynamic biomarker, and not a true PK measurement. As such, interpretation of the elimination process is ambiguous and clearance values should be interpreted with caution.
3. In the data sets for NONMEM analysis, amount of tinzaparin administered to each patient was listed as dose/kg of weight, instead of the usual total dose. The sponsor should clarify the reasoning for this.
4. Several tables in Study Report DM&P 99-014 (e.g. Table 8 and Table 9) list PK parameters without providing units. For future submissions, units should be provided whenever parameters are listed.
5. The sponsor did not provide a rationale for the method that was used for model validation.
6. Clearance does appear to be influenced by renal function and body weight. Estimates of the effect of renal function and body weight on clearance should be interpreted with caution since the model used did not account for the non-linearity of the anti-factor Xa seen with higher doses.

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Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Peer reviewed by Joga Gobburu, Ph.D.

cc:
NDA 20-484
HFD-870 (Huang S-M, Alfayoumi S, Doddapaneni S, Haidar S)
HFD-860 (Gobburu J.)
HFD-850 (Lee P.)
CDR (Barbara Murphy For Drug)

Appendix A

DUPONT

DuPont Pharmaceuticals Company

February 9, 2000

Lilia Talarico M.D.
Division of Gastrointestinal and Coagulation
Drug Products
Food and Drug Administration
VIA FEDERAL EXPRESS

RE

RE: NDA No. 20-484; innohep® (tinzaparin sodium injection)
General Correspondence: Response to FDA Request for Information

Dear Dr. Talarico:

Reference is made to our NDA #20-484 for innohep® (tinzaparin sodium) submitted June 30, 1999. Reference is also made to the telephone requests from Ms. Karen Oliver of the Division on behalf of Dr. Suliman Al Fayoumi on January 11, 2000 and February 8, 2000. A reanalysis of Phase I Study DMP 702-919 was requested, which was to include non-compartmental modeling and appropriate statistical analyses. In addition, information on the availability of bioanalytical methods validation reports for the following studies was requested: DMP 702-919 and DMP 702-920 (requested on 1/11/00) and DMP 702-921, DMP 702-922, DMP 702-924, DMP 702-925, and DMP 702-926 (requested on 2/8/00).

We are submitting the requested re-analysis as an addendum to Clinical Study Report DMP 702-919 at this time. To assist the reviewer, the SAS data *sets as* well as an Excel® Workbook containing the anti-Xa and anti-Ha profiles and analyses for study 702-919 are also being provided electronically.

Regarding the bioanalytical methods validation, a history of the bioanalytical methodology was included in the NDA (Volume 1.32, Pages 75-90). This discussion included a table of methods, laboratories, and availability of methods validation reports

Response to FDA Request for Reanalysis of Study DMP 702-919 (S/LOG/001/KIN), DM&P 00-010

SUMMARY

Based on the request from FDA, we have undertaken the reanalysis of Study DMP 702-919 (S/'LOG/001/KIN). The primary focus of the study was the characterization of the pharmacodynamics of tinzaparin following single intravenous and subcutaneous administration to healthy volunteers. Subcutaneous heparin was administered, as well as comparative treatments completing the six period crossover design. Activated partial thromboplastin times (aPTT), eubglobin clot lysis (ECLT), tissue plasminogen activator (tPA) and anti-thrombin RI (AT III), plasminogen, and a2-antiplasmin were also assessed as secondary markers. Based on the request of the reviewer we have confined our reanalysis to the pharmacodynamics of anti-Xa and anti-Ha activities. The source data was not available in electronic form. More problematic is the fact that the listed individual activity data was manually entered in the Appendix tables and only summary data was typed in the body of the report. We have entered this data into an electronic format for subsequent processing. The individual anti-Xa and anti-Ha activity data, pharmacodynamic parameters derived from the non-compartmental analysis, and the summary statistics have been provided with this reanalysis to assist FDA with this review.

The study duration was from November 1984 to February 1985. The analytical and pharmacodynamic analyses are somewhat dated relative to other studies in the NDA. The analytical methodology used to quantify anti-Xa and anti-IIa activities has evolved over time as discussed in detail in the Section 6 summary of the NDA. Hence, particularly with respect to the choice of calibrator (4^{th} vs. 1st International Standards), this study cannot be compared to others (the 4th International Standard was used as the calibrator in this study). In addition, the compartmental-analysis used to assess the pharmacodynamics of tinzaparin and heparin is no longer common practice especially given the limited sampling and variability in the data. The six-way crossover design with

Response to FDA Request for Reanalysis of Study DMP 702-919 DM&P 00-010

1. METHODS

Individual data (anti-Xa and anti-IIa activity determinations for individual subjects following each of the 6 study treatments) was not contained in the body or appendices of the DMP 702-919 report. While mean activity and pharmacodynamic metrics were provided in the report, the only record of the source data is contained on the case report forms (starting on Item 6, Volume 12, Page 135). Data have been hand entered and are available in both MS Excel and SAS formats. Table 1 contains a listing of all electronic files provided with the reanalysis.

Anti-Xa and anti-IIa activity time course data for each subject following each of the six study treatments have been reanalyzed by standard non-compartmental analysis using a validated software package, SAS PH.Kinetics, running under Windows NT v. 4.1. Area under the activity-time curve (AUC) was calculated using a combined log-linear interpolation method. The terminal rate constant was determined via regression of the terminal log-linear activity-time phase. Activity half-life was determined by the quotient of the natural logarithm of 2 and 3. Clearance and steady-state volume of distribution were likewise derived from AUC, dose and 3,. In several cases, the data were inadequate to determine the terminal phase rate constants. Even when sufficient terminal phase data exist, there are spurious observations in several subject profiles. The Appendix contains the individual subject data along with the terminal phase regression statistics (regression interval, number of observations in regression, and r-square).

Given the few observations (evaluable metrics) without replication, regressions of AUC and Cmax have not been performed. Descriptive statistics (mean and standard deviation) for each treatment group have been provided per the reviewer's request. Data are expressed by arithmetic mean and standard deviation.

WWI: REP0000575
February 8, 2000

Response to FDA Request for Reanalysis of Study DMP 702-919

DM&P 00-010

2. RESULTS

There was no validation of anti-IIa or anti-Xa activity provided with the original clinical study report. While controls were done with each standard curve, there was no attempt to define the lower limit of quantification and all non-zero data have been reported (see Item 6, Volume 12, Page 54). In addition, activity greater than 0.8 IU/mL was extrapolated from the standard curve. Both of these practices cast uncertainty around the data particularly at the low and high ends of the standard curve. In general, the method utilized is consistent with the package insert provided with the Kabi Diagnostica kit, which was used to generate the anti-Xa results.

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February 8, 2000

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ON ORIGINAL

Response to Questions Concerning Bioanalytical Methods Validation

As we have previously outlined, the bioanalytical methods surrounding the biomarker assays determining anti-Xa and anti-IIa activity have evolved over the span of time that tinzaparin was developed. These methods are also distinctly unique relative to conventional assays used to quantify drag concentrations in biological matrices. Specifically, the methods more closely resemble clinical pathology methods which don't typically involve the same sort of validation rigor, A dally standard curve with high and low controls is typically the benchmark for ensuring a lab / site can perform the assay. The response of the kit calibrators should also compare to the data in the package insert. This practice is commonly adhered to in most clinical settings for which anti-Xa activity in particular is assessed in order to monitor heparin therapy. This was the common practice for all tinzaparin pharmacokinetic studies as well. More rigorous validations were undertaken by the [redacted] which did support many of the bioanalytical component of many of the studies in which pharmacokinetics were assessed (see Table 4. I from NDA Volume 1.32, Pages 87-89, copy attached). [redacted] validation report is contained in the NDA (Study Report Appendix C.3; Volume 1.39, Pages 233-401).

More recently, in a paper by Kitchen et. al. (Thromb Haemost 82: 1289-93, 1999), chromogenic versus clotting anti-Xa methods have been compared. While the authors point out the differences between the various techniques, the performance of the chromogenic methods for a particular drug substance is surprisingly robust. Given that the chromogenic method was used in all tinzaparin pharmacokinetic studies, this information should be portable to the studies in question. In support of this, the reanalyzed DMP 702-919 data compare reasonably well with study DMP 702-918 (a more recent study with more rigorous bioanalytical standards).

We recognize the lack of validations in place to support the early pharmacokinetic studies with tinzaparin. Given the evolution and nature of the methodologies and the current common practices, this is somewhat understandable. We have made every effort to improve the analytical methods associated with the quantification of anti-Ha and anti-Xa activity as evidenced by our most recent bioequivalence trial (see analytical validation report for DMP 702-001; Study Report Appendix C.3; NDA Volume 1.36, Pages 2-235) and continue to promote this methodology in ongoing studies with tinzaparin.

For the above reasons, the pharmacokinefic and pharmacodynamic characterization presented in the labeling is derived from more recent trials with tinzaparin (primarily DMP 702-001 and DMP 702-918). Other studies are referenced only by their qualitative findings which we believe are still valid. Again, the robustness of these methods seem adequate based on the comparability of the data across studies.

