

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020164, S015

MEDICAL REVIEW(S)

Oliver

DIVISION OF-GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

February 17, 1998

NDA#20-164/S015

FEB 19 1998 ✓

Submission: EFFICACY SUPPLEMENT FOR NEW INDICATION and DOSING
(Pivotal Studies: CPK-2091, and 529)

Drug: Lovenox® (enoxaparin sodium) injection
Category: Anticoagulant. LMWH.

Indication: Treatment DVT. Support for outpatient treatment when possible.
Dose: 1mg/kg, q12h, or 1.5 mg/kg, qd. Both for ~7 days followed by warfarin maintenance.

Administration: Subcutaneous injection.
Package Size: Prefilled syringes 30mg/0.3mL, plus calibrated prefilled syringes with 60mg/0.6mL, 80mg/0.8mL, and 100mg/1.0mL (strength 100mg/mL).

Sponsor: Rhone Poulenc Rorer Pharmaceuticals, Collegeville, PA. Represented by Thomas E. Donnelly, Ph.D., Director Worldwide Regulatory Affairs. Tel. 610-454-3023

Date submitted: 02/28/97
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Date Completed: 01/29/98 - 02/17/98

Action Proposed: The fixed*, weight-adjusted dose of Lovenox® Injection in conjunction with warfarin is

1. APPROVABLE FOR:

- Outpatient Treatment of Acute Symptomatic DVT Without PE;
- Inpatient Treatment of Acute DVT With and Without PE.

2.

Medical Officer: Nenad Markovic, M.D.
Review File: N:\SUPP15H.R53

INDEX

Front Page	1
Index	2
A. INTRODUCTION	3
1.0 Material Utilized in Review	3
2.0 Background	4
2.1 Indication and Dosing	5
2.2 Important Information from Related INDs and NDAs and from Pharmacologically Related Agents	5
2.3 Administrative History	6
2.4 Proposed Direction for Use - Related Labeling Review	6
2.5 Miscellaneous Background - Foreign Marketing History	7
3.0 Chemistry	8
4.0 Pharmacology	8
5.0 Description of Clinical Data Sources	9
5.1 List of Studies	9
5.2 Study Characteristics - Summary	9
5.3 Introduction to the Review	10
B. PIVOTAL STUDIES	
6.0 Pivotal Study 2091	11
6.2 Table and Content of the Study	12
6.3 Identity of the Test Material	12
6.4 Synopsis	13
6.5 Objective	13
6.6 The Investigational Plan	14
6.7 Statistical Methods	20
6.8 Disposition of Patients Entered	21
6.9 Study Results	22
6.10 Summary	41
7.0 Pivotal Study 529	41
7.2 Table and Content of the Study	42
7.3 Identity of the Test Material	42
7.4 Synopsis	43
7.5 Objective	44
7.6 The Investigational Plan	44
7.7 Statistical Methods	49
7.8 Disposition of Patients Entered	52
7.9 Study Results	53
7.10 Summary	68
C. INTEGRATED SUMMARY AND RISK/BENEFIT ASSESSMENT	
8.0 Integrated Summary of Controlled Trials	69
8.1 ISE	69
8.2 ISS	70
8.3 Sponsor's Risk/Benefit Assessment for Pivotal Studies	74
9.0 Post-Marketing Studies	75
9.1 Study Description	75
9.2 Efficacy Summary	76
9.3 Safety Summary	77
9.4 Sponsor's Risk/Benefit Assessment for the Proposed Indication	78
D. REVIEWER'S SUMMARY AND RECOMMENDATION	
10.0 Reviewer's Appraisal of the Supplement 20-164/S-015. Introduction (10.1)	78
10.2 Outline of the Analysis of Evidence	79
10.3 Review Summary and Recommendation	84
E. APPENDIX	85-101

1.0 MATERIAL UTILIZED IN REVIEW

1.1 Submission: Supplement 015 to NDA#20-164, Lovenox® (enoxaparin sodium) injection.

Summary of the content of the Supplement as presented by the sponsor is included in Table 1-1. A more detailed content of this submission is presented in Appendix 1.

