CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020164/S010

MEDICAL REVIEW(S)

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

MAR 5 1997

NDA#20-164/SE1-010

Document:	SUPPLEMENT FOR A NEW INDICATION: DOSE (40mg/0.4mL) AND DURATION (21 days post hospital discharge) IN PATIENTS UNDERGOING HIP REPLACEMENT SURGERY. Two pivotal studies included: Study ENOX 491001, France, 179 pts, and Study PK-537, Sweden, 262 pts.
Drug:	LOVENOX® INJECTION (enoxaparin sodium)
Category:	ANTICOAGULANT
Indication:	Approved for perioperative prophylaxis against DVT and PE in patients undergoing hip and knee replacement surgery at a dose of 30 mg q12h for up to 14 days.
Sponsor:	RHONE-POULENC RORER PHARMACEUTICALS Collegeville, PA 19426-0107
Managing Info:	
Date Received:	04/05/96
Date completed:	02/20/97
Action Proposed:	**APPROVABLE** for the **NEW DOSE** and the **EXTENDED PROPHYLAXIS** against DVT and PE after Hip Replacement Surgery
Medical Officer:	Nenad Markovic, M.D.

APPEARS THIS WAY
ON ORIGINAL

INDEX

A. INTRODUCTION

1.0 MATERIAL UTILIZED IN REVIEW

1.1 Materials from NDA/IND for Lovenox® Injection.
1.2 Materials from reviews on drugs related to Lovenox® Injection.
1.3 Other Resources.

1.1 Materials from NDA/IND for Lovenox® Injection

This submission is a supplement for a new dose and new duration of Lovenox®(enoxaparin sodium) Injection in the prophylaxis of deep vein thrombosis [DVT] and pulmonary embolism [PE] following hip replacement surgery. It was received on April 5, 1996 and registered as Supplement No. 010 (M43.1-18) to NDA#20-164. The submission contains 18 volumes, including two pivotal studies ENOX 491001 (Vol. 2-7) and PK-537 (Vol.10-13), executive summary (Vol.1), integrated summaries of safety (Vol.15) and efficacy (Vol.14), and individual patient reports (Vol. 17-18). A separate volume (Vol.8) contains related publications. Content of each volume is summarized in the Appendix.

Other material from related NDA/IND used for this review includes NDA#20-164/SE001 and SE002, . The original NDA for Lovenox injection (NDA#20-164/SE001 from March 1993), contains information on the use of enoxaparin in prevention of DVT and PE following hip replacement surgery. Additional information was collected from the Supplement No.008 (December 27, 1995) also under review at DGCDP.

1.3 Other Resources

1.3.1 MEDLINE DATA BASE

MEDLINE data base (period: 1990-6/1996), was searched for: *low-dose heparin* (103 reports), and *low molecular weight heparin* (142 reports). Both abstracts and articles from this list were used in the review.

1.3.2 TEXTBOOKS

The following textbooks were used as reference for different aspects of the review.

1.3.2.1 Sabiston D. Textbook of Surgery. W.B.Saunders Co., 1986

1.3.2.2 Coleman M. Colon and Rectal Surgery. J.B. Lippincot Co., 1993

1.3.2.3 Schwarts, Shires, Spenser. Principles of Surgery, 6th ed. McGraw-Hill, Inc. 199

1.3.2.4 Way LW. Current Surgical Diagnosis and Treatment. 10th ed., New York: Lange Medical Book, Inc., 1995.

1.3.2.5 Kempcziski J. Vascular Surgery. 3d ed. Sounders Co., 1989.

1.2.3.6 Crenshaw AH. Campbell's Operative Orthopaedics. Eight ed. Philadelphia:Mosby Year Book, 1994.

1.3.3 RELATED MEDICAL LITERATURE

Scientific papers cited in the review are referenced in this section. See section on Literature (Appendix)

2.0 BACKGROUND

2.1 Indication
2.2 Rationale
2.3 Target population
2.4 Enoxaparin and related drugs for prevention of DVT and PE in hip surgery.
2.5 Administrative History
2.6 Foreign Marketing
2.7 Proposed Directions for Use

2.1 Indication

2.1.1 *Approved Dose and Duration of Treatment*

Lovenox® injection is already approved in the U.S. for prevention of DVT and PE in patients undergoing hip (NDA#20-164/SE001) and knee (NDA#20-164/SE002) replacement surgery. Dose approved is 30 mg q12h, to start 12-24 hours after surgery (permitting hemostasis is established) and to continue for the entire postoperative inhospital period usually from seven to 14 days after surgery.