1 *Regarding Study DMP 702-922, Group 2 received a single dose of 250 IU/kg tinzaparin, then that group was discontinued due to "unacceptable" coagulation parameters. Please clarify what was meant by "unacceptable" and provide the individual patient data from Group 2.*

Response:

In study DMP 702-922, a multiple-dose study in healthy volunteers, Group 2 was initially intended to receive 250 IU/kg tinzaparin once daily for 5 days. After the first dose was administered to this group, dosing was discontinued due to unacceptable coagulation parameters. Specifically, four subjects received a single 250 IU/kg dose (subject numbers 7, 8, 9, and 11). At four hours post-dose, no clot was detected on thrombin time for all four of these subjects. Of note, the aPTT values increased by 1.3 to 3.5-fold (subject 7 = 3.5 X, subject 8 = 1.3 X, subject 9 = 3.1 X, and subject 11 = 2.0 X). Ratios in excess of a two-fold increase exceed the target therapeutic range for intravenously administered unfractionated heparin. A/though there was no clinical bleeding, the investigators judged this to be an unacceptable level of anticoagulation. Subsequently, the dose of Group 3 was reduced from the planned dose of 350 IU/kg once daily to 200 IU/kg once daily.

The individual subject anticoagulation data for group 2 were provided in the original study report, NDA volume 1.44, pages 240-242.

2. *Regarding Study DMP 702-922, please provide the rational for how protamine was administered in this study.*

APPEARS THIS WAY
ON ORIGINAL

Response:

In study DMP 702-922, protamine sulfate was administered at a dose of I rag protamine to 100 units of anti-Factor Xa activity, which is the same dose specified in other low molecular weight heparin package inserts. The anti-Factor Xa activity used in the dose calculation was that obtained 4 hours after dosing, approximating the Tmax. The time of protamine administration was specified in the protocol as 16 hours after the last dose in the first group (150 IU/kg bid) and 4 hours after the last dose in the second and third groups (250 IU/kg qd and 200 IU/kg qd, respectively). The [redacted] protocol did not contain a rationale for this dosing time of protamine, however ~DA volume 1.44, page 340). It is likely that the group which received protamine 16 hours after the last tinzaparin dose (a time where the anti-Xa activity from the tinzaparin would be expected to be low) was intended to serve as a control group to insure the anti-coagulant effects of protamine alone were also evaluated.*3. Regarding study DMP 702-924, please indicate the location of sampling time point data in the study report, or provide that data if not in the study report.*

Response:

A summary of sampling times by group for study DMP 702-924 is located in the "Second Addendum" to the clinical study report (NDA volume 1.45, pages 268-272). The individual subject data listings for actual sampling dates/times are located in NDA Volume 1.46, pages 96-110. The individual subject listings for coagulation parameters at each sampling time are located in NDA Volume 1.46, pages 128-141.

4. Please provide a status update for study 702-945.

Response:

Study DMP 702-945 is an ongoing Phase I study evaluating multiple subcutaneous doses of 175 IU/kg tinzaparin in healthy male volunteers. The dosing phase of this study has been completed, however a clinical study report is not available at this time. Data analysis and preparation of the report are currently in progress.

7 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-484

JUL 10 2000

Name of Drug: Innohep® (tinzaparin sodium injection)

Sponsor: DuPont Pharmaceuticals Company

Material Reviewed

Submission Date: July 6, 2000

Receipt Date: July 6, 2000

Background and Summary Description: One June 30, 1999, the DuPont Pharmaceuticals Company submitted NDA 20-484 for Tinzaparin Sodium Injection for the following indications: (1) Treatment of acute deep vein Thrombosis (DVT), with and without pulmonary embolism (PE) when administered in conjunction with warfarin sodium; and ([redacted] On April 28, 2000, an approvable letter was issued by the Agency for the following indication: [redacted] treatment of acute symptomatic deep vein thrombosis when administered in conjunction with warfarin sodium". On May 15, 2000, the sponsor submitted a full response to that action letter. On June 30, 2000, the sponsor was faxed a copy of the "FDA revised labeling". On July 6, 2000, the sponsor submitted their counter proposal for the text for the package insert. An internal divisional labeling meeting was convened and the labeling reviewed. Attendees at the labeling meeting were, Dr. Talarico, Division Director, Dr. Robie-Suh, Hematology Medical Team Leader, Dr. He, Medical Reviewer, Ms. Oliver, Regulatory Health Project Manager, and Ms. Kacuba, Regulatory Health Project Manager.

Review

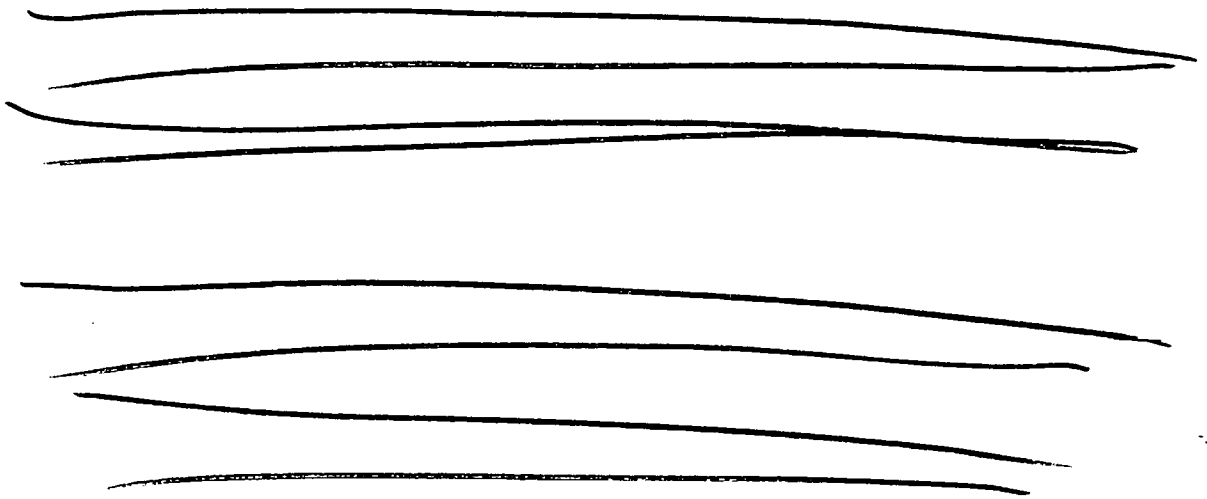
The submitted package insert, identified as "6536/July 2000", was compared to the FDA revised labeling that was faxed to the sponsor on June 30, 2000. The revisions that the sponsor made that are what we asked for are not mentioned here. Only the points where there is a difference between the Agency and the sponsor are discussed here. The following revisions were discussed. Additions are shown as <u>double underlines</u> and strikeouts are shown as ~~strikeouts~~. A clean copy of the FFDA revised labeling is attached at the end.

1. In the CLINICAL STUDIES section, "Treatment of Acute Deep Vein Thrombosis (DVT) With or Without Without Pulmonary Embolism (PE) subsection, the first three sentences were revised from:

   "In a randomized, multicenter, double-blind trial, Innohep was compared to unfractionated heparin in 435 hospitalized patients with symptomatic, proximal DVT. The study patients

ranged in age from 19 to 92 years (mean 61 ± 17 years), 55% were male, 88% were white and 8% black."

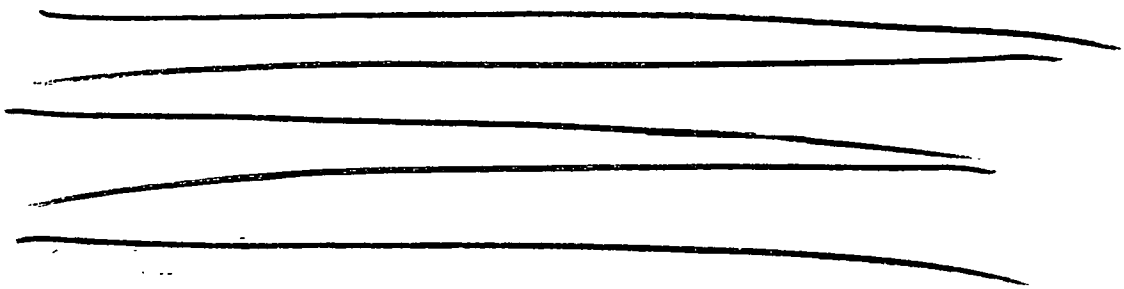
to:



2. In the CLINICAL STUDIES section, "Treatment of Acute Deep Vein Thrombosis (DVT) With or Without Without Pulmonary Embolism (PE) subsection, the last two sentences prior to Table 3 were revised from:

"90-day cumulative thromboembolic (TE) rate [recurrent DVT or PE] with Innohep was not significantly different than unfractionated heparin (p= 0.071). The data are provided in Table 3.

to:



3. Following Table 3, the following has been revised from:

[redacted]

In a multicenter, open-label, randomized clinical trial, Innohep was compared to unfractionated heparin as initial treatment for patients with symptomatic PE not requiring thrombolytic therapy, embolectomy, or vena cava interruption. Patients were excluded if they carried an unusually high risk for thromboembolic and/or bleeding events or other complications. Of the 608 patients treated, 422 had documented DVT. [redacted]

Innohep was administered SC once daily, 175 IU/kg body weight; heparin as an initial IV bolus (50 IU/kg) followed by continuous IV infusion with the rate adjusted according to the aPTT (2-3 times control value). For both groups, treatment continued for approximately 8 days. All patients also received oral anticoagulant treatment starting in the first 3 days which continued to Day 90."

to:

"Mortality with INNOHEP was 4.6% (10 patients) and with heparin 9.6% (21 patients). The 95% confidence interval (CI) for the mortality difference was 0.16%, 9.76%.

[redacted]

4. The INDICATIONS AND USAGE section has been revised as follows:

"Innohep is indicated for the ~~inpatient~~ treatment of acute symptomatic deep vein thrombosis with or without pulmonary embolism when administered in conjunction with warfarin sodium."

5. The CONTRAINDICATIONS section, a comma has been removed in the first sentence.

Comment: The review team recommends that the comma remain for the sentence to read:

"INNOHEP is contrindicated in patients with active major bleeding, in patients with (or history of) heparin-induced thrombocytopenia, or in patients with hypersensitivity to tinzaparin sodium."

6. The only sentence in the third paragraph of the WARNINGS section has been deleted.

Comment: The review team recommends that the paragraph remain and remain bolded to read:

"INNOHEP should be used in patients with a history of heparin-induced thrombocytopenia."

7. In the WARNINGS section, "Miscellaneous" subsection, the text has been revised from:

"Miscellaneous: Innohep multiple dose vial contains benzyl alcohol as a preservative. The administration of medications containing benzyl alcohol as a preservative to premature neonates has been associated with a fatal "Gasping Syndrome". Because benzyl alcohol may cross the placenta, Innohep preserved with benzyl alcohol should be used with caution in pregnant women (see **PRECAUTIONS**, Pregnancy,

[redacted]

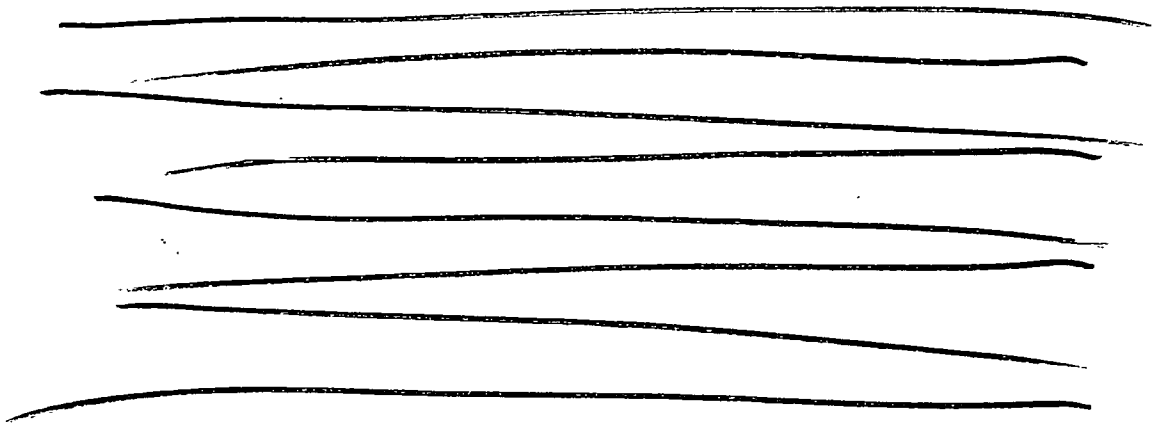
8. In the PRECAUTIONS section, "Pregnacy" subsection, the "Non-teratogenic Effects sub-sub-section has been revised from:

[redacted]

to:

"Non-teratogenic Effects: There have been four reports of fetal death/miscarriage in pregnant women receiving INNOHEP who had high risk pregnancies and/or a prior history of spontaneous abortion. Approximately 6% of pregnancies were complicated by fetal distress. There have been spontaneous reports of one case each of [redacted] pulmonary dysplasia or muscular hypotonia in infants of women receiving INNOHEP during pregnancy. A cause and effect relationship for the above observations has not been established.

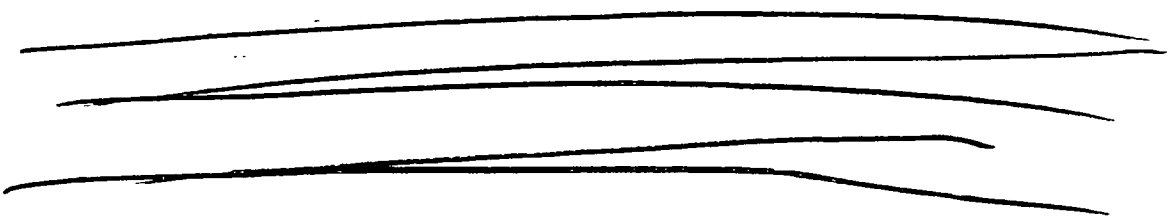
Approximately 10% of pregnant women receiving INNOHEP experienced significant vaginal bleeding. A cause and effect relationship has not been established."

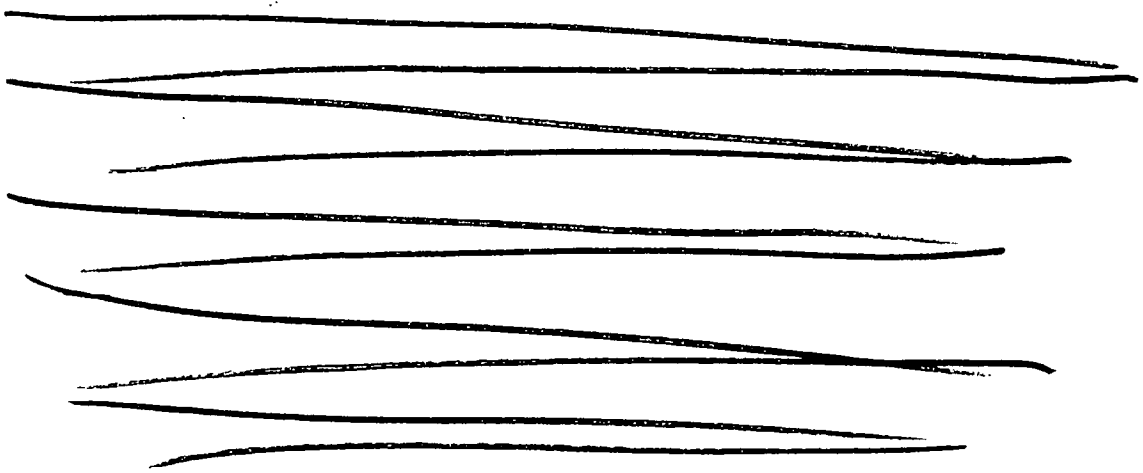


If Innohep is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of potential hazards to the fetus."

9. In the ADVERSE REACTIONS section, the "Other Adverse Events" subsection, the review team recommends deleting Table 6, entitled "Table 6. Other Adverse Events (≥1%) in Clinical Trials" and replace it with the following text:

"*Body as a Whole:* injection site hematoma, reaction unclassified.
Cardiovascular Disorders, General: hypotension, hypertension.
Central & Peripheral Nervous System Disorders: dizziness.
Gastro-Intestinal System Disorders: flatulence, gastro-intestinal disorder (not otherwise specified), dyspepsia.
Heart Rate and Rhythm Disorders: tachycardia.
Myo-, Endo-, Pericardial & Valve Disorders: angina pectoris.
Platelet, Bleeding & Clotting Disorders: hematoma, thrombocytopenia.
Psychiatric Disorders: insomnia, confusion.
Red Blood Cell Disorders: anemia.
Resistance Mechanism Disorders: healing impaired, infection.
Respiratory System Disorders: pneumonia, respiratory disorder.
Skin and Appendages Disorders: rash erythematous, pruritus, bullous eruption, skin disorder.
Urinary System Disorders: urinary retention, dysuria.
Vascular (Extracardiac) Disorders: thrombophlebitis deep, thrombophlebitis leg deep."





Conclusions

The "FDA revised labeling" agreed upon by the division should be forwarded to Victor Raczkowski, along with the action package for Office review.

/S/ 7-7-00
Regulatory Health Project Manager

/S/ 7-10-00
Division Director

cc:
Original NDA 20-484
HFD-180/Div. Files
HFD-180/A.Kacuba
HFD-180/K.Oliver

Draft: A.Kacuba/July 10, 2000
Final: AK/July 10, 2000

CSO REVIEW

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-484

JUL 6 2000

Name of Drug: Innohep® (tinzaparin sodium injection)

Sponsor: DuPont Pharmaceuticals Company

Material Reviewed

Submission Date(s): May 15, 2000

Receipt Date(s): May 16, 2000

Background and Summary Description:

One June 30, 1999, the DuPont Pharmaceuticals Company submitted NDA 20-484 for Tinzaparin Sodium Injection for the following indications: (1) Treatment of acute deep vein Thrombosis (DVT), with and without pulmonary embolism (PE) when administered in conjunction with warfarin sodium; and (2) prevention of DVT, which may lead to PE, in patients undergoing knee or hip replacement surgery. On April 28, 2000, an approvable letter was issued by the Agency for the following indication: "the initial inpatient treatment of acute symptomatic deep vein thrombosis when administered in conjunction with warfarin sodium".
On May 15, 2000, the sponsor submitted a full response to that action letter.

Review

PACKAGE INSERT

The draft package insert (PI) labeling text (located in volume 2, behind tab labeled "Proposed Annotated Package Insert"), identified as "6536-00/May 2000, was compared package insert text enclosed in the April 28, 2000 approvable letter. The package inserts are identical except for the following:

1. In the DESCRIPTION section:

   a. [redacted]

      This is UNACCEPTABLE. The sentence should be revised to read as follows:

      It is available in a multiple dose 2 mL vial.

b. The second paragraph has been changed

from:

to:

> Each 2 mL vial contains 20,000-anti-Factor Xa IU (anti-Xa) of tinzaparin sodium per mL, for a total of 40,000 IU, and 3.1 mg/mL sodium metabisulfite as a stabilizer. The vial contains 10 mg/mL benzyl alcohol as a preservative. Sodium hydroxide may be added to achieve a pH range of 5.0 to 7.5.

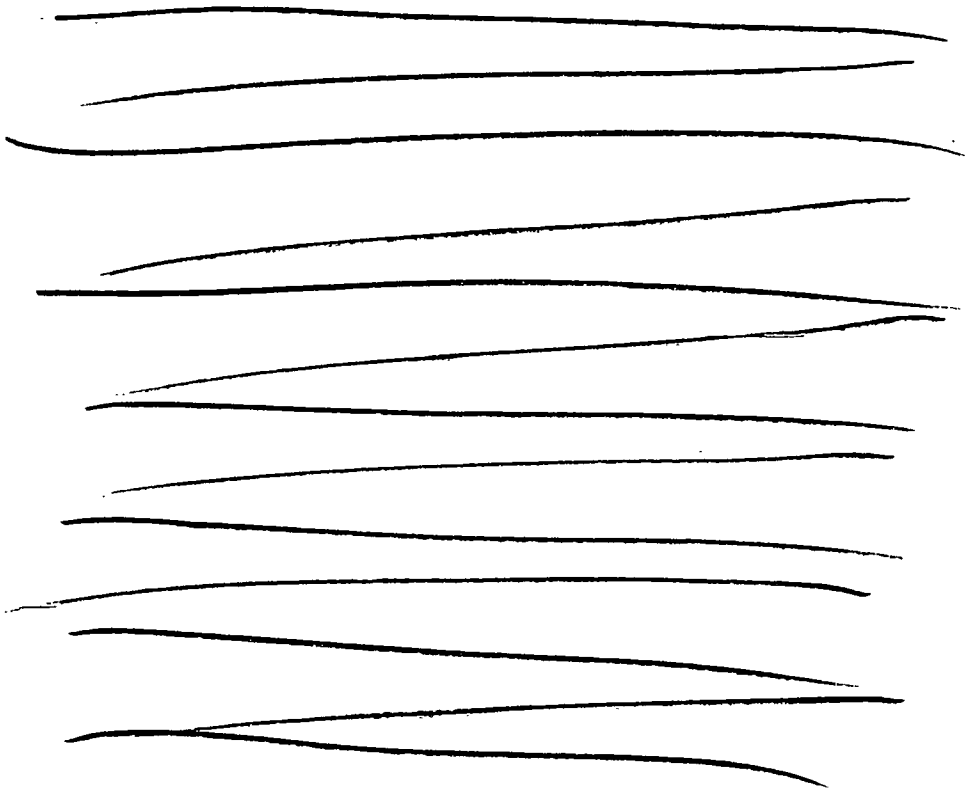
This change is UNACCEPTABLE. The dash (-) after the number "20,000" should be deleted.

c. As requested in the April 28, 2000 letter, Table 1 was added after the second paragraph of the section to read as follows:

Table 1. Composition of 20,000 anti-Xa IU/mL TRADENAME (tinzaparin sodium) Injection

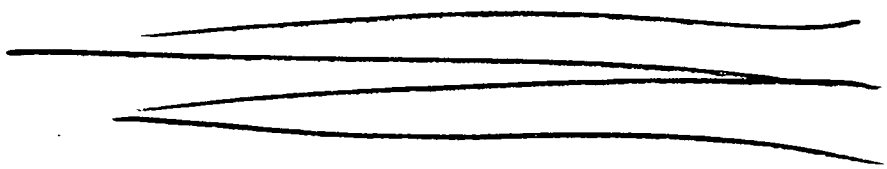
Component	Quantity per mL
Tinzaparin sodium	20,000 anti-Xa IU
Benzyl alcohol, [redacted] USP	10 mg
Sodium metabisulfite, [redacted] /USP	3.106 mg[1]
Sodium hydroxide, [redacted] USP	as necessary
Water for Injection, [redacted] USP	q.s. to 1 mL

[1]Corresponding to 3.4 mg/mL sodium bisulfite



d. In the third paragraph, the first sentence, the underlined words were deleted. The sentence was changed

from:



to:

Tinzaparin sodium is the sodium salt of a low molecular weight heparin obtained by controlled enzymatic depolymerization of heparin from porcine intestinal mucosa using heparinase from *Flavobacterium heparinum*.

This deletion was reviewed by the CHEMISTRY REVIEWER, Dr. Ali Al-Hakim, and it is ACCEPTABLE.

e. In the fourth paragraph, the first sentence, the underlined words were added to the following sentence to read:

> Potency is determined by means of a biological assay and interpreted by the first International Low Molecular Weight Heparin Standard as units of anti-factor Xa (anti-Xa) activity per milligram.

This addition is ACCEPTABLE.

f. In the fourth paragraph, the third sentence, the underlined word was added to the sentence to read as follows:

> The mean tinzaparin sodium anti-factor Xa activity is approximately 100 IU per milligram.

This addition is ACCEPTABLE. The reviewer notes that throughout the text, when the word "tinzaparin" was printed, the word "sodium" was added after it to read "tinzaparin sodium". This is ACCEPTABLE.

2. In the CLINICAL PHARMACOLOGY section:

a. In the first paragraph, the first and the second sentence, the underlined words were change

from:

> Tinzaparin sodium is a low molecular weight heparin which has antithrombotic properties. Tinzaparin inhibits reactions that lead to the clotting of blood and the formation of fibrin clots both *in vitro* and *in vivo*.

to:

> Tinzaparin sodium is a low molecular weight heparin with antithrombotic properties. Tinzaparin sodium inhibits reactions that lead to the clotting of blood including the formation of fibrin clots, both *in vitro* and *in vivo*.

These changes were reviewed by the BIOPHARMACEUTICS REVIEWER, Dr. Suliman Al-Fayoumi, and it is ACCEPTABLE.

b. In the "Pharmacokinetics/Pharmacodynamics" subsection:

(1) In the first paragraph, the second sentence, the underlined words were changed

from:

[redacted]

to:

Because of analytical assay limitations, anti-Xa activity is the more widely used biomarker.

This change should be reviewed by the BIOPHARMACEUTICS REVIEWER, Dr. Suliman Al-Fayoumi, and it is ACCEPTABLE.

(2) The underlined words in the title of "Figure 1" has been changed

from:

[redacted]

to:

Mean and Standard Deviation Anti-Xa Activity Following a Single SC Administration of 175 IU/kg and 4,500 IU* Tinzaparin Sodium to Healthy Volunteers

This change should be reviewed by the BIOPHARMACEUTICS REVIEWER, Dr. Suliman Al-Fayoumi, and it is ACCEPTABLE.

c. In the "Absorption" subsection:

(1) In the second sentence, the underlined word was changed

from:

to:

> Maximum concentrations (Cmax) of 0.25 and 0.87 IU/mL are achieved following a single SC fixed dose of 4,500 IU (approximately 64.3 IU/kg) and weight-adjusted dose of 175 IU/kg of tinzaparin sodium respectively.

This change should be reviewed by the BIOPHARMACEUTICS REVIEWER, Dr. Suliman Al-Fayoumi, and it is ACCEPTABLE.

(2) In the third sentence, a comma was added after the word "ratio" to read as follows:

> Following a single SC injection of tinzaparin sodium, the mean anti-Xa to anti-IIa activity ratio, based on the area under the anti-Xa and anti-IIa time profiles, is 2.8 and is higher than that of unfractionated heparin (approximately 1.2).

This addition is ACCEPTABLE.

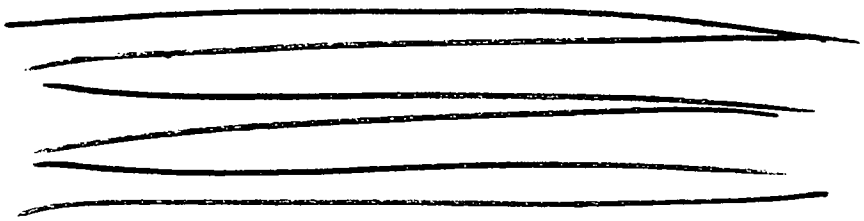
d. In the "Population Pharmacokinetics" subsection, in the first sentence, the word "tinzaparin sodium" was inserted in place of the TRADENAME, as requested in the April 28, 2000 letter. The sentence was changed

from:

to:

Anti-Xa concentrations from approximately 180 patients receiving SC tinzaparin sodium once daily (175 IU/kg body weight) as the initial treatment of proximal DVT and approximately 240 patients undergoing elective hip replacement surgery receiving SC tinzaparin sodium once daily (~65 IU/kg body weight) were analyzed by population pharmacokinetic methods.

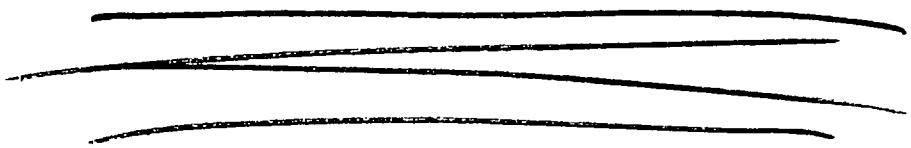
This change was reviewed by the BIOPHARMACEUTICS REVIEWER, Dr. Suliman Al-Fayoumi, and it is UNACCEPTABLE. The text should be revised to read as follows:



e. In the "Renal Impairment" subsection:

(1) In the first sentence, the underlined words were changed

from:



to:

> In 6 patients undergoing hemodialysis for chronic renal failure, the half-life of anti-Xa activity following a single IV dose of 75 IU/kg of tinzaparin sodium was prolonged compared to that for healthy volunteers (5.2 versus 1.6 hours).

This change should be reviewed by the BIOPHARMACEUTICS REVIEWER, Dr. Suliman Al-Fayoumi, and it is ACCEPTABLE.

(2) In the fourth sentence, the underlined words were changed

from:

to:

This change should be reviewed by the BIOPHARMACEUTICS REVIEWER, Dr. Suliman Al-Fayoumi, and it is UNACCEPTABLE. The sentence should be revised to read as follows:

> **Patients with severe renal impairment exhibited a 24% reduction in tinzaparin sodium clearance relative to the remainder of the patients in the study.**

3. In the CLINICAL TRIALS section., in the "Treatment of DVT" subsection:

a. The title of the subsection has been changed

from:

[redacted]

to:

Treatment of Deep Vein Thrombosis (DVT) and
Pulmonary Embolism (PE)

This change was reviewed by the MEDICAL OFFICER, Dr. Ruyi He, and it is UNACCEPTABLE. The subsection title should be revised to read as follows:

Treatment of Acute Deep Vein Thrombosis (DVT) with or without Pulmonary Embolism (PE)

b. The description of the clinical trials was extensively revised (therefore, the entire text will be provided)

from:

[redacted]

Table 2. Efficacy of Tinzaparin Injection in the Treatment of Deep Vein Thrombosis (Adjudicated Assessments at 90 Days)

INDICATION	[redacted]		
[redacted] population	216	219	
Patient Outcome			
Total TE[2] Events	6 (2.8%)[3]	15 (6.8%)	
DVTs	3 (1.4%	9 (4.1%)	
PEs	3 (1.4%)	6 (2.7%)	

[1] [redacted] patients were also treated with warfarin sodium commencing within 24-48 hours of tinzaparin or standard heparin therapy.
[2]TE = thromboembolic events (DVT and/or PE)
[3]The 95% Confidence Interval (CI) : [redacted] for total thromboembolic events was (0.07%, 8.07%).

Mortality with TRADENAME was 4.6% (10 patients) and with heparin 9.6% (21 patients). The difference was [redacted]

In a multicenter, open-label, randomized clinical trial TRADENAME was compared to unfractionated heparin as initial treatment for patients with symptomatic PE not requiring thrombolytic therapy or embolectomy. Of the 608 patients, 422 had documented DVT. TRADENAME was administered SC once daily, 175 IU/kg body weight; heparin as an initial IV bolus (50 IU/kg) followed by continuous IV infusion with the rate adjusted according to the aPTT (2-3 times control value). For both groups, initial treatment continued for approximately 8 days. All patients also received oral anticoagulant treatment starting in the first 3 days which continued to day 90.

Thromboembolic events were infrequent for both treatment groups. No difference was observed between the two treatment groups for incidence of recurrence of thromboembolic events.

1 page(s) of revised draft labeling has been redacted from this portion of the review.

[redacted]

These changes were reviewed by the MEDICAL OFFICER, Dr. Ruyi He, and they are UNACCEPTABLE. The section should be revised (See Attachment entitled "Red-line/Strike-Out Version of the Labeling").

4. In the INDICATIONS section, the indication was changed

from:

[redacted]

to:

> TRADENAME is indicated for the treatment of acute symptomatic deep vein thrombosis with and without pulmonary embolism when administered in conjunction with warfarin sodium.

This change was reviewed by the MEDICAL OFFICER, Dr. Ruyi He, and it is UNACCEPTABLE. The indication should be revised to read as follows:

[redacted]

5. In the WARNINGS section:

a. In the third paragraph was deleted.

This is UNACCEPTABLE. The last paragraph should be re-instated, in bolded type-face, to read as follows:

> **Innohep should be used with [redacted] patients with a history of heparin-induced thrombocytopenia.**

b. In the "Hemorrhage" subsection, in the third paragraph, the second sentence, the underlined word was changed

from:

[redacted]

to:

> **The risk of these events is higher with the use of post-operative indwelling epidural catheters or with the concomitant use of additional drugs affecting hemostasis such as NSAIDs (see boxed WARNING and PRECAUTIONS, Drug Interactions).**

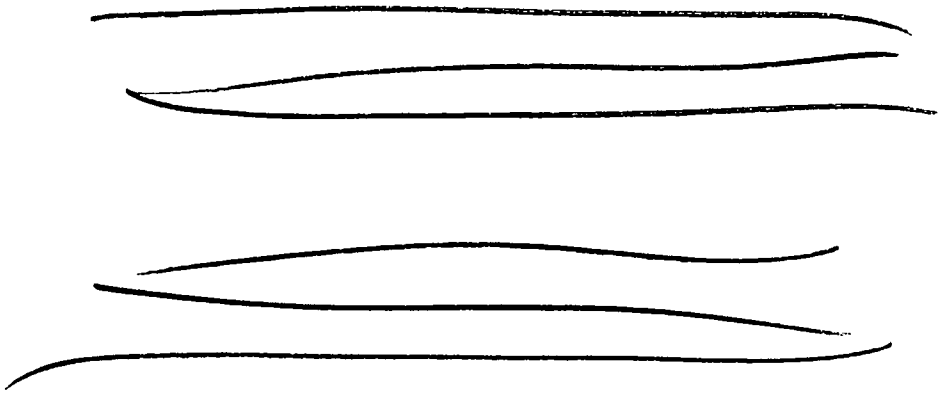
This change was reviewed by MEDICAL OFFICER, Dr. Ruyi He, and it is ACCEPTABLE.

c. In the "Thrombocytopenia" subsection:

(1) The second paragraph was changed

from:

[redacted]



These changes was reviewed by the MEDICAL OFFICER, Dr. Ruyi He, and they are UNACCEPTABLE. The second paragraph should be revised to read as follow:

> **In clinical studies, thrombocytopenia (platelet count if baseline value ≥150,000/mm^3, ≥50% decline if baseline <150,000/mm^3) was identified in 1% of patients given Innohep; severe thrombocytopenia (platelet count less than 50,000/mm^3) occurred in 0.13%.**

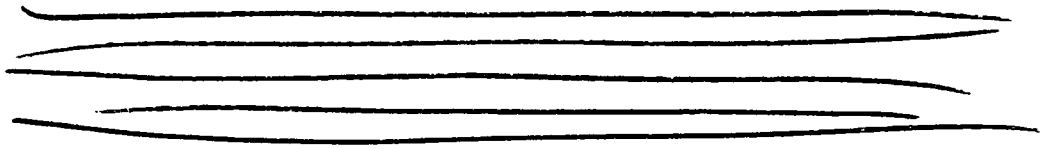
(2) In the third paragraph, the second sentence. the word "tinzaparin" was replaced with the word "TRADENAME" to read as follows:

> If the platelet count falls below 100,000/mm^3, TRADENAME should be discontinued.

This change is ACCEPTABLE.

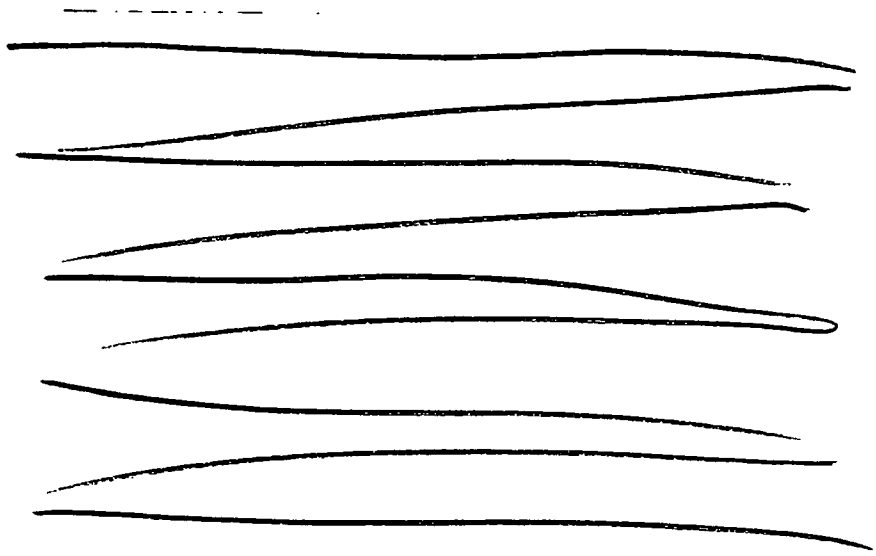
(3) In the third paragraph, the third sentence, the underlined word was changed from singular to pleural to read as follows:

> Cases of thrombocytopenia with disseminated thrombosis have also been observed in clinical practice with heparins, and low molecular weight heparins, including tinzaparin sodium.



d. In the "Hypersensitivity" subsection, the third paragraph has been given a new subsection titled "Miscellaneous" and has been changed

from:



These changes were reviewed by the MEDICAL OFFICER, Dr. Ruyi He, and they are UNACCEPTABLE. In addition, a subsection entitled "Priapism" with appropriate information, should be added after the "Miscellaneous" subsection. The "Miscellaneous" subsection should be revised to read as follows:

Miscellaneous

Miscellaneous: Innohep multiple dose vial contains benzyl alcohol as a preservative. The administration of medications containing benzyl alcohol as a preservative to premature neonates has been associated with a fatal

"Gasping Syndrome". Because benzyl alcohol may cross the placenta, Innohep preserved with benzyl alcohol should used with extreme caution in pregnant women (see PRECAUTIONS, Pregnancy, Non-teratogenic Effects).