Table 1-1

INDEX: SUPPLEMENT 015 SUBMISSION

ITEM	VOLUME RANGE (volumes)	SUBJECT	VOLUME LOCATION	
Index and Application Summary	(1) 1	-	1	
Chemistry, Manufacturing and Control	(2) 2-4	Drug Substance	2	
		Drug Product	2	
		Environmental Assessment	4	
Samples, Methods Validation and Labeling	(1) 5	-	-	
Human Pharmacology and Toxicology	(9) 6-14	Summary Information	6	
Clinical Data Section	(27) 15-41	Summary Information with references.	Clinical Pharmacology	15
			Efficacy	37 rpp.87-458
		Integrated summary of:	Safety	38 rpp.103-8
			Study Reports	Clinical Pharmacology
		Controlled Trials	22-32	
		Uncontrolled Trials	34	
		Other Studies	35	
Case Report Form Tabulations	(46) 42-87		42	
Case Report Forms	(53) 88-140		88	
Patent Information and Certification	(1) 1		1	
Selected References	(3) 141-143	Pharmacological Class, Scientific Rationale, Intended Use, Product Development and Potential Clinical Benefits. Clinical Data Summary and Results of Statistical Analysis (pp.132)	141	
		Integrated Summary of benefits and Risks	142	
		Background and Overview of Clinical Investigations.	143	

From Item 1.3: Statement of Organization (Vol.1, p.6). Legend: r= reference

2.0 BACKGROUND

Deep vein thrombosis (further: DVT) occurs frequently in patients with one or more risk factors. These factors include age (above 40), body weight (obese subjects are more prone to this disease), prolonged immobilization (due to all causes), orthopedic surgery (hip, knee), cancer (hypercoagulable state), varicose veins, prior venous thrombotic events (further: VTE) etc. Untreated DVT is a progressive disease (extension of the clot) which may have fatal outcome (massive pulmonary embolism). Pulmonary embolism (further: PE) is considered a natural complication of DVT (particularly proximal).

In the Worcester deep vein thrombosis study, Anderson et al (Anderson FA, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, Forcier A, Dalen JE. A population based perspective of the hospital incidence and case fatality rates of deep vein thrombosis and pulmonary embolism. *Arch Intern Med.* 1991; 151:933-938) have presented the annual incidence of DVT alone to be 48 per 100,000, while the incidence of pulmonary embolism is estimated to be 23 per 100,000.

Acute DVT is a debilitating disease sharply reducing the ascending blood flow and producing symptoms (dependent upon the size of the obstructed blood vessel) such as pain, swelling of the leg below thrombosis, and loss of function (immobilization). Left pharmacologically untreated, recurrent venous thromboembolic disease complication occur in between 31.4% and 51.7% of conservatively treated (defined as strictly bed rest) patients (Bruzelius S. Dicoumarin in clinical use. *Acta Chir Scand.* 1945; *Suppl.* 100:11-187). Fatal pulmonary embolism occurs in 8.0% to 26.2% of cases so treated. In 1992, the *Third American College of Chest Physician's Conference* recommended unfractionated heparin for the initial treatment of patients with DVT (Hyers TN, Hull RD, Weg JG. Antithrombotic therapy for venous thromboembolic disease. *Chest* 1992; 102:408S-425S).

Treatment of DVT has changed due to accruing new experience. Current treatment includes hospitalization, bed rest, intravenous heparin (APTT between 60-90 sec) for 5-10 days, warfarin to be started after heparin, and when INR reaches 2.0 - 3.0 to be continued instead of heparin as maintenance therapy for 3-6 months (Hirsh J, Dalen JE, Deykin D, Poller L. Oral anticoagulants. Mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest.* 1992; 102:313S-326S). Successful treatment prevents extension of thrombosis, prevents occurrence of PE, and sometimes may improve the affected vein patency.

In many anecdotal studies, and several clinical trials, LMWH have been shown as alternative to heparin. Because of their route of administration (subcutaneous) and lesser need for permanent laboratory control (i.e., by routine coagulation tests such as APTT), the use of these drugs is more convenient for hospital staff, and they are appropriate for outpatient DVT treatment. This makes LMWH attractive competitors for socioeconomic advantage in DVT treatment. The *Fourth American College of Chest Physicians Conference* (1995) recommended that in addition to continuous infusion heparins, subcutaneous LMWH could be used for the management of patients with acute venous thromboembolic disease (Haers TM, Hull RD, Weg J. Antithrombotic therapy for venous thrombotic disease. *Chest.* 1995; 108:335 S-351 S.).

Enoxaparin sodium is a low-molecular-weight-heparin manufactured by Rhone Poulenc Rorer, Pharmaceuticals, under the names Lovenox (U.S.A.), Clexane (Europe), Klaxane (Germany). In the U.S. Lovenox® Injection is approved for prophylaxis of DVT which may lead to PE in patients undergoing hip or knee replacement surgery, and for patients undergoing abdominal surgery who are at risk for thromboembolic complications. Lovenox has not been approved for treatment of either DVT, PE or both.

2.1 Indication and Dosing

Dose Justification

The sponsor proposed use of Lovenox for "treatment of DVT and PE." For this indication, the dose selection was made by a scientifically doubtful, but practically very straightforward approach. The effective dose of heparin in the treatment of DVT is three to four times higher than the preventive dose. Heparin is the "golden standard" for evaluation of enoxaparin. If similar dose of Lovenox (solution strength 100 mg/mL) is to be used, than the efficacy of enoxaparin should be proven by study of clinical equivalence with heparin standard. This concept was used by the sponsor as a basis for designing clinical trials to study enoxaparin in the treatment of DVT and PE.

Several studies provided evidence that enoxaparin may be important drug for treatment of DVT. Huet et al, have demonstrated the efficacy and good tolerance of the 100 mg/mL solution of enoxaparin. Two preliminary studies were carried out with enoxaparin in the treatment of established DVT. One study was in nine patients with pulmonary embolism (Huet Y, Gouault-Heilmann, Contant G, Brun-Buisson C. Treatment of acute pulmonary embolism by a low-molecular-weight heparin fraction. A preliminary study. *Intensive Care Med.* 1987; 13:126-30). The other was in 50 patients with established DVT and increased hemorrhagic risks (Huet Y, Gadelfa-Parente T, Benvenuti C et al. Interet d'une fraction d'heparine de bas poids moleculaire, l'Enoxaparine, chez des patients a hauts risques hemorrhagiques et thrombotiques. *Ann Med Interne.* 1988; 139-349-53),

Two phase-2 trials showed the safety and efficacy of enoxaparin for DVT treatment. Huet et al, indicated enoxaparin for this indication (Huet Y, Janvier G, Bendriss PH et al. Treatment of established venous thromboembolism with enoxaparin: preliminary report. *Acta Chir Scand.* 1990; *Suppl 556:116-20*; Janvier G, Freyburger G, Winnock S, et al. An open trial of enoxaparin in the treatment of DVT of the leg. *Haemostasis.* 1991; 21:161-68) and proposed a fixed dose of 1.0 mg/kg sc q12h with no laboratory adjustment.

The clinical study PK-528 (Simonneau G, Charbonnier B, Decousus H et al. Subcutaneous low-molecular-weight-heparin compared with continuous intravenous unfractionated heparin in the treatment of proximal vein thrombosis. *Arch Intern Med.* 1993; 153:1541-46) was conducted in France and Belgium as an open label, controlled clinical trial to compare fixed dose enoxaparin (1 mg/kg, sc, bid) and adjusted dose unfractionated heparin (bolus 5,000 IU, followed by a 1,250 IU per hour continuous dose-adjusted [APTT control 1.5-2.0 times the reference APTT]). On 134 patients (67 in each treatment group), this trial documented a significant difference in favor of enoxaparin in terms of clot regression based on both Marder's and Arneson's venography scores. The risk of hemorrhage was similar and no major hemorrhage appeared.

Clinical pharmacology studies (*vide infra*) and the cited clinical trials made the basis for the two phase-3 clinical trials (CPK-2091 and 529) submitted in this application as pivotal studies to present evidence of enoxaparin equivalence with the continuous infusion heparin for the treatment of DVT with or without PE.

2.2 Important Information from Related INDs and NDAs

a. NDA#20-164/S-016

The sponsor has submitted a single study, RP54563q-303, the ESSENCE trial, in support of the use of enoxaparin for the new indication of the treatment of unstable angina and non Q-wave myocardial infarction, concurrently administered with aspirin, at a recommended dose of 1.0 mg/kg sc bid with 100-325 mg of daily aspirin for "a minimum of 2 days and continued until clinical stabilization. The usual duration of treatment is two to eight days." This study was found to be sufficient as evidence for approval

of the new indication (the Cardio-Renal Advisory Committee, June 1997). Therefore, the dose of 1.0 mg/kg/bid for 2-5 days has already been approved for treatment in the U.S.

2.3 Administrative History

In a submission to this Agency on May 4, 1993 the sponsor announced their wish to further develop Lovenox injection for DVT treatment as a new indication. On September 26, 1994 a meeting was held to discuss several clinical studies with Lovenox. It was agreed the study 529 may be used as pivotal study (efficacy parameters venograms and ventilation-perfusion lung scan), the study 528 would be included as supportive, and a new clinical trial was required for the second pivotal study.

This application contains two pivotal studies as requested. The new study is CPK-2091. Both studies are multicenter (one is open-label [CPK-2091], other is partially blinded [PK-529]). They compare the efficacy and safety of enoxaparin at doses of 1.0 mg/kg bid or 1.5 mg/kg qd (only 529), sc, vs. unfractionated heparin administered intravenously as continuous infusion in the treatment of DVT, and DVT associated with PE (only 529). The primary efficacy outcome was the incidence of recurrent Venous thrombotic disease (VTD) within three months of randomization. Patients with symptoms or signs of recurrent DVT underwent objective testing using one or more of the following methods: impedance plethysmography, duplex ultrasonography and venography. Patients suspected of having PE were to undergo a lung scan or a pulmonary angiography. According to the sponsor, the results demonstrated that enoxaparin (1.5 mg/kg qd sc or 1.0 mg/kg q12h sc) was as effective as unfractionated heparin in the treatment of DVT (with or w/o PE), and was not less safe. Since the pivotal studies met the requirements discussed previously, the sponsor expect approval of the supplement #015.

2.4 Proposed Direction for Use - Related Labeling Review

Proposed revision to the *Indication*:

DRAFT LABELING

Proposed revision to the *dosage and administration*:

DRAFT LABELING**2.5 Miscellaneous Background - Foreign Marketing History**

Marketing history for enoxaparin is summarized on Table 2-1

Table 2-1

LOVENOX® (CLEXANE®) MARKETING HISTORY UPDATED WITH S-015

INDICATION		COUNTRY	DOSING	Duration	
				Start	End
DVT Prophylaxis	Hip & Knee	U.S.A.	30 mg sc bid	within 24h of surgery	until hospital discharge
		Europe	40 mg sc qd	12 h prior to surgery	until ambulatory
	Long term (Extended)	New Zealand, Finland (U.S.A. S-010)	40 mg sc qd	after successful completion of perioperative proph.	~21 days
Treatment of DVT		Australia, Austria, Denmark, France, Greece, Guatemala, India, Italy, Sweden, Iceland, Finland, Belgium, Luxembourg, Netherlands, Norway, Singapore, New Zealand, U.K. (U.S.A. S-015)	1 mg/kg q12h sc, followed by warfarin (levels adjusted for INR)	Symptomatic DVT	Enoxaparin for ~10 days. Warfarin for 3 to 6 months
Prevention of thrombosis in extracorporeal circulation during hemodialysis		Australia, Austria, Chile, Colombia, Egypt, El Salvador, Guatemala, Finland, France, Germany, Greece, Iceland, India, Ireland, Israel, Mauritius, Morocco, Mexico, Norway, Philippines, Portugal, Singapore, Spain, Sweden, Switzerland, Tunisia, Turkey, U.K.	1 mg/kg, IV or reduced dose to 0.5 or 0.75 mg/kg	During hemodialysis	
Abdominal Surgery	General	Australia, Austria, Belgium, Denmark, El Salvador, Finland, France, Germany, Greece, Iceland, Israel, Italy, Kuwait, Malaysia, Mexico, Netherlands, New Zealand, Norway, Portugal, South Africa, Spain, Switzerland, Tunisia.	20 mg sc qd	Following surgery	As long as the risk exists usually 7-14 days following surgery
	Higher risk U.S.A. S-008		40 mg sc qd		

From Item 2.3: Foreign Marketing History (Vol. 1, pp. 87-89). Legend: Within (.) = submitted for approval

Enoxaparin sodium is marketed as Lovenox®(U.S.A.), Clexane and Klexane world wide. It is approved in many countries for thromboprophylaxis in patients undergoing surgery (general, abdominal, orthopedic),

treatment of DVT, prevention of thrombosis in extracorporeal circulation, and during hemodialysis. The newest indication approved in the U.S. was "concurrently with aspirin for the management of unstable angina." For more information on this indication see Supplement 015(NDA#20-164).

3.0 CHEMISTRY

For information in the section see CMC information (Vol.2-4) and Chemistry Review.

4.0 PHARMACOLOGY

For more information in this section see Human Pharmacology and Toxicology sections (Vol.6-14) and Pharmacology Review. The following is only a summary of related pharmacological data.

4.1 CLINICAL PHARMACOLOGY

According to the sponsor "no new clinical pharmacology reports are contained in this supplemental new drug application."

Background

The dissociation between antithrombotic and hemorrhagic effects (as compared with unfractionated heparin) stimulated clinical development of enoxaparin in the field of prevention of venous thromboembolic disease in surgical patients and other high risk clinical settings.

PK/PD Studies

Pharmacokinetics of enoxaparin was measured by anti-IIa and anti-Xa activities, tolerance was measured by assessing of TT (thrombin time), aPTT, recalcification time, and antithrombin-III. After subcutaneous administration AUC was measurable only for anti-Xa activity. Anti-IIa activity was measurable only after intravenous administration. Anti-Xa activity AUC curve vs. time and the elimination half lives after intravenous and subcutaneous administration were virtually identical.

Absorption of enoxaparin following subcutaneous injection is linear over the dose range from 20 to 80 mg. Only small, painless hematoma were reported at injection site in 8 of 13 volunteers.

The elimination half-life of enoxaparin ranges from three to five hours, much longer than heparin (~0.6h). It is extended in elderly (mean half-life 6.8h, mean residence time 7.05h)

After multiple doses, the total body clearance of anti-Xa activity of enoxaparin was much lower than that of unfractionated heparin ($p < 0.0001$). The plasma anti-Xa activity of enoxaparin was significantly increased compared to unfractionated heparin.

The elimination of enoxaparin is delayed in patients with renal failure (not undergoing dialysis) compared to healthy volunteers.

Toxicity

Clinical tolerance during clinical development:

Increase in the risk of overt hemorrhagic complications (wound complications, ecchymosis and non-operative site hemorrhage). Complications are minor and readily manageable by usual clinical methods. At injection site enoxaparin cause transient lowering of the pain threshold; the change in pain is not related to dose. Significant increase in hepatic enzymatic markers is observed in some subjects. The mechanism

is not known. The incidence of thrombocytopenia in clinical trials is approximately 2.0% and sporadic HIT have been reported.

Efficacy

Clinical pharmacological effect: Enoxaparin may indirectly inhibit thrombin (IIa) by preventing its formation as well as by directly inhibiting thrombin (IIa) activity including conversion of fibrinogen to fibrin and feedback on the coagulation cascade factors.

5.0 DESCRIPTION OF CLINICAL DATA SOURCES

5.1 List of Studies

Pivotal studies: CPK-2091 and 529. Supportive studies: 100554, 105338, 105336, PK-528, and the study published by Pini et al.

5.2 Summary of Submitted Studies

Summary of clinical studies included in this supplement is presented on table 5-1. It includes information from 2 pivotal clinical trials, 3 clinical trials considered supportive for this indication, and 2 other studies related to the same indication.

Table 5-1
CLINICAL STUDIES

STUDY	DESIGN/PATIENTS	DOSE	EFFICACY	SAFETY
Controlled Clinical Trials (PIVOTAL STUDIES); #8.6.1. Study of Eff+Saf equivalency between enoxaparin and heparin				
CPK-2091 (Vol.22-24) CA(1992-5) Savings: \$2,500 p/pt	Phase III. Open-label, randomized, patients with proximal DVT. E:outpatient vs. H:inhospital. Pts. total:501; E:254, H:247 NEJM. 1996;334:677-81	5 days therapy → 3 months warfarin maintenance E:1.0mg/kg, bid H:continuous infusion FUP=3 mo.	Recidiv DVT ⊕ (venogr.or US). H:6.7%; E:5.3% D=1.4 CI=-2.72, 5.68 Equiv: low>-3%	Hemorrhage during 5 days of study H:3.9%(1.2% maj) E:4.5%(2.0)
529 (Vol.25-32) WW(1994-96)	Phase III. Partially-blind (E1/2 dose blinded), randomized, parallel group, in patients with DVT with or w/o PE. Pts. total :900, H:290, E1:298, E2:312	5 days therapy → 3 months warfarin maintenance E1: 1.5mg/kg qd E2: 1.0mg/kg bid H:continuous infusion FUP=3 mo.	Recidiv DVT ⊕ (venogr.or US). H:4.1;E1:4.4;E2:2.9% D:E1/H=0.2(-3,3.5) D:E2/H=-1.2(-4,1.8) Equiv:upper<10	Hemorrhage during 5 days of study H:13.4%(2.1 maj) E1:15.4%(1.7 maj) E2:17.3%(1.3 maj) ⊕ 1 immune th- penia
Uncontrolled Clinical Trials (SUPPORTIVE STUDIES); #8.6.2				
100554 (Vol. 34) (FR,1984)	Open-label, nonrandomized. Treatment of acute PE N= 10 pts	E: start 0.5mg/kg IV + infusion 2mg/kg/day for 12 days, → 1mg/kg sc bid for 14 days. Total 26 days.	No recurrence of PE. Local improvement. Disappearance of DVT	No major hemorrhage No thrombocytopenia
105338 (Vol. 34) (FR, 1986)	Open-label, nonrandomized. Treatment of acute PE in man N=19	E: start 0.5mg/kg IV + 1mg/kg/d, → anti-Xa adjusted (mean 1.8mg/kg/d) for 20 days	1 recurrence, 18 improvement DVT disappeared for 5 days.	One hemorrhagic colitis. One mild thrombocytopenia

105336 (Vol. 34) (FR, 1990)	Open-label, nonrandomized. Treatment of constituted DVT N=36 (surg + med)	E: 1mg/kg bid for 10 days	No progression or PE. Clin.score reduction in 30%	1 GI hemorrhage (cancer). Hematoma post venopuncture
Other Studies and Information, #8.6.3				
PK-528 (Vol.35-36) (FR, 1989- 90)	Phase III. Open-label, randomized, fixed dose E vs. H (intravenous) in patients with established DVT Pts:134, H:67, E:67	E:2mg/kg/24h for 10 days after 24h H. H:intravenous (APTT adjusted)	Clin. score regression E:42.5% H:27.3% P=0.007	Any hemorrhage H:0; E:4(6%) 57% asymptomatic PE. (H) 1 immune thrombocytopenia
Pini et al. (Vol.36) (IT, 1993)	Phase III. LMWH vs. warfarin in the prevention of recurrences after DVT. Pts:187, E:93, H:94 <i>Thrombosis & Haemostasis</i> . 1994; 72:191-9	10 days H (APTT adjusted) → E: 40mg/qd for 3 mo., or W:(INR adjusted) for 3 mo (many extended)	Recurrence DVT: E:6%; W:4% Late recurrence (one year): E:17%; W:9%	Any hemorrhage ⊕ E: 4%; W:12%
Integrated Summaries of Efficacy and Safety, #8.7				
Efficacy (Vol. 37)	Safety (Vol. 38)	Eff+Saf Summary Tables (Vol.39)	Summary of Benefits and Risks (Vol. 41)	Drug Abuse and Overdosage (Vol.41)

From #8.1: Clinical Data Section (Vol.1, p.25-28). Legend: Pts= patients; →=followed by; ⊕= within 3 months; E=enoxaparin; H=heparin; FUP=follow-up period; D=difference between incidence of the study outcomes, as measured from the means of test and control study groups; CI=confidence interval; low/upper=estimated threshold for qualifying two results as equivalent. Eff=efficacy; Saf=safety.

5.3 INTRODUCTION TO THE REVIEW

a. Sponsor's Conclusion

In an overview of clinical trials submitted in support of this Supplement (Vol.1, p113, section Clinical Data Summary and Results of Statistical Analysis), the sponsor has made the following conclusion:

"The two clinical trials are presented at this time to compare the safety, efficacy, and cost-benefit of fixed and weight-adjusted dose of Lovenox subcutaneously administered once (#529) or twice-daily (#CPK 2091, #529) to intravenous continuous infusion heparin therapy in the treatment of lower extremity DVT (#CPK 2091 and #529), and pulmonary embolism (#529), and to compare the patient mortality of these two anticoagulant regimens at three months. The analysis of this clinical program's outcomes provides convincing evidence for the equivalence of efficacy and safety of Lovenox administered as a 1.0 mg/kg bid regimen, or a 1.5 mg/kg qd to adjusted dose continuous infusion heparin therapy for the prevention of recurrent venous thromboembolic disease in patients with acute DVT."

b. Outline of the Review

This review was focused to:

- Verify whether the pivotal studies were adequate and well controlled clinical trials admissible as evidence for the sponsor's claim.
- Assess the supportive evidence for efficacy of Lovenox in treatment of acute symptomatic DVT.
- Assess the overall evidence of Lovenox safety in the proposed dose and duration of therapy.
- Estimate the risk/benefit ratio and recommend an appropriate change in the current Labeling for Lovenox® Injection.

NDA 20-164/S-015

Page 11

6.0 PIVOTAL STUDY CPK-2091
(Submission Vol. 22-24, 42-51, 88-104)

6.1 TITLE PAGE

Study Phase: Phase III
Drug Identifier: RP 54563q.

Protocol Number: 2091

Protocol Title: *Phase III Study: Efficacy and Safety of an outpatient anticoagulant regimen consisting of a fixed dose of 1 mg/kg of enoxaparin administered subcutaneously twice daily compared with a standard inpatient anticoagulant regimen consisting of unfractionated heparin administered by continuous intravenous infusion: a randomized open-label study inpatients with proximal deep vein thrombosis.*

Authors*: Mary Donnelly, Eric Genevois, M.Lynn Walsh, Theodore Spiro. RPR
(* = The sponsor has submitted this Study Report with four authors)

Investigators:

The study was conducted at 16 centers in Canada. The list of centers, investigators, and number of patients per treatment group assigned to each investigator is available in Appendix 2.

Study Start Date: 07/13/92
Study Competition Date: 04/28/95
Date of Report: 06/17/96
Date of Submission: 02/28/97

APPEARS THIS WAY ON ORIGINAL

6.2 TABLE AND CONTENT OF THE STUDY

STUDYCPK-2091: CONTENT			
6.1	Title Page	6.9	Study Results
6.2	Table and Content of the Study	6.9.1	Data Sets Analyzed
6.3	Identity of the Test material	a.	Patients Disposition
6.4	Synopsis	b.	Demographics
6.5	Study Objective	c.	Risk Factors
6.6	The Investigational Plan	d.	Diagnostic Method Presenting Symptoms
a.	Study desing	e.	Prior Medication
b.	Discussion on the Design & Choice of Control Group.	f.	Concomitant Medication
c.	Study Population (Eligibility Criteria)	g.	Duration of Hospitalization
d.	Patient Assignment (Randomization)	6.9.2	Efficacy Analyses Results
e.	Dose Selection (Study Medication)	a.	Primary Efficacy Endpoint
f.	Blinding	1)	Incidence of VTE recurrence
g.	Efficacy and Safety Variables	2)	Site of VTE recurrence
•	Efficacy: VTE	b.	Secondary Efficacy Analyses
•	Safety: Hemorrhage, Adverse Events	1)	Reccurence VTE in Evaluable Population
•	Laboratory Tests	2)	Time to First VTE
h.	Concomitant medication	4)	Subgroup Analysis
6.7	Statistical Methods	5)	Investigator and Strata Interaction
a.	Statistical Plan	6)	Investigator ans Adjudication Committee Interaction
b.	Efficacy Analysis	c.	Summary of Efficacy Analyses
c.	Safety Analysis	6.9.3	Safety Evaluation
d.	Non-evaluability criteria	a.	Extent of Exposure
6.8	Disposition of Patients Entered	b.	Incidence of Hemorrhage
a.	Demographics	c.	Adverse Events
b.	Risk Factors	1)	AE during the Treatment Period
c.	Exposure to Study Medication	2)	AE Leading to Discontinuation
d.	Concomitant Medication	3)	AE Related to Study Medication
e.	Dropouts	4)	Serious AE
f.	Protocol Violations	e.	Clinical Laboratory Evaluation
g.	Study Discontinuation	f.	Deaths
h.	Deaths	g.	Summary of Safety Analyses
		6.10	Review Summary

For details see Appendix 1: Study CPK-2091 Report (Vol.22-24), Case Repopr Tabulations (Vol.42-48), Patient Profiles (Vol.49-51), Case Report Forms for Patient who Discontinued (Vol.88-104), ISE (Vol.37), ISS (Vol.38), ISE and ISS Summary Tables (Vol. 39-41), Drug Abuse and Overdose (Vol.41), and Integrated Summary of Benefits and Risks (Vo.41).

6.3 IDENTITY OF THE TEST MATERIAL

The following drugs were used as study medications: Lovenox® (enoxaparin sodium) injections, Heparin sodium injection, and Coumadin®(warfarin) tablets. Identification numbers are available for enoxaparin lots only (Table 6.3-1)

Table 6.3-1
STUDY CPK-2091: IDENTITY OF THE TEST MATERIAL

STUDY MEDICATION	LOT NUMBER
Enoxaparin (Drug Identifier: RP 54563q)	CB5826 (October 1995), CB5325 (February 1995)
Heparin:	Not Available (?)
Warfarin:	Commercial supply (Coumadin, DuPont-Merck Pharmaceuticals, Inc.)

From Table 2 [Vol.22,p.22]

6.4 INTRODUCTION - SYNOPSIS

The study CPK-2091 is included in the Supplement No. 015 as the first pivotal clinical trial to support the sponsor's claim that Lovenox injection can be used for treatment of DVT and PE. In this study Lovenox is used in a regimen with warfarin; it is not used alone for treatment of DVT and PE. This same indication has already been approved in Europe. In the U.S., Lovenox is approved for prophylaxis of DVT which may lead to PE in orthopedic (Suppl.:001, 002, and 010) and abdominal surgery (Suppl.: 008).

This study was designed to demonstrate that for patients with acute proximal DVT, whose clinical condition allows treatment at home, an outpatient regimen based upon subcutaneous enoxaparin might be equivalent (with regard to the incidence of recurrent VTE as outcome measure) to the conventional in-hospital intravenous heparin therapy.

The study was conducted as a multicenter (16 in Canada), randomized, open-label, assessor-blinded, parallel group, active treatment controlled clinical trial. Five hundred-one (501) patients presented in participating hospitals with acute symptomatic DVT that was confirmed by venography, were centrally randomized to receive in-hospital intravenous heparin infusion or subcutaneous enoxaparin in outpatient setting. Heparin or enoxaparin were given to achieve a rapid anticoagulation needed to prevent extension of thrombosis and embolization. Both drugs were followed by oral warfarin for maintenance of anticoagulation (INR between 2.0-3.0) for three months. Both drugs were ceased after the targeted INR was reached (approximately 5-10 days). Primary efficacy variable used for comparison of treatment effect was the incidence of recurrent VTE (DVT, PE, or death by thromboembolism) in all-treated patient population within these three months. Safety variables included the incidence of hemorrhage, adverse events and deaths by any reason.

Statistical analysis based on the confidence interval approach demonstrated that the outpatient treatment with enoxaparin and the in-hospital treatment with heparin, both followed by warfarin maintenance, were equivalent with regard to the primary efficacy variable, and both had a comparable safety. However, some imperfections during the conduct of this trial do not allow inferences as proposed by the sponsor, and require a more restricted labeling with regard to the targeted population.

The review has found the study CPK-2091 to be an adequate and well controlled clinical trial which is admissible as evidence to support the sponsor's claim that Lovenox can be used for treatment of DVT.

6.5 OBJECTIVE

The primary objective was to compare the efficacy and safety of an outpatient anticoagulation regimen (consisting of a fixed-dose subcutaneous enoxaparin injection) with a standard inpatient anticoagulation regimen (consisting of unfractionated heparin administered by continuous infusion) in patients with acute proximal deep vein thrombosis (DVT). Clinically symptomatic DVT had to be confirmed by objective assessment prior to randomization. In both groups the second anticoagulant was warfarin.

The second objectives were to compare:

- Patient mortality at three months, and
- The cost-effectiveness of these two anticoagulant regimens.

APPEARS THIS WAY ON ORIGINAL