In Europe, enoxaparin is approved for prophylaxis of DVT and PE in General Surgery, too. The approved dose is 40 mg, qd, to start 2-12 hours prior to surgery and to continue for 6-12 days after surgery.

In the medical review used for the FDA approval of enoxaparin in the U.S., there is an important information related to the effective dose. The reviewer has found the dose of enoxaparin (40 mg, qd) to be as effective as 30 mg q12h. It was not recommended because, at this time (1993), Lovenox® Injection was available only in prefiled syringes containing 30 mg/0.3mL. Today, Lovenox® Injection is also available in syringes of 40 mg/0.4 mL (pending approval of NDA#20-164/SE008).

2.1.2 *Proposed New Dose and Duration of Treatment*

To improve a long-term prognosis of patients undergoing hip replacement surgery, with this supplement, the sponsor proposes extension of prophylaxis with Lovenox® Injection (new dose: 40 mg/0.4mL, sq, qd) for 21 days (new duration) after a successful completion of surgery and perioperative prophylaxis with the same drug. Under the provision of this indication/instruction for use, patients undergoing hip replacement surgery in Europe would receive enoxaparin postoperative prophylaxis (40 mg/0.4 mL, sq) beginning 12±2 hours before surgery. Patients in the U.S. would receive 30 mg/0.3mL, sc BID or 40 mg, qd, with the first dose beginning 12-24 hours post-operatively. The extension of prophylaxis will continue with 40mg,sc, daily after discharge for a total of 5 weeks. The extension of prophylaxis is intended to further reduce probability of surgery-induced DVT, probably from [redacted], and PE accordingly (goal in study ENOX 491001).

2.2 *Rationale*

Pulmonary embolism [PE] is the most common preventable cause of death following major operations[1]. In the United States, 90,000 deaths per year may be attributed to PE. Of 200 patients who undergo a major operative procedure, one will die of a massive PE. Certain groups are at greater risk. Ten percent of elderly patients who undergo repair of a fractured hip will suffer a PE. It presents a high risk in comparison with an incidence of 0.2% PE occurring in the general surgical population older than 40 years of age[12].

In 1976, Johnson et al.[6] published their experience with PE after hip operation. In a period of 12 years (1962-73), the authors have operated 7,959 hips, and have recorded 83 fatal and 628 nonfatal PE. Two tables (2-4, and 2-5) from this report are of considerable interest for understanding the RPR proposal in this supplement.

Table 2-4
INCIDENCE OF FATAL AND NON-FATAL PULMONARY EMBOLISM FOLLOWING HIP SURGERY

Day of Embolus	Number (Fatal PE)	Number(Non-fatal PE)
O -7	8(9.7%)	73(11.6%)
8 - 14	45(54.2%	265(42.2%)
15 - 21	19(22.9%)	204(32.5%)
22 - 28	7(8.4%)	64(10.2%)
28 +	4(4.8)	22(3.5%)
Within one year	2(0.41%)	10(2.05%)
Later than 1 year	0	13(3.25%)
TOTAL	85(100%)	651(100%)

According to Johnson et al.Vol.8, page 8-7-3/12

Another table (2-5) presents PE in many patients not receiving any prophylaxis and some experience with initial attempts for DVT prophylaxis.

Table 2-5

REDUCTION OF PE FOLLOWING INITIAL PROPHYLAXIS FOR DVT

DATE	METHOD	NUMBER	FATAL	%	NON-FATAL	%
1962-73	NONE	1,174	26	2.3	179	15.2
1966	DINDEVAN	450	3	0.8	29	6.5
1970	iv HEPARIN	138	1	0.7	13	9.5
1970-73	MACRODEX	4,096	46	1.1	339	8.2
1974-75	PLAQUENIL	1,054	4	0.4	45	4.2
1962-75	total	7,959	83	1.04	628	7.89

According to Johnson et al (Vol.8, page 8-7-7)

According to these data, more than 75% of the fatal embolism appears within seven and 21 days, while nonfatal PE appear with wider distribution curve including a tail after the first year. Fredin et al.[7], in a retrospective study of 1,324 cases of total hip replacement, found that nine patients died of PE within three months of surgery. Reference articles suggest first three months to be considered a period of increased risk for postoperative PE.[TB1,4,6]