6. In the PRECAUTIONS section:

a. In the "General" subsection:

(1) In the second paragraph, the first sentence, a comma has been added after the word "hypertension" to read as follows:

> TRADENAME should be used with care in patients with a bleeding diathesis, uncontrolled arterial hypertension, or a history of recent gastrointestinal ulceration, diabetic retinopathy, and hemorrhage.

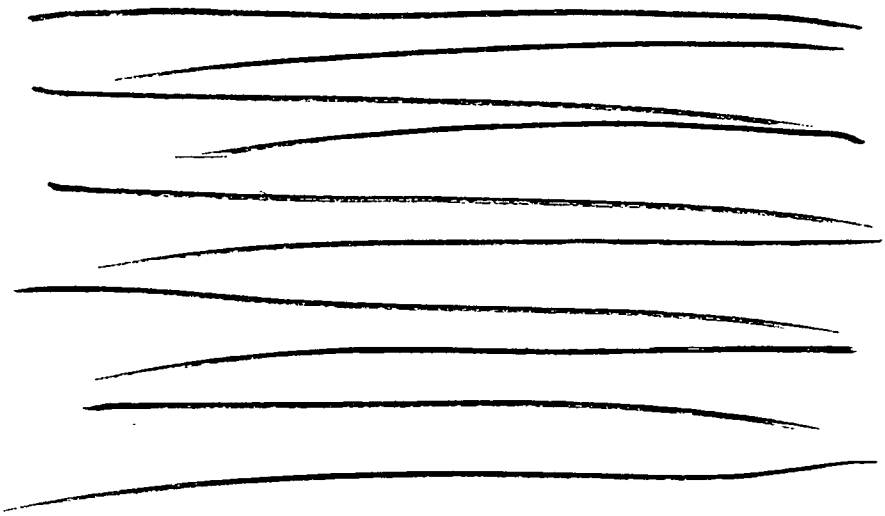
This addition is ACCEPTABLE.

(2) In the second paragraph, the first sentence, the "TRADENAME" was deleted and replaced with the words "tinzaparin sodium" to read as follows:

> Consistent with expected age-related changes in renal function, elderly patients and patients with renal insufficiency may show reduced elimination of tinzaparin sodium.

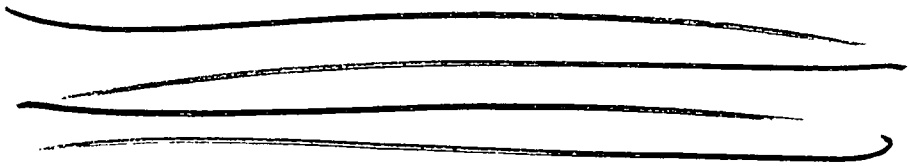
This change is ACCEPTABLE.

b. In the "Laboratory Tests" subsection, the second sentence, the underlined words have been changed



These changes was reviewed by the MEDICAL OFFICER, Dr. Ruyi He, and they are ACCEPTABLE.

c. In the "Drug Interactions" subsection, the first sentence has been changed from:



to:

> Because of increased risk of bleeding, TRADENAME should be used with caution in patients receiving oral anticoagulants, platelet inhibitors (e.g., salicylates, dipyridamole, sulfinpyrazone, dextran, and NSAIDs including ketorolac tromethamine), and thrombolytics.

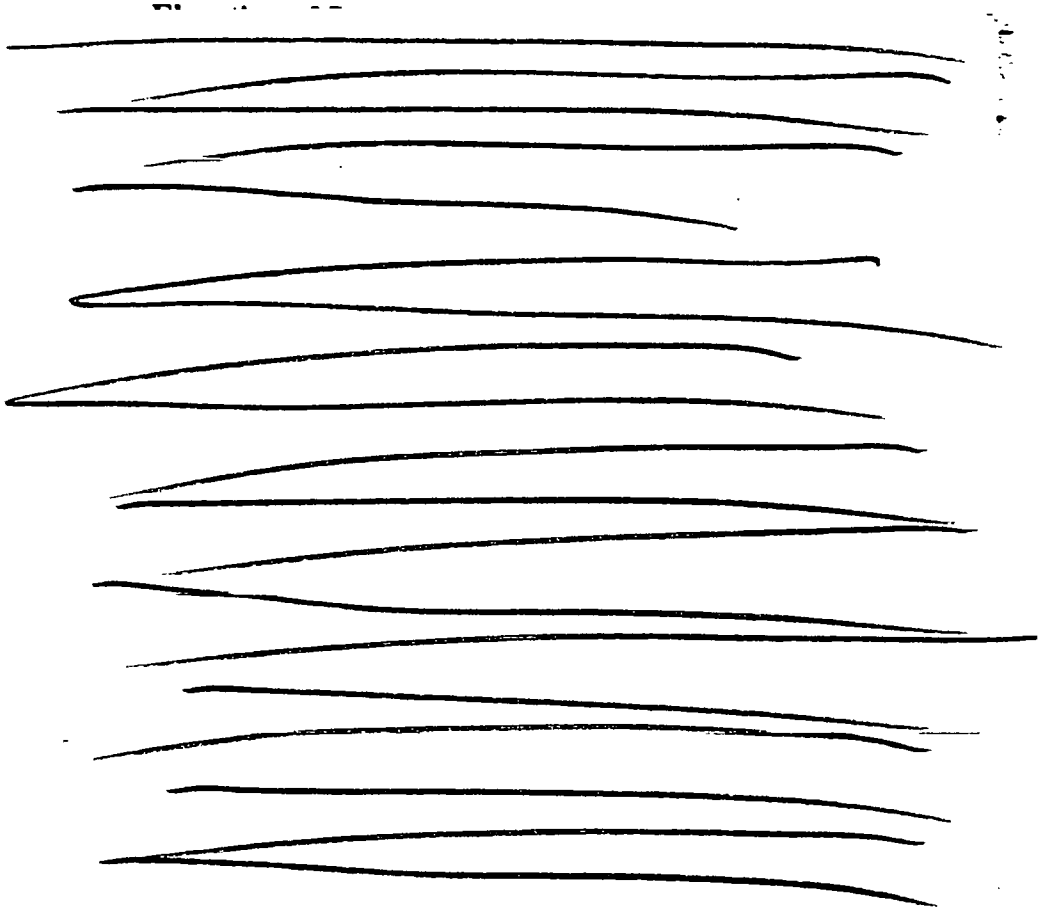
These changes were reviewed by the MEDICAL OFFICER, Dr. Ruyi He, and they are ACCEPTABLE.

d. In the "Laboratory Test Interactions" subsection, in the first sentence, the "TRADENAME" has been changed to the word "tinzaparin sodium" in the following sentence to read:

> Elevation of Serum Transaminases: Asymptomatic reversible increases in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels have occurred in patients during treatment with tinzaparin sodium (see **ADVERSE REACTIONS, Elevations of Serum Aminotransferases**).

This change was reviewed by the MEDICAL OFFICER, Dr. Ruyi He, and it is UNACCEPTABLE. The sentence should be revised to read as follows:

e



1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

[redacted]

d. In the "Nursing Mothers" subsection, in the second sentence, the "TRADENAME" has been changed to the words "tinzaparin sodium" in the to read as follows:

> It is not known whether tinzaparin sodium is excreted in human milk.

This change is ACCEPTABLE.

e. In the "Geriatric Use" subsection, the first two sentences were changed from:

[redacted]

to:

> In clinical studies for the treatment of DVT, 58% of patients were 65 or older and 29% were 75 and over.

These changes were reviewed by the MEDICAL OFFCICER, Dr. Ruyi He, and they are ACCEPTABLE.

7. In the ADVERSE REACTIONS section:

a. In the "Bleeding" subsection:

(1) In the first paragraph, the second sentence, the underlined abbreviation was added to read as follows:

> In clinical trials, the definition of major bleeding included bleeding accompanied by ≥2 gram/dL decrease in hemoglobin, requiring transfusion of 2 or more units of blood products, or bleeding which was intracranial, retroperitoneal, or into a major prosthetic joint.

This addition is ACCEPTABLE.

(2) The table was re-numbered from Table 3 to Table 4.

This change is ACCEPTABLE.

(3) The title of Table 4 was changed

from:

[redacted]

to:

> "Major Bleeding[1] Events in Studies of the Treatment of Deep Vein Thrombosis With and Without Pulmonary Embolism"

This is UNACCEPTABLE. The title should be revised to read:

[redacted]

(4) Information was added to the table, as requested in the April 28, 2000 action letter. However, the information is incomplete.

This is UNACCEPTABLE. The table should be revised (See Attachment entitled "Red-line/Strike-Out Version of the Labeling").

(5) After Table 4, the following sentence was added to read:

> The 95% CI on the difference in bleeding event rates (1.9%) was 0.33%. 3.47%.

This additional information was reviewed the MEDICAL OFFICER, Dr. Ruyi He, and it is UNACCEPTABLE. The information should be included in Table 4 (See Attachment entitled "Red-line/Strike-Out Version of the Labeling").

b. In the "Thrombocytopenia" subsection, the underlined words in the sentence were changed

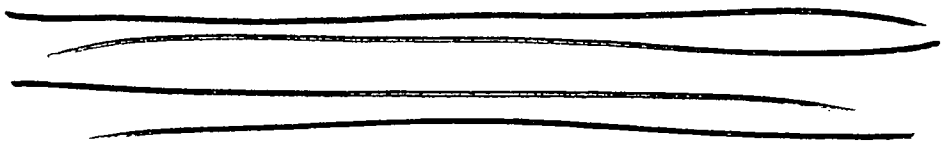
from:

> Thrombocytopenia: In clinical studies thrombocytopenia was identified in 1% of patients treated with TRADENAME. Severe thrombocytopenia (platelet count <50,000/mm^3) occurred in 0.13% (see **WARNINGS, Thrombocytopenia**).

to:

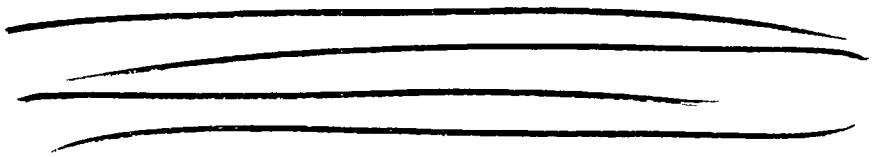
[redacted]

These changes were reviewed by the MEDICAL OFFICER, Dr. Ruyi He, and they are UNACCEPTABLE. The subsection should be revised to read as follows:



c. In the "Elevations of Serum Aminotransferases" subsection, the underlined words in the first sentence were changed

from:



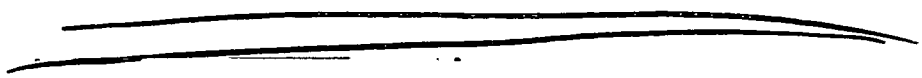
to:

> Asymptomatic increases in aspartate (AST [SGOT]) and/or alanine (ALT [SGPT]) aminotransferase levels greater than 3 times the upper limit of normal of the laboratory reference range have been reported in up to 8.8% and 13% for AST and ALT, respectively, of patients receiving tinzaparin sodium for the treatment of DVT.

These changes were reviewed by the MEDICAL OFFICER, Dr. Ruyi He, and they are ACCEPTABLE.

d. In the "Local Reactions" subsection, in the second sentence, the underlined words were change

from:



to:

> Injection site hematoma has been reported in approximately 16% of tinzaparin sodium treated patients.

This change was reviewed by the MEDICAL OFFICER, Dr. Ruyi He, and it is UNACCEPTABLE. The sentence should be revised to read as follows:

[redacted]

e. In the "Other Adverse Events" section, the information was re-formatted in text format, as requested in the April 28, 2000 action letter, to read as follows:

Adverse Events: Adverse events reported at a frequency of ≥1% in clinical trials with patients undergoing treatment for proximal DVT with and without PE, are provided in Table 5.

Table 5. Adverse Events Occurring in ≥ 1% of Patients in Studies of the Treatment of Deep Vein Thrombosis With and Without Pulmonary Embolism

	Treatment	
Adverse Event	**Tinzaparin Sodium 175 IU/kg Once Daily SC (N=519) n (%)**	**Heparin Bolus then Continuous Infusion IV (N=524) n (%)**
Urinary Tract Infection	19 (3.7%)	18 (3.4%)
Embolism Pulmonary	12 (2.3%)	12 (2.3%)
Chest Pain	12 (2.3%)	8 (1.5%)
Epistaxis	10 (1.9%)	7 (1.3%)
Headache	9 (1.7%)	9 (1.7%)
Nausea	9 (1.7%)	10 (1.9%)
Hemorrhage NOS	8 (1.5%)	23 (4.4%)
Back Pain	8 (1.5%)	2 (0.4%)
Fever	8 (1.5%)	11 (2.1%)
Pain	8 (1.5%)	7 (1.3%)
Constipation	7 (1.3%)	9 (1.7%)
Rash	6 (1.2%)	8 (1.5%)
Dyspnea	6 (1.2%)	9 (1.7%)
Vomiting	5 (1.0%)	8 (1.5%)
Hematuria	5 (1.0%)	6 (1.1%)
Abdominal Pain	4 (0.8%)	6 (1.1%)
Diarrhea	3 (0.6%)	7 (1.3%)
Anemia	0	7 (1.3%)

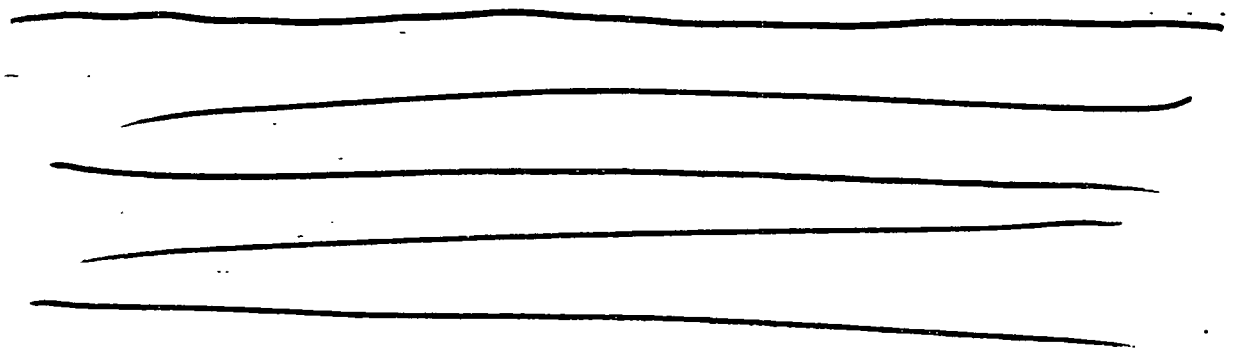
NOS = not otherwise specified

These changes were reviewed by the MEDICAL OFFICER, Dr. Ruyi He, and they are UNACCEPTABLE. Table 5 should be revised (See Attachment entitled "Red-line/Strike-Out Version of the Labeling").

f. In the "Other Adverse Events" subsection, the information was re-formatted in text format, as requested in the April 28, 2000 action letter, to read as follows:

Other Adverse Events: Other adverse events reported at a frequency of ≥1% in 4,000 patients who received tinzaparin sodium in completed or on-going clinical trials are listed by body system:

Body as a Whole: injection site hematoma, reaction unclassified.
Cardiovascular Disorders, General: hypotension, hypertension.
Central & Peripheral Nervous System Disorders: dizziness.
Gastro-Intestinal System Disorders: flatulence, gastro-intestinal disorder (not otherwise specified), dyspepsia.
Heart Rate and Rhythm Disorders: tachycardia.
Myo-, Endo-, Pericardial & Valve Disorders: angina pectoris.
Platelet, Bleeding & Clotting Disorders: hematoma, thrombocytopenia.
Psychiatric Disorders: insomnia, confusion.
Red Blood Cell Disorders: anemia.
Resistance Mechanism Disorders: healing impaired, infection.
Respiratory System Disorders: pneumonia, respiratory disorder.
Skin and Appendages Disorders: rash erythematous, pruritus, bullous eruption, skin disorder.
Urinary System Disorders: urinary retention, dysuria.
Vascular (Extracardiac) Disorders: thrombophlebitis deep, thrombophlebitis leg deep.



These changes were reviewed by the MEDICAL OFFICER, Dr. Ruyi He, and they are UNACCEPTABLE. The presentation of the information should be formatted such that it appears in a meaningful, understandable, and easy to read format. In addition, an

[redacted]

8. In the OVERDOSAGE section:

a. In the second paragraph, the underlined words in the sentence were changed

from:

[redacted]

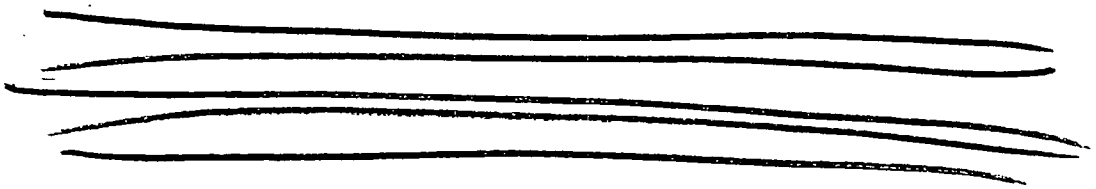
to:

> Of patients known to have received an overdose of tinzaparin sodium in clinical trials, defined as one or more doses >200 IU/kg for the treatment of DVT or >100 IU/kg for the prevention of DVT, approximately 16% experienced a bleeding complication.

This change was reviewed by the MEDICAL OFFICER, Dr. Ruyi He, and it is ACCEPTABLE. For additional changes requested by the Agency in paragraphs 3 and 4 of this section, see Attachment entitled "Red-line/Strike-Out Version of the Labeling".

b. The following information was added as the third, stand-alone paragraph to read as follows:

> Of spontaneous reports of probable overdosing with tinzaparin sodium, approximately, [redacted] were accompanied by bleeding, usually hematoma. [redacted]



c. In the paragraph beginning with the words "In case of serious bleeding...", several changes are requested by the Agency.

The paragraph is UNACCEPTABLE. The paragraph should be revised (see Attachment entitled "Red-line/Strike-Out Version of the Labeling").

d. In the paragraph beginning with the words "Singe subcutaneous doses...", the word "sodium" was added after the word "tinzaparin", and commas were added in the numbers "22000" and "7700" to read as follows:

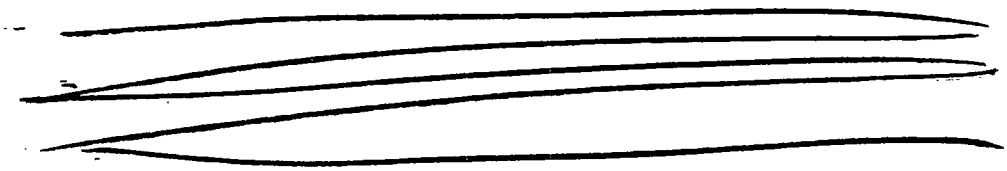
> Single subcutaneous doses of tinzaparin sodium at 22,000 and 7,700 IU/kg (about 10 and 7 times the maximum recommended human dose, respectively, based upon body surface area) were lethal to mice and rats, respectively.

These changes are ACCEPTABLE.

9. In the DOSAGE AND ADMINISTRATION section, in the "Adult Dosage" subsection:

a. In the first paragraph, the first sentence has been changed

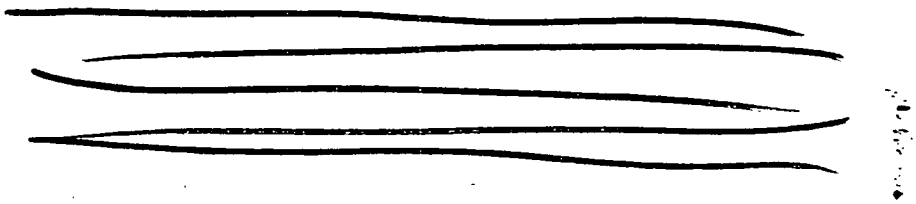
from:



to:

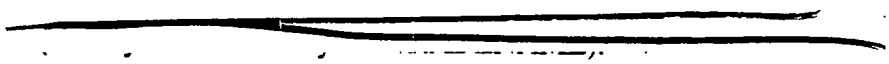
> The recommended dose of TRADENAME for the treatment of DVT with and without PE is 175 anti-Xa IU/kg of body weight, administered SC once daily for at least 6 days and until the patient is adequately anticoagulated with warfarin (INR at least 2.0 for two consecutive days).

This change is UNACCEPTABLE. The sentence should be revised to read as follows:



b. In the first paragraph, the second sentence has been revised (added word underlined)

from:



to:

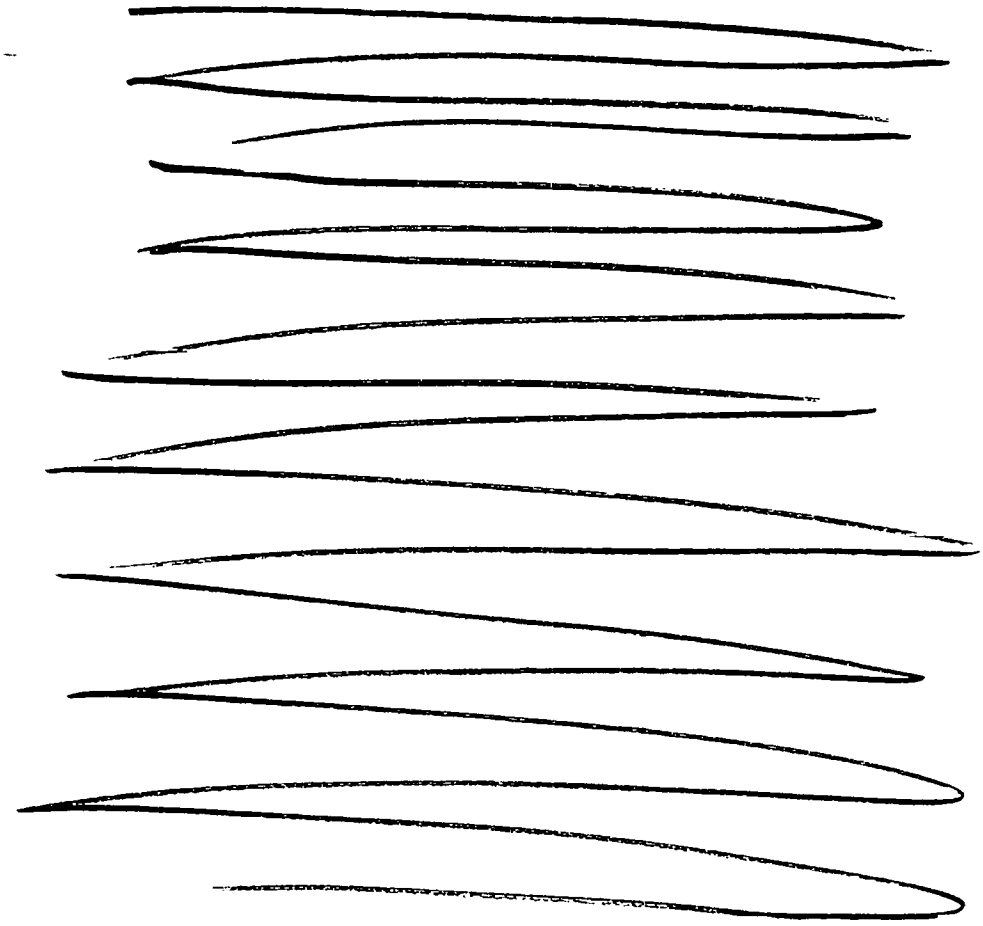
> Warfarin sodium therapy should be initiated when appropriate (usually within 1-3 days of TRADENAME <u>initiation</u>).

This change was reviewed by the MEDICAL OFFICER, Dr. Ruyi He, and it is ACCEPTABLE.

c. The second paragraph described the conversion to oral heparin therapy.

This is UNACCEPTABLE. The paragraph should be deleted.

d. The fourth paragraph was revised to read (as requested in the April 28, 2000 approvable letter):



g. Table 9 was revised and re-numbered to Table 6 entitled "TRADENAME Weight-based Dosing for Treatment of Deep Vein Thrombosis With and Without Pulmonary Embolism" to read as follows:

Table 6. TRADENAME Weight-based Dosing for Treatment of Deep Vein Thrombosis With and Without Pulmonary Embolism

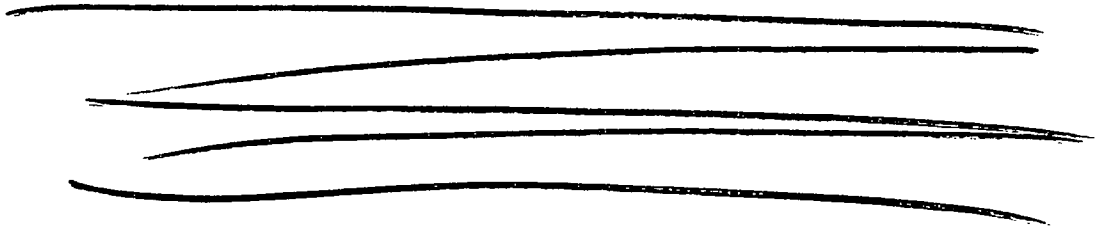
Patient Body Weight In Pounds	*DVT Treatment* 175 IU/kg SC Once Daily 20,000 IU per mL		Patient Body Weight
	Dose (IU)	Amount (mL)	
68 - 80	6,000	0.3	31 – 36
81 - 94	7,000	0.35	37 – 42
95 - 107	8,000	0.4	43 – 48
108 - 118	9,000	0.45	49 – 53
119 - 131	10,000	0.5	54 – 59
132 - 144	11,000	0.55	60 – 65
145 - 155	12,000	0.6	66 – 70
156 - 168	13,000	0.65	71 – 76
169 - 182	14,000	0.7	77 – 82
183 - 195	15,000	0.75	83 – 88
196 - 206	16,000	0.8	89 – 93
207 - 219	17,000	0.85	94 – 99
220 - 232	18,000	0.9	100 – 105
233 - 243	19,000	0.95	106 – 110
244 - 256	20,000	1	111 – 116
257 - 270	21,000	1.05	117 – 122

To calculate the volume (mL) of a TRADENAME 175 anti-Xa IU per kg subcutaneous dose for treatment of deep vein thrombosis:

Patient weight (kg) X 0.00875 mL/kg = volume to be administered (mL) subcutaneously

The table is UNACCEPTABLE. The title of the table should be revised (see Attachment entitled "Red-line/Strike-Out Version of the Labeling").

10. In the HOW SUPPLIED section, the following table has been provided (as requested in the April 28, 2000 approvable letter):



This table was reviewed by the CHEMISTRY REVIWER, Dr. Ali Al-Hakim, and it is UNACCEPTABLE. Since there will only be one marketed strength at this time, the table should be deleted and replaced with the following:

TRADENAME is available in a multiple dose 2 mL vial in the following packages:

Box of 1	**2 mL vial (20,000 anti Xa IU per mL)** **NDC 0056-0342-08**
Box of 10	**2 mL vials (20,000 anti Xa IU per mL)** **NDC 0056-0342-53**

11. After the HOW SUPPLIED section, the following information has been added to read as follows:

6536-00/May, 2000

This additional information is ACCEPTABLE.

4 page(s) of revised draft labeling has been redacted from this portion of the review.

[redacted]

4. On Friday, June 30, 2000, the Attachment to this review, entitled "Red-Line/Strike-Out Version of the Labeling", was provided via facsimile to James Gaskill, Regulatory Affairs, DuPont Pharmaceuticals Company, for the sponsor's review and comment(s). The sponsor anticipates that their response will be available for the Agency review on Thursday, July 06, 2000. Mr. Gaskill states that the sponsor's revision(s) to the labeling will be provided via facsimile, then followed by a hard copy submission as an amendment to their NDA 20-484.

/S/

07/06/00

Karen Oliver, RN, MSN
Regulatory Health Project Manager

/S/

Lilia Talarico, M.D. 7-6-00
Division Director

[redacted]

18 page(s) of revised draft labeling has been redacted from this portion of the review.