adverse clinical events during the treatment period for all-treated patients in both studies was 41.8% (585/1401). The incidence of all adverse events observed among patients treated with heparin was lower than for patients treated with enoxaparin qd, but greater than for patients treated with enoxaparin bid.

Table 8-5 (Vol.1, p.201. Table 10: Summary of All Serious Adverse Events Reported in More than One Patient During the Treatment Period) and table 8-6 (Vol.1, p.204. Table 11: Summary of Adverse Clinical Events Leading to Discontinuation of Study Medication) present comparable distribution of events between treatment groups, except for minor hemorrhage. Injection-site hemorrhage was significantly less in heparin than in both enoxaparin treated groups ($p<0.0001$ for both analyses).

Subgroup analyses compared the incidence of clinical adverse events in patients with cancer, and patients with a medical history of prior DVT or PE. There was no significant difference with respect to treatment groups.

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Serious Adverse Events

The combined incidence of serious adverse clinical events during treatment period was greater for heparin group than for the enoxaparin qd group and similar to the incidence for the enoxaparin bid group. The most commonly reported serious adverse event was hematuria (3 patients in the heparin group), DVT and gastrointestinal hemorrhage (two patients for each event in the enoxaparin qd group), and DVT (3 patients in the enoxaparin bid group).

Adverse Events Leading to Discontinuation

Table 8-5

Table 8-6 (Vol.1, p.205, Table 11: Summary of Adverse Clinical Events Leading to Discontinuation of Study Medication) presents, by COSTART terminology 37 patients who had to discontinue study due to serious adverse events which, according to investigators, were related to study medications. Hemorrhage (14 cases), and particularly gastrointestinal hemorrhage (9 cases) was the leading common cause.

Only 160 patients (160/1401; 11.4%) prematurely discontinued study medication. They were comparably distributed between treatment groups (H=80/544;14.7%/ E1=34/298;11.4%/ E2=46/559;8.2%). The most frequent reason for discontinuation was deviation from protocol for 75 patients (5.4% of 1401). The most frequently reported adverse experience causing discontinuation were GASTROINTESTINAL hemorrhage (3 heparin patients, 3 enoxaparin qd) and chest pain (4 enoxaparin bid). Life-threatening PE occurred in one heparin-treated and one enoxaparin qd-treated patient.

There was no significant difference of study discontinuation causes between treatment groups.

Mortality

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Mortality was considered as a specific clinical event. It was included as primary efficacy endpoint (death by thromboembolic event), but only if autopsy was performed and if the causality with thromboembolism was established. Otherwise, mortality was recorded as of "any" cause and was related, upon the investigators' assessment to the study medication. Narratives for all deaths are included (Appendix 2 and 3). No deaths were attributed to enoxaparin. Possibility to add to other causes has not been ruled out, either.

Five patients died during the treatment period: two heparin-treated patients (one fatal PE, another from carcinoma of lung associated with PE), two enoxaparin qd (one retroperitoneal hemorrhage, another was second to chronic pulmonary disease associated with PE) and one enoxaparin bid (gastrointestinal hemorrhage).

Fifty patients died between the end of the treatment and the follow-up period. Within the first month six deaths were associated with PE, and 9 with hemorrhage. A total of 15 deaths occurred after the treatment period. This is the period when heparin or enoxaparin were discontinued, and patients were left on warfarin alone. An impact of heparin or enoxaparin withdrawal on patient survival has never been studied. During the rest of two months only one death was associated with PE, and three with hemorrhage. All other deaths were not related to study medication.

Although more deaths occurred in the heparin group, their incidence was not statistically significant in comparison with enoxaparin groups. The sponsor hypothesized that enoxaparin may not have any direct toxic effect and, at least in the reported cases, the pharmacological efficiency (anticoagulation) only contributed to other co-morbid causes of the fatal outcome.

Table 8-6

Table 11: Summary of Adverse Clinical Events Leading to Discontinuation of Study Medication[a]

	Heparin		Enoxaparin Once-Daily		Enoxaparin Twice-Daily		Combined	
	N	%	N	%	N	%	N	%
Patients With AEs[b]	16	2.9	9	3.0	12	2.1	37	2.6
Patients Without AEs[b]	528	97.1	289	97.0	547	97.9	1364	97.4
Adverse Clinical Events by COSTART[c] Body System								
Body as a Whole[d]	3	0.6	3	1.0	5	0.9	11	0.8
Allergic reaction			1	0.3			1	0.1
Asthenia			1	0.3			1	0.1
Fever	1	0.2					1	0.1
Headache	1	0.2					1	0.1
Accidental injury					1	0.2	1	0.1
Accidental overdose	1	0.2					1	0.1
Pain			1	0.3			1	0.1
Chest pain					4	0.7	4	0.3
Reaction unevaluable	1	0.2					1	0.1
Cardiovascular System[d]	3	0.6	4	1.3	2	0.4	9	0.6
Bradycardia			1	0.3			1	0.1
Pulmonary embolus	1	0.2			1	0.2	2	0.1
Hemorrhage	2	0.4	1	0.3	1	0.2	4	0.3
Hypotension			1	0.3			1	0.1
Myocardial infarct			1	0.3			1	0.1
Digestive System[d]	5	0.9	3	1.0	2	0.4	10	0.7
Gastrointestinal hemorrhage	3	0.6	3	1.0	1	0.2	7	0.5
Hematemesis	1	0.2			1	0.2	2	0.1
Nausea	1	0.2					1	0.1
Vomiting			1	0.3			1	0.1
Hemic and Lymphatic System[d]	1	0.2	0	0.0	1	0.2	2	0.1
Prothrombin decreased	1	0.2			1	0.2	2	0.1
Metabolic and Nutritional Disorders[d]	0	0.0	1	0.3	0	0.0	1	0.1
Edema peripheral			1	0.3			1	0.1
Musculoskeletal System[d]	1	0.2	0	0.0	1	0.2	2	0.1
Joint disorder	1	0.2			1	0.2	2	0.1
Nervous System[d]	2	0.4	0	0.0	1	0.2	3	0.2
Anxiety	1	0.2					1	0.1
Dizziness	1	0.2					1	0.1
Intracranial hemorrhage					1	0.2	1	0.1

[a] Extracted from Table [illegible], Appendix I
[b] Adverse clinical events
[c] Coding Symbol for the Thesaurus of Adverse Reaction Terms
[d] Body system totals for all patients who experienced any event.

continued on following page

Integrated Summary of Benefits and Risks
Protocol Numbers [illegible]
[illegible]
[illegible] February, 1997

Laboratory Tests

Thrombocytopenia

Only one patient out of 1401 developed a documented immune HIT without thrombosis. This patient was treated

with enoxaparin. Only two patients (including the first one) developed severe thrombocytopenia. They both received enoxaparin treatment. The second patients had concurrent chemotherapy. Moderate thrombocytopenia was seen in 14 patients (all treatment groups: H=4;1.4%/E1=4;1.3%/E2=6;1.9%).

Hemoglobin

The distribution of hemoglobin levels below 8 g/dL during the treatment period was similar for the three treatment groups. The trend was less favorable for heparin (6.9%) than enoxaparin qd (4.7%) and enoxaparin bid (3.8%).

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AST and ALT

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A trend for more frequent elevation of serum aminotransferases was observed for enoxaparin. No significant difference vs. heparin was noted.

Primary Conclusion

The safety profile of both enoxaparin regimens was similar to continuous infusion of heparin.

Table 8-7

Table 12: Summary of Deaths for All-Treated Patients During the Study Period[a]

	Heparin		Enoxaparin Once-Daily		Enoxaparin Twice-Daily		Combined	
	N	%	N	%	N	%	N	%
Number of Patients	544		298		559		1401	
Study Period								
Number of Deaths	26	4.8	11	3.7	18	3.2	55	3.9
Cause of Death[b]								
Caused by PE[c] (Treatment Failure)	1	0.2	0	0.0	0	0.0	1	< 0.1
Associated with PE[c]	3	0.6	1	0.3	2	0.4	6	0.4
Caused by Hemorrhage	2	0.4	1	0.3	3	0.5	6	0.4
Associated with Hemorrhage	2	0.4	4	1.3	0	0.0	6	0.4
Other Reason	23	4.2	11	3.7	15	2.7	49	3.5
Death During Treatment Period								
Classified Non-Failure	0	0.0	2	0.7	1	0.2	3	0.2
Classified Failure	2	0.4	0	0.0	0	0.0	2	0.1
Death During Follow-up								
Classified Non-Failure	16	2.9	7	2.3	15	2.7	38	2.7
Classified Failure	8	1.5	2	0.7	2	0.4	12	0.9
1 Month Follow-up								
Number of Deaths	7	1.3	5	1.7	8	1.4	20	1.4
Cause of Death[b]								
Caused by PE[c] (Treatment Failure)	1	0.2	0	0.0	0	0.0	1	< 0.1
Associated with PE[c]	2	0.4	1	0.3	2	0.4	5	0.4
Caused by Hemorrhage	1	0.2	1	0.3	3	0.5	5	0.4
Associated with Hemorrhage	1	0.2	3	1.0	0	0.0	4	0.3
Other Reason	4	0.7	5	1.7	5	0.9	14	1.0
2 Month Follow-up								
Number of Deaths	7	1.3	2	0.7	5	0.9	14	1.0
Cause of Death[b]								
Caused by hemorrhage	1	0.2	0	0.0	0	0.0	1	< 0.1
Associated with hemorrhage	0	0.0	1	0.3	0	0.0	1	< 0.1
Other	7	1.3	2	0.7	5	0.9	14	1.0
3 Month Follow-up								
Number of Deaths	12	2.2	4	1.3	5	0.9	21	1.5
Cause of Death[b]								
Associated with PE[c]	1	0.2	0	0.0	0	0.0	1	< 0.1
Associated with hemorrhage	1	0.2	0	0.0	0	0.0	1	< 0.1

[a] Extracted from Table 8.7.34, Appendix 1
[b] Multiple answers possible
[c] PE: Pulmonary Embolism

8.4.3 SPONSOR'S RISK/BENEFIT ASSESSMENT AND CONCLUSION
(Vol. 1, p.210)

Citation: "These studies demonstrate that enoxaparin administered as a 1.0 mg/kg twice-daily regimen or a 1.5 mg/kg once-daily was equivalent to adjusted-dose, continuous infusion heparin therapy for the prevention of recurrent Venous thromboembolic disease in patients with acute deep vein thrombosis with or without pulmonary embolism. The safety profile of enoxaparin administered subcutaneously once or twice-daily was comparable to that of continuous infusion heparin therapy. The incidence of major hemorrhages did not statistically differ in the three treatment groups and a trend toward an increased occurrence of discontinuation due to hemorrhage was noted in the heparin-treated patients. However, the incidence of all hemorrhages, specifically injection-site hemorrhages, was statistically lower with heparin than with enoxaparin administered once or twice-daily. The safety profile of the two enoxaparin regimens was similar to that of the heparin regimen for other safety parameters including clinical and laboratory adverse events."

9.0 POST-MARKETING STUDIES

9.1 DESCRIPTION OF OTHER CONTROLLED AND SUPPORTIVE CLINICAL STUDIES

Five studies have been submitted to support the use of enoxaparin for the treatment of DVT and PE.

1. **Study DN 100553**: *Study of the efficacy and tolerance of subcutaneous administration of enoxaparin in the prevention and treatment of thromboembolic episodes in patients with systemic hemorrhage or a major risk of hemorrhage.*

This was a single center, open-label, non comparative clinical trial to demonstrate that enoxaparin (0.75 mg/kg bid sc) may be helpful for prophylaxis or treatment of VTE. Fifty patients were studied: evolving VTE (26 patients), isolated high thromboembolic risk (12), and both (12). Patients received enoxaparin for 47±22 days (range 25-69). One patient died of GI bleeding while on enoxaparin therapy. Five patients had hemorrhagic complications. Efficacy was judged to be very good (?) in 43 of 49 (88%) patients.

Comment: This study provide information on safety of enoxaparin administration for about two months.

2. **Study DN 100554**: *Study of the efficacy and tolerance of enoxaparin administered by the intravenous route in the treatment of pulmonary embolism.*

In this open-label, non comparative study, enoxaparin was given to 10 patients who presented with symptomatic mild PE. Enoxaparin dose was 0.5 mg/kg iv bolus, then an intravenous infusion 2-3 mg/kg/24h for 12 days, and from day 12-26 patients received enoxaparin 0.5 mg/kg/day sc. The precipitating causes of PE were proximal DVT (7 patients), distal DVT (1 patient), humeral vein (1 patient) and no DVT (1 patient).
Enoxaparin infusion was adjusted on the basis of anti-Xa activity. Enoxaparin was found effective for PE and underlying DVT. No adverse events were reported.

3. **Study DN 105338**: *Study of subcutaneously administered enoxaparin in the treatment of pulmonary embolism.*

In this single center, open-label, non comparative, prospective clinical trial, 17 patients with mild PE (scintigraphically confirmed) with or without symptomatic DVT (50% of cases) were exposed to enoxaparin (initial dose 0.5 mg/kg bid, than dose adjusted to maintain a mean peak anti-Xa activity of 0.42 IU/ml (WHO international heparin standard) for 20 days.

One case of PE recurrence was observed. The angiographic index showed significant regression in 56%. Clinical symptoms of DVT regressed by day 5 in most patients. One patient developed thrombocytopenia, and one with hemorrhagic coloproctitis had a major hemorrhagic event.

The average adjusted dose of enoxaparin was found to be 1.8 mg/kg/24h.

Comment: This result was used for calculating the initial dose in clinical trials for the treatment of DVT. These trials confirmed that enoxaparin dose of 1.0 mg/kg q12h is effective and safe.

4. **Study DN 105336**: *Open-label study of subcutaneously administered enoxaparin in the treatment of established deep vein thrombosis.*

In this single center, open-label, non comparative, prospective clinical trial in consecutively recruited patients enoxaparin was given (1.0 mg/kg q12h for 10 days) to 36 patients who developed acute proximal DVT either postoperatively (22 patients) or spontaneously (14 cases). Efficacy was evaluated by the change of Marder's and Arnesen's scores. There was no thrombosis extension in any patient, no score progression was seen in 5 patients, and score regression of over 35% in 15 patients. Treatment was withdrawn in 2 patients due to bleeding complication. One case of gastric carcinoma, and one case of subcutaneous hematoma at venipuncture site were recorded.

Pharmacodynamic evaluation revealed no relationship between anti-Xa activity, efficacy and safety of enoxaparin. According to the sponsor, this study indicates to another, yet unknown, mechanism for the efficacy of enoxaparin in DVT treatment.

5. **Study DN 105377**:PK 528: *Safety and Efficacy of enoxaparin in the treatment of established deep vein thrombosis.*(Vol.141, p.183-4)

In this multicenter, randomized, open-label, parallel group clinical trial, the efficacy and safety of enoxaparin (1.0 mg/kg q12h, sc, for 10 days) was compared with heparin infusion (5,000 IU bolus + 500 IU/kg/24h for 10 days) in 134 patients (67 patients each group) whith diagnosis of DVT. All patients received 24 h heparin infusion prior to randomization.

Efficacy was evaluated by comparing changes in venograms score between the start and the end of treatment. Enoxaparin was significantly better in both Marder (42.5% vs. 27.3%; p=0.007) and Arnesen (42.4% vs. 25.0%; p=0.02) score. At time of inclusion, over 55 percent of patients in each group presented asymptomatic PE documented by scintiscan or angiography.

This study showed no relationship between anti-Xa activity and body weight or area, or changes in venography scores, occurrence of hemorrhagic manifestation or recurrence of PE. As in the previous study, the sponsor suggests a new mechanism, other than anti-Xa activity, to be responsible for the role of enoxaparin in DVT treatment.

Safety analysis showed one case of immune thrombocytopenia in the heparin group, and one hematoma at the venipuncture site, one of ecchymosis at the injection site, one ankle hematoma, and one case of nose bleed, all in the enoxaparin group.

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9.2 EFFICACY SUMMARY
(Vol.1, p.137-143)

Five clinical trials were conducted in France and Belgium from 1983 to 1993 in patients with DVT (105336, 105337), or PE (100554, 105338) or both as separate diseases (K91107). DVT included postoperative DVT regardless of the type of surgery. All studies were open labeled and uncontrolled except for one study (105337) that was controlled.

Patients included in those studies were comparable at baseline according to age, gender, weight and height. Enoxaparin was given in dose of 1.0 mg/kg/bid, 1.5 mg/kg/qd, sc or iv. Efficacy endpoints were recurrent VTE (DVT or PE) and Marder's score or Miller's Index. Recurrent VTE had to be confirmed by objective measurements: venography for DVT or pulmonary scintigraphy/angiography for PE.

Table 9-1
PRIMARY EFFICACY ANALYSIS OF SUPPORTIVE STUDIES

Study	Treatment	Recurrence VTE (%)*		Marder		Miller Index
		DVT	PE	Score	p=	
105337	Enoxaparin	2 (3.5%)	-	42.5±31%(58)	0.007	Day0=10.3±5.8(3) Day10=9.5±7.8(2)
	Heparin	4 (7.3%)	-	27.3±27% (55)		Day0=11.3±5.7(6) Day10=
K91107	Enoxaparin	0	2	NA		NA
100554	Enoxaparin	-	0	NA		NA
105336	Enoxaparin	0	0	Day0=28±16(34) Day10=20±18(34)	<0.001	
105338	Enoxaparin	-	1			D1=41±16(19) Day20=18±15(17)

From Table 12: Summary of Efficacy Outcomes in Other Controlled and Supportive Clinica. Trials (Vo. 1, p.143)

No recurrence of DVT was observed in those studies. In all studies clinical outcomes (lower limb pain and edema, and chest pain) were improved. The Marder's score significantly improved. Three PE recurrence were observed: two asymptomatic (K91107) and one recurrence for an under-dosed patient in study 105338. During 3-month follow-up period in study K91107, no recurrence or extension has occurred.

9.3 SAFETY SUMMARY

Safety of enoxaparin was evaluated in seven studies, five already described and two pharmacokinetic studies (PK 133, and K91006). The two PK studies were single center (France, 1991, and 1995) and open-label. Study PK 133 was a controlled study evaluating two enoxaparin formulations (100 and 200 mg/ml) and the other study was uncontrolled. Enoxaparin was administered sc at the 1.5 mg/kg/d dose in PK 133, and in ascending dose at 1.0 to 2.5 mg/kg/d in dose ranging K91006 study.

Duration of treatment was four periods of one day each (K91006), three periods of five days each (PK 133), 10 days (K91107, 105336, 105337) and 20 or 26 days (105338, 100554). Patients were followed-up for three months only in K91107.

A total of 218 patients (106 male and 112 female) and 41 healthy volunteers (M=28/F=13) were included. One hundred ninety-two patients received enoxaparin, and 67 patients received control heparin.

Only occurrences of hematomas and hemorrhagic episodes were systematically recorded (Table 9-2)

Table 9-2
SAFETY ANALYSIS OF SUPPORTIVE STUDIES

STUDY	Treatment	Patients treated	Hemorrhage			Hematoma		Related Adverse Event
			All	Major	Minor	Significant	Insignificant	
PK 133	Enoxaparin	25	0			0	5	5
K91006	Enoxaparin	16	0			0	12	0
105337	Enoxaparin	67	3	0	3	0	5	0
	Heparin	67	0			0	0	0
K91107	Enoxaparin	19	1	0	1	0	2	0
100554	Enoxaparin	10	1	0	1	0	1	0
105336	Enoxaparin	36	2	2	0	0	0	0
105338	Enoxaparin	19	na			na		na

From Table 15: Summary of Safety Outcomes in Other Controlled and Supportive Clinical Studies (Vol.1, p.147). na=Not available

According to the sponsor, laboratory safety was satisfactory. A few abnormal values were without clinical significance.

One type of thrombocytopenia was reported with enoxaparin on Day 10 (study 105338). It was confirmed as immune type (HIT). Another thrombocytopenia (not confirmed as immune) was observed in a patient on heparin. It led to treatment discontinuation (study 105337). Few events of thrombocytosis without clinical signifcance were also reported.

9.4 SPONSOR'S RISK/BENEFIT ASSESSMENT AND CONCLUSION FOR THE PROPOSED INDICATION. (Vol. 1, p.210)

Based on previously described two controlled clinical trials ('2091' and '529') and other studies presented in this section, the sponsor concludes that they have sufficient evidence to claim that the weight-adjusted enoxaparin is effective and safe drug as heparin for treatment of DVT and PE.

As individual drug, enoxaparin carries risk of bleeding which is mostly minor and, according to the sponsor, clinically irrelevant. Enoxaparin induced thrombocytopenia is a rare disorder. Prior to this study, the comparator drug heparin has been approved for treatment of DVT and PE. The incidence of VTE recurrence in patients with DVT and PE treated with heparin is almost ten times less than in the historic control. This benefit, transferred by comparison (equivalent drug) to Lovenox, gives this drug a reasonable advantage vs. risks.

Therefore, the sponsor proposes change of Labeling for Lovenox Injection. A proper change will add a new indication and new dosing in the appropriate sections of the Labeling (see section Proposed Direction for Use, and Labeling Annotated).

10.0 REVIEWER'S APPRAISAL OF THE NDA#20-164, SUPPLEMENT N-015.

10.1 INTRODUCTION

The sponsor requested approval to add a new indication in the labeling for Lovenox®Injection "Use for treatment of DVT and PE." Two pivotal studies, CPK-2091 and 529 were submitted to provide "substantial evidence" in support of this claim.

The general idea for the new indication of enoxaparin is based on the following:

- Acute symptomatic DVT if untreated with anticoagulants could result in thrombus extension or other thromboembolic complication (VTE recurrence) including massive pulmonary embolism and death. This outcome (VTE recurrence) used to be seen in more than 50% - 60% patients who had not been treated with anticoagulation therapy.

- Therapeutic regimens including heparin for rapid anticoagulation and warfarin for its maintenance, have reduced the probability for venous thromboembolic recurrences to approximately 5%-7%.

- In several clinical studies, including the two pivotal clinical trials submitted in this Supplement, enoxaparin has been shown to be equivalent to heparin in regimens designed for treatment of patients with DVT and with or without PE at presentation.

- Conclusion: enoxaparin can exchange heparin for treatment of DVT.

Is it true? BEST POSSIBLE

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10.2 OUTLINE OF THE ANALYSIS OF EVIDENCE

The review has focused to analyze the evidence in support of the sponsor's claim: use of Lovenox Injection for treatment of DVT and PE.

A. STUDY DESIGN

The two pivotal studies are independent clinical trials. They were designed by RPR and conducted by two groups of investigators in multiple centers in Europe, U.S., Canada and Australia. Both studies were planned as prospective, randomized, parallel group, active treatment controlled clinical trials.

Due to different route of drug administration (enoxaparin - subcutaneous injection; heparin - continuous intravenous infusion; warfarin - oral) the study 2091 was open-label, and 529 was partially blinded (only for the enoxaparin dose level). However, the sponsor took appropriate measure to minimize the possibility for bias. In both studies they used independent adjudication committees for assessment of primary study outcomes (DVT, PE and hemorrhage).

This design can be considered as appropriate for an adequate and well controlled study.

B. STUDY POPULATION:

Both trials enrolled 1,401 patients with acute DVT with or w/o PE. The study populations in the two trials had much in common, but differed in few substantial aspects.

- In the '529' study (900 patients; three groups) the enrollment included patients with presenting acute symptomatic DVT (and/or PE), and presenting symptomatic PE (and/or DVT). An active

search for asymptomatic DVT and PE was conducted at admission. Due to this active search, more patients were classified into DVT and/or PE category. The increased number of patients per category did not influence the baseline balance between the study groups. However, it has produced a systematic difference in comparison with the study '2091'.

- In the study '2091' (501 patients, two groups) investigators enrolled patients with DVT, while PE was considered only if it was recognized by clinical symptoms. Patients with asymptomatic (venographically confirmed) DVT, or asymptomatic (lung scan confirmed) PE, were not included in this study.

- Patients enrolled into study '2091' were in clinical condition suitable to receive outpatient therapy. Patients with co-morbid conditions requiring inpatient treatment were excluded. Patients randomized into the enoxaparin group had the opportunity to decide whether to accept enoxaparin outpatient therapy, or to stay in hospital on heparin regimen. This choice was used by 236 patients who transferred to the heparin regimen. Thus, this exclusion criterion, and the choice offered post-randomization, created at baseline, a subset of selected patients different from the targeted population ("all patients with acute DVT with and without PE"). This subset received enoxaparin outpatient regimen. Recognition of difference between this sample in '2091' and the targeted population in the Supplement, is important for judging the requested change of Labeling.

- According to other studies, the prevalence of asymptomatic VTE (DVT and PE) is about 10 times the symptomatic. The asymptomatic population should be considered at risk and subject to prophylaxis only. Thus, clinical wisdom teaches to restrict therapeutical dosing of enoxaparin exclusively to symptomatic DVT and PE, as it was successfully done in both trials.

C. STUDY MEDICATION: BEST POSSIBLE

Current objective for treatment of DVT is to stop extension of thrombosis, reduce or abolish clinical symptoms, and prevent PE. Restitution of vein patency, although the ultimate goal, is not considered as the main therapeutical aim. A "golden standard" to meet this objective is a regimen that includes intravenous heparin (for rapid achievement of effective anticoagulation, APTT 60-90 sec.) followed by gradual increase of warfarin to achieve and maintain anticoagulation at a range of INR 2.0-3.0. In both trials the "golden standard" was set to be:

1) heparin (intravenous, continuous infusion) dose adjusted according to targeted APTT, for minimum 5 days, and
2) warfarin, peroral, dose adjusted to targeted INR for 3 minimum months. Warfarin therapy began 48h (study '2091') and 70h (study '529') after randomization. Targeted INR (2.0-3.0) was reached within 3-5 days, and was maintained for three months.

Enoxaparin was planned to be given as alternate to heparin. The enoxaparin regimen included:

1) enoxaparin fixed dose, weight adjusted (subcutaneous, 1.0 mg/kg bid, or 1.5 mg/kg qd), for a minimum of 5 days (inpatient or outpatient), and
2) warfarin, as above.

The clear pattern described above could not be followed for all patients. Two questions arised from the analysis of study results. They are related to clinical interaction between study medications.

1) Pre-randomization heparin vs. post-randomization heparin or enoxaparin

Patients who were admitted during weekend and holiday days, had to wait for the objective assessment of DVT and/or PE. Objective confirmation of DVT and/or PE was a protocol prerequisite for enrollment and randomization. In this interim period of one to three days, about one third of all patients enrolled in study '2091', and almost one half of patients in study '529', received heparin infusion as emergency therapy. Therefore, one large group of patients in both trials, instead of two, had three periods for receiving active treatment: pre-randomization, treatment period, and the follow-up period.

This pre-randomization treatment with heparin was without impact on patients in both trials who were randomized on heparin. Simply, they continued with heparin, received warfarin and discontinued heparin after five days or when targeted INR was reached.

The introduction of the pre-randomization heparin doubled the enoxaparin treatment groups in this submission. To assess whether pre-randomization heparin had any significant effect on the incidence of VTE, additional analyses were requested by the Agency and provided by the sponsor (documents of October 8 and 23, 1997). The analysis included assessment of the incidence of VTE in patients who received enoxaparin at the Once Daily Dose and Twice Daily Dose. These patients were selected into two groups: heparinized enoxaparin and non-heparinized enoxaparin group. Incidence of VTE was assessed at the end of the treatment period, at 1 month, and at 3 months. Two-sided Fisher Exact test was performed. At the significance level of α=0.05, only significant difference was found between heparinized and non-heparinized patients who received twice daily enoxaparin at the end of the three months.

This analysis does not imply that pre-randomization heparin could have influenced efficacy endpoints. However, in a broader sense, this analysis implies that enoxaparin could be considered for the first line therapy in patients who can sustain outpatient treatment of acute DVT.

2) Warfarin vs. heparin or enoxaparin

These trials contain an active treatment follow-up period with warfarin intended to maintain the anticoagulation state achieved by heparin or enoxaparin. Warfarin blocks the liver synthesis of vitamin K dependent coagulation factors. A period of 3-5 days is needed between beginning of warfarin administration until the plasma level of these factors is reduced to the targeted anticoagulation state (measured as INR). Protocols in these two trials were designed to expect warfarin full protection between day 5 and day 8 after randomization. Heparin and enoxaparin were used to achieve an immediate state of anticoagulation. Warfarin was used to maintain this state. Oral warfarin was given for three months as an active therapy.

Almost all patients completed heparin or enoxaparin treatment within two weeks after randomization (in '2091', median 6.0 days, range 1-17 days). During the first two weeks all patients received warfarin together with heparin or enoxaparin. All patients received warfarin for a total of three months minus 2 or 3 days (study '2091' or '529' respectively). The relation between warfarin and other treatments duration is 1:6 (two weeks: 12 weeks).

The goal of heparin, enoxaparin and warfarin in these trials was to induce and maintain a state of anticoagulation. Change of this state may induce occurrence of primary efficacy (increased coagulability may produce VTE recurrence) and safety (decreased coagulability may produce hemorrhage) endpoints. The question is whether warfarin, used in all treatment groups and for the entire period of observation for efficacy and safety endpoints, was responsible for the equivalent results more than heparin and enoxaparin used only at the beginning of this period. In other words, can the sponsor claim the efficacy and safety observed in this study to enoxaparin and heparin alone, or warfarin should be included?

Based on data presented in these studies, this reviewer concluded that the regimens (heparin+warfarin, and enoxaparin+warfarin) rather then individual drugs (heparin, enoxaparin, or warfarin), were responsible for the observed equivalence of efficacy and safety. This conclusion should be incorporated in the labeling.

D. STUDY OUTCOMES:

Study outcomes were comparable across the trials.

Efficacy:

The primary efficacy endpoint was 'any' VTE event. VTE was defined as extension of primary DVT, occurrence of new DVT, PE or death due to thromboembolism. Any clinically suspicious DVT had to be verified by venography or duplex ultrasound, and suspect PE by lung scan respectively.

A total of 30 (501, 5.98%) VTE among all-treated patient population was reported in the study '2091'. Seventeen (6.69%) VTE were reported in the heparin regimen group, and 13 (5.26%) in the enoxaparin bid regimen group. This difference was not significant. In '529', a total of 34 VTE (900, 3.8%) was reported in the all-treated patients population. In the heparin group there were 12 (4.1%) VTE, comparing to 13 (4.4%) in the enoxaparin qd, and 9(2.9%) in the enoxaparin bid group. The difference was not significant. Using a confidence interval for the difference of means approach, the sponsor concluded equivalence between heparin intravenous infusion and all enoxaparin regimens (outpatient bid, and inpatient bid, qd). The FDA statistical reviewer confirmed that enoxaparin regimens (particularly twice-daily) were not inferior to heparin by 3% (study '2091') or 10% (study '529').

The secondary efficacy variables included the incidence of recurrent VTE in the evaluable population, site of recurrence, time to first recurrent VTE (study '529'), strata interaction (study '2091'), investigator and adjudication committee assessment concurrence (study '2091'), and interactions by demographic characteristics, country and investigator and risk factors. They supported the conclusion of equivalence between treatments.

In a subgroup analysis in both trials, a major impact to the incidence of DVT recurrence came from cancer as a concurrent disease. Presence of cancer was recorded in 26 patients of 64 who experienced recurrent VTE. The percents are highly indicative: total 26/64 VTE (40.6%; H=41.3% /E1=46.1% /E2=36.3%). Another aspect is to compare the percent of recurrent VTE in patients with cancer, with the incidence of VTE in the entire population. Numbers are again impressive. In cancer patients recurrent VTE appeared in 26/244 (10.7%), while in the whole population there were 64/1401 (4.6%) recurrent VTE. This difference was significant. Apparently, this therapy for prophylaxis of VTE recurrence was not efficient in patients with cancer. Cancer induced hypercoagulability is frequently associated with spontaneous release of tissue factor VII. Maybe the inducers of tissue factor pathway inhibitor (TFPI) like heparin and enoxaparin, should be considered for longer administration in these cases. The sponsor did not provide any comment on this issue.

Additional support for the sponsor's claim was provided in study '529' by the analysis of subgroup of patients who underwent sequential assessment of the Marder's score and/or ventilation perfusion lung scan on day 8. A total of 264 was evaluated for the Marder's score, and 265 (31.9%) underwent sequential lung scan. The results have shown a slight improvement of the Marder's score (median from 22 to 19), and significant improvement of the lung scan findings (40% improved for one category). There was no significant difference between treatments.

In a study of equivalency, the crucial question is whether the test and control regimens are interchangeable. It cannot be applied in this situation. Outpatient treatment is not for heparin infusion or

for patients who are morbid enough to require hospital stay, or patients who cannot self-administer injection, or do not wish to undertake this experience. Outpatient treatment should be reserved only for the selective group of patients as the one used in this study ('2091').

For inpatients, smaller differences between regimens should be considered, and individual decision should be made. For instance, the convenience of once-daily enoxaparin should be judged against larger pharmacokinetic variability (almost complete disappearance of activity prior to the next injection 24h later), twice-daily enoxaparin against prolonged state of bleeding diathesis within 24 hours (may be a problem for withdrawal of indwelling catheters, spinal injections, or smaller interventions), intravenous heparin against patient acceptance of a continuous infusion, personnel engagement, and laboratory controls (APTT).

Safety: [redacted] BEST POSSIBLE

In both trials, the primary safety endpoint was hemorrhage reported in all-treated patient population between administration of the first dose of study medication and 48h after cessation of either heparin or enoxaparin (end of the treatment period). Warfarin effect was not considered in this evaluation. The second primary endpoint was hemorrhage during the study period (treatment + follow-up). This evaluation included warfarin maintained anticoagulation state. Hemorrhage occurring during the treatment and the follow-up period was categorized as any, major, minor, or hemorrhage requiring transfusion (Table 10-1)

Table 10-1
SUMMARY OF HEMORRHAGIC EVENTS DURING STUDY 2091 AND 529

HEMORRHAGE^		Heparin		Enoxaparin qd		Enoxaparin bid		Combined	
		N=544	Both	N=298		N=559	Both	N=1401	Both
TREATMENT PERIOD	Any	10+39	49	46		11+54	66	21+139	160
	Major	3+6	9	5		5+4	9	8+15	23
	Minor only	6+33	39	41		6+50	56	12+124	136
	Discontinuation	4+5	9	4		3+1	4	7+10	17
	Transfusion	2+4	6	2		1+3	4	3+9	12
STUDY PERIOD	Any	24+68	92	77		18+81	99	42+226	268
	Major	6+15	21	10		8+6	14	14+31	45
	Minor only	18+53	71	67		10+75	85	28+195	223
	Transfusion	4+10	14	6		1+4	5	3+20	23

From Table 6.9-13 and 7.9-12

One out of five patients treated with either regimen faced the risk of hemorrhage during the entire study. All three drugs, heparin, enoxaparin and warfarin produce a permanent condition of increased tendency for bleeding after trauma (*drug induced hemorrhagic diathesis*). These drugs do not induce spontaneous bleeding such as aspirin or other antiplatelet agents. Tissue injury, such as injections and installation or removal of catheters, was the most frequent cause for bleeding (83.2%). Major bleedings were seen rarely. In both trials, injection site hemorrhage was significantly more frequent in enoxaparin regimens than in control, due to the route of drug administration.

More than a half of these events were reported during the treatment period. However, 'any' hemorrhage appeared with incidence of 3% per day during the entire study, or 12% during the treatment period. This calculation gives a probability of 1:33 for an individual patient to bleed during the study. During the treatment period this probability was increased four times. It was 1:9. These numbers are important for the assessment of risks vs. benefit. There was no significant difference between treatment groups. It can be considered in favor of enoxaparin regimens.

10.3 REVIEW SUMMARY AND RECOMMENDATION

The review has found:

- Two pivotal studies '2091' and '529' were adequate and well-controlled clinical trials. Therefore, they are admissible as evidence to support the sponsor's claim.

- In these trials, the enoxaparin regimens with respepct to safety and efficacy were comparable to the standard heparin regimen for "treatment of DVT and PE" but only in a broad interpretation of the phrase.

  Data show that enoxaparin was not interchangeable with heparin for treatment of all DVT and PE and in all patients.

  The outpatient enoxaparin regimen should be restricted only to patients who are eligible for home therapy.

  [redacted]

- The proposed labeling change should be limited to the indication that is actually supported by trial data. This review has revealed many fine details limiting the sponsor's claim for indication as proposed.

Recommendation

Based in these premises I would recommend Lovenox® Injection in conjunction with warfarin to be

A. APPROVABLE FOR:
- Outpatient treatment of acute symptomatic DVT without PE.
- Inpatient treatment of acute DVT with and without PE.

[redacted]

Further studies are recommended to elicit whether the weight-adjusted dose could be lower for elderly, and higher for obese patients or patients with cancer. .

/S/ [redacted] 2/19/98
/S/
Nenad Markovic, M.D.

cc:
NDA 20-164
HFD-180
HFD-180/LTalarico /S/ 2-19-98
HFD-180/NMarkovic
HFD-181/CSO
HFD-180/JChoudary
HFD-180/EDuffy
f/t 2/19/98 jgw
MED\N\20164802.0NM

[redacted]

APPENDIX 1