Postoperative pulmonary embolism is an uncommon event in healthy young patients. It is more common in elderly (age >60 years). In general surgical population leg DVT is the most common preventable precursor of this event. Following a better understanding of risk factors for DVT and PE, a perioperative prophylaxis of DVT became a mainstream for reduction of postoperative PE and the related deaths. The risk factors for development of DVT and PE, as suggested by an NIH Consensus Conference are summarized on Table 2-2(cited from: JAMA 1986; 286:745-9).[1] Surgical books suggest a reduced table for quick reference (Table 02-1). Hip replacement surgery belongs to the procedures with high risk for developing DVT and PE (Table 2-1).[11]

DVT is usually a silent (asymptomatic) disease. Only of patients with DVT may develop clinical syndrome of significance.[15] It is an incorrect procedure to diagnose DVT by clinical examination only. In general, half of the patients with DVT have no physical signs, and half of signs are not specific. Leg DVT can be diagnosed with ascending phlebography (the most accurate method); Ultrasound (Doppler; non-invasive method with moderate accuracy; Duplex ultrasound (combination of real time B-mode ultrasound imaging with Doppler flow analysis (specificity and sensitivity rates are for the femoral region, but only 75% below knee); Plethysmography (relatively insensitive in asymptomatic patients); and Radioactive fibrinogen (the most sensitive, but less specific method). Introduction of these methods for detection of DVT had revealed the incidence of "silent" DVT in % of surgical patients.[15] One third of "silent" DVT resolve after surgery, one third may organize into partial thrombi, and only one third may generate occlusion (clinically overt DVT), propagation to upper veins, or/and PE.[15]

Table 2-1

Table 2.1.1[24]
RISK FACTORS FOR DEVELOPMENT OF VENOUS THROMBOSIS

Cancer
Oral contraceptive use
Operations of hips or pelvis
High blood viscosity (polycythemia)
Obesity
Varicose veins
Obstructed venous return
Immobility
Childbirth or pregnancy
Previous history of DVT
Old age (over 60)
Prolonged or complex surgical procedures

Table 2-2

Table 2.1.2[31]
RISK FACTORS PREDISPOSING TO THROMBOEMBOLISM

Inherited risk factors
Antithrombin III deficiency
Protein C deficiency
Protein S deficiency
Dysfibrinogenemia
Disorders of plasminogen and plasminogen activation
Acquired risk factors
Lupus anticoagulant
Nephrotic syndrome
Paroxysmal nocturnal hemoglobinuria
Cancer
Stasis - CHF, MI, etc
Advancing age
Estrogen therapy
Sepsis
Immobilization
Stroke
Polycythemia rubra vera
Inflammatory bowel disease
Obesity
Prior thromboembolism

According to the Consensus Conference, the incidence of postoperative DVT and PE can be reduced by employing a suitable

prophylactic regimen. It may include physical measures to reduce venous stasis, and/or anticoagulation. However, the controlled trials strongly suggest that prophylactic anticoagulation in high risk patients have markedly decreased the incidence of postoperative DVT and PE. The following agents have been studied: prothrombin depressants (warfarin and phenindione derivatives), platelet function suppressants (dextran 40, dextran 70, aspirin, dipyridamole, sulfinpyrazone), and heparins (unfractionated heparin - low-dose regimen, and low-molecular weight heparins, such as enoxaparin). LMWH are derived from standard unfractionated heparin. They inhibit an activated factor X but do not affect the aPTT.

Enoxaparin is a member of LMWH family of drugs. In USA enoxaparin is approved for prophylaxis of DVT and PE in hip and knee surgery. Another supplement, related to prophylaxis of DVT and PE in patients at risk who undergo abdominal surgery, is under consideration at DGCDP (NDA#20-164/SE008).

2.3 *Target Population*

The initial indication for total hip arthoplasty was "to alleviate the incapacitating pain in patients older than 65 years who could not be relieved sufficiently by nonsurgical means" (Harkess, 1994; p473).[11] Today indications for hip arthroplasty have been largely extended (Table 2-2a).

Table 2-2a

DISORDERS OF THE HIP JOINT FOR WHICH TOTAL HIP ARTHROPLASTY MAY BE INDICATED

Arthritis	Rheumatoid	Avascular necrosis	Postfracture
	Juvenile rheumatoid		Renal disease
	Ankylosing spondylitis		Cortisone induced
Degenerative joint disease	Osteoarthritis hypertrophic		Alcoholism
	Slipped capital femoral epiphysis	Pyogenic arthritis or osteomyelitis	Hematogenous, postoperative
	Congenital dysplasia		Tuberculosis
	Legg-Perthes disease	Congenital subluxation	
	Traumatic Dislocation	Pseudoarthrosis	
	Fracture (acetabulum)	Failed reconstruction	
	Hemophilia	Bone tumor	

From Harkess JW. Arthroplasty of Hip, in Cambell's Operative Orthopaedics, 8 ed. Mosby Year Book, 1994,p.473.

Comment: Surgical indications for hip arthroplasty cited above (Table 2-2a) are deemed to be a continuously evolving issue.

This Supplement (#SE010) presents two studies with enoxaparin 40 mg, qd. The drug was administered for extension of prophylaxis in patients who underwent elective hip surgery and had successfully completed the perioperative prophylaxis with the same drug. The population was older (>40 in PK-537, >45 in ENOX), non-obese (weight limited to kg ENOX), and without cancer or VTE within six months. These precautions were taken in the Exclusion Criteria of both studies, to minimize, at the baseline, the risk factors for DVT. Majority of patients, >95%, suffered from chronic osteoarthritis (coxarthrosis, -itis), and had long life expectancy.

2.4 *Enoxaparin and Other Heparin Related Drugs in Prevention of DVT and PE in Elective Hip Surgery.*

Currently available treatments for heparin-related prophylaxis of DVT and PE in patients undergoing hip replacement surgery include low-dose heparin (5,000 IU BID or TID) and several low molecular weight heparins (enoxaparin [Lovenox ,

Although all are LMWH these drugs differ between each other (average molecular weight, different pharmacokinetics[15], effective dose), but have similar clinical activity.

Enoxaparin was compared *vs.* placebo in patients undergoing elective hip arthroplasty[4]. The incidence of DVT (^{125}I-fibrinogen uptake test + impedance plethysmography + venography) was significantly lower in the enoxaparin group (enoxaparin 6/50 *vs.* control 21/50, $p<0.05$). Bleeding complications were mild and similar in both groups. There was no PE, and only one patient died in the control group. Other studies on LMWH *vs.* placebo presented similar results. In a meta-analysis of seven studies, Jorgensen[2] showed a DVT incidence of 48.4% in control groups (169/349) *vs.* 25%(87/348) in LMWH groups, but no difference in PE during the observation period (days, median 42 days). These results are presented in the Supplement Appendix (Table A #2).

Enoxaparin was compared with low-dose heparin in controlled trials with patients undergoing hip surgery, and indirectly with other LMWH in the same indication in another meta-analysis[3]. In two cited studies, enoxaparin (applied 30 mg, sc, BID for 10 days, or 40 mg, sc, qd, for 12 days) significantly reduced the incidence of DVT (40 mg enoxaparin: DVT 15/120; heparin 5,000 IU TID: DVT 27/108), presented a significantly lower rate of hemorrhagic events (no major hemorrhage), and lower, but not significantly, rate of PE than the control group. Other LMWH in this meta-analysis, Fragmin

There was no significant difference between LMWH with respect to prevention of DVT and PE. In total, all LMWH have protected patients from DVT more than heparin but this difference was not significant (low-dose heparin DVT 21.62% [275/1272]; LMWH 16.89% [222/1314]). Protection of PE during the observation period days, was also better in LMWH groups (incidence of PE 0.27%[4/1456]) than in heparin groups (PE 1.35; 19/1408). Bleeding complications were not compared.

In the U.S. enoxaparin was approved for prophylaxis of DVT and PE following hip replacement surgery on March 29, 1993 (NDA#20-164/S001). The approval was based upon two pivotal ENO884 and PK-526, and one range-finding study PK526. In these studies,

enoxaparin was given to patients undergoing hip surgery at dose 30 mg BID *vs.* placebo (ENO884), 40 mg, qd, and 30 mg BID *vs.* low-dose heparin (PK-526), and at 10 mg, qd, 40 mg, qd, and 30 mg BID (PK-526) (Table 2-3: *RPR Lovenox Development Program and Hip Surgery*). The first dose to begin hours postoperatively and after hemostasis was established. These results showed that for days after surgery, enoxaparin (40 mg, qd, or 30 mg BID) prevented DVT better than placebo, and not worse than low-dose heparin. The total number of PE was inadequate to conclude how much enoxaparin might be efficient for reduction of their incidence.

The Supplement (#SE010) presents first two studies in which enoxaparin 40 mg is tested for a prophylactic effect longer than the usual perioperative period of days. In the studies ENOX491001 and PK-537, the first dose of enoxaparin during the open-label period was given within hours before operation. This reflects a European fashion of enoxaparin administration for perioperative prophylaxis. DVT negative patients were randomized to receive either enoxaparin 40 mg daily or placebo for additional 21 days. The first dose of enoxaparin or placebo during the double-blind period was given within 24 hours after the last hospital dose. In these studies enoxaparin was packaged as solution 100 mg/mL strength in prefilled syringes of 0.4 ml. The incidence of DVT, objectively detected by a bilateral ascending phlebography at the end of study, was the primary efficacy endpoint. Such an option for prophylaxis of DVT with enoxaparin administration extended for up to 35 days following hip replacement surgery has not been studied previously.

The enoxaparin dose of 40 mg, qd, to be used in prophylaxis of DVT in the two pivotal studies submitted with Supplement #010, was selected according to "lessons learned" from specific studies (See Table 2-3). The rationale for this dose is summarized below.

- Enoxaparin in a dose of 30 mg, BID (total 60 mg daily) was better than placebo (saline) (PK-884).

- Enoxaparin in a dose of 30 mg, BID was comparable to low-dose heparin 15,000 IU, qd (7,500 IU BID) [PK-523], and was comparable to both low-dose heparin 5000 IU TID, and enoxaparin 40 mg, qd (PK-525).

- Enoxaparin in a dose of 10 mg was safe but not effective in comparison with 40 and 60 mg (PK-526). In the same study, enoxaparin in a dose of 40 mg, qd, was as effective as enoxaparin 30 mg, BID. Enoxaparin 30 mg had more injection site hematomas than enoxaparin 40 mg.

- The sponsor has selected enoxaparin 40 mg for further development. (See Dose Justification, page 2-1-179).

2.5 Administrative History

Prior to submission of this supplement, RPR representatives met with DGCDP on September 26, 1994 to discuss the RPR submission from August 30, 1994. At this meeting RPR proposed to submit a supplement for a long-term prophylaxis of DVT in patients undergoing hip or knee replacement. They presented data of one ongoing study PK-537 (Sweden) and one planned PK-307 (planned for the U.S. study). A background package was submitted on October 11, 1995. The actual supplement submitted April 4, 1996, included only PK-537 study and a French study ENOX 491001 that were not discussed earlier.

In the Attachment to Patent/Exclusivity Information the sponsor describes: "The published studies and reports presented in the clinical data section (publications) *are insufficient as a basis for approval of Lovenox for long-term prophylaxis* of thromboembolic disease in patients undergoing hip replacement surgery. The pivotal studies contained in this sNDA *are the only studies that specifically demonstrate the efficacy of Lovenox in the prophylaxis of late-occurring VTE* in hip replacement surgery patients who received ongoing, outpatient prophylaxis with a dose enoxaparin 40mg once daily for 21 days after the initial in-hospital venous thromboembolic disease prophylaxis with Lovenox had been completed."

2.6 Foreign Marketing History

Enoxaparin is marketed in the U.S. as Lovenox, and internationally as Clexane. It is approved for DVT prophylaxis (worldwide), treatment of DVT (Australia, Austria, Belgium,

Finland, France, Iceland, Luxembourg, Netherlands, New Zealand, Norway and Sweden), hemodialysis (Australia, Austria, Colombia, Egypt, El Salvador, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Malaysia, Mauritius, Mexico, Morocco, Norway, Philippines, Portugal, Spain, Sweden, Switzerland, Tunisia, Turkey, and UK), and abdominal surgery (Australia, Austria, Belgium, Colombia, Czech Republic, Denmark, Egypt, El Salvador, Finland, France, Germany, Greece, Iceland, Israel, Italy, Kuwait, Luxembourg, Malaysia, Mauritius, Morocco, Netherlands, New Zealand, Norway, Portugal, South Africa, Spain, Sweden, Switzerland, and Tunisia).

In the U.S. and Canada enoxaparin is approved for prevention of DVT in patients undergoing hip and knee surgery. Dose, 30 mg q12h, to begin _____ hours postoperatively and to continue until hospital discharge. Another indication available in Europe, the treatment of DVT, is not approved in the U.S. The therapeutic dose is 1mg/kg q12h. This dose is anticipated for patients on hemodialysis (not approved in the U.S.). Twenty mg daily is indicated in patients undergoing general abdominal surgery. The dosing regimen begins two hours before surgery and continues during the risk for thromboembolic events exists. It is not approved in the U.S. Patients with high risk, such as cancer, should receive 40mg daily (Supplement #008).

2.7 Proposed Directions for Use

There are two different approaches for use of enoxaparin in surgery. In Europe and elsewhere outside the U.S., enoxaparin prophylaxis begins _____ h before surgery. In the U.S. it is approved to begin _____ hours after surgery and only if hemostasis has been established. There is no data to compare these two approaches in a single study.

In this supplement the two pivotal studies are done in Europe (France and Sweden). They suggest enoxaparin prophylaxis to begin before surgery. However, in the proposed directions for use in the U.S., the sponsor repeats the current labeling ". . . enoxaparin prophylaxis of DVT leading to PE in patients undergoing hip replacement surgery to begin within 24 hours post-operation, followed by 30mg q12h or 40mg, qd, until hospital

discharge," and adds a new sentence "In addition, Lovenox Injection is indicated after hospital discharge for long term prevention of DVT following hip replacement surgery."

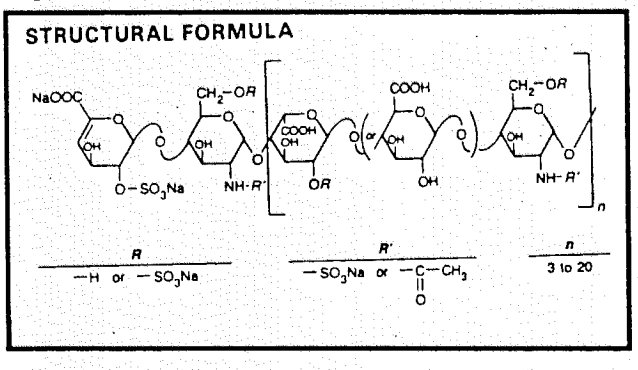
For the extension of prophylaxis into the outpatient period, the sponsor proposes only one dose, and a single dosing regimen (40 mg, qd for 21 days). The dosing should begin within 24 hours of the "successful completion of the perioperative prophylaxis." It implies that only DVT negative patients should continue with prophylaxis. DVT positive patients should undergo appropriate therapy.

3.0 DRUG CHEMISTRY

For more information see NDA#20,164, Submission, July 1991 (Vol 1) CMC Summary, and Submission December 1991 (Vol. 2.3) Drug Product.

Lovenox, Klexane, or Clexane, is a low molecular weight heparin [LMWH] originally manufactured by Pharmuka, Gennevilliers, France (Vinnazer 1985). Enoxaparin is obtained by alkaline degradation of heparin benzyl ester derived from porcine intestinal mucosa. The final substance is sodium salt with MW ~ 4,500 daltons (range

Figure 3-1



It is a sterile, LMWH for injection. In the two pivotal studies, each syringe contained 0.2 mL 200 mg/mL enoxaparin sodium, or 40mg per syringe. However, in the Labeling Annotated, the sponsor is proposing only new syringe size 0.4mL, and the same drug formulation strength 100 mg/mL. The new version of enoxaparin sodium formulation will be a single-dose syringe containing 40mg/0.4 mL.

4.0 PHARMACOLOGY

Enoxaparin is LMWH which has anticoagulation properties. In man, enoxaparin is characterized by a higher anti-Factor Xa to anti-Factor IIa activity ratio(Xa/IIa =3.35) than heparin (Xa/IIa=1.22). It is indicated in venous thromboembolism, particularly for prevention of deep venous thrombosis (DVT). It should be less effective in arterial thrombosis that are mediated by platelet aggregation related processes.

Comment: Recent reports indicate that both heparin and LMWH may have effect on a tissue factor pathway inhibitor (TFPI, Factor VIIa inhibitor, extrinsic pathway of coagulation). In a revised concept of blood coagulation (Broze, 1995)[8] factor VIIa/tissue factor is responsible for the initiation of coagulation, owing to TFPI-mediated feedback inhibition. Amplification of the procoagulant response though the actions of factor VIII, IX and XI is required for sustained hemostasis. The new revision of the role of heparin and LMWH in coagulation came from observations that LMWH bioavailability was greater than 100% as measured by chromogenic anti-Xa method (Hoppensteadt,1995)[10]. For the observed therapeutic and prophylactic actions of heparins, the authors have proposed a theory that besides ATIII mediated antiprotease actions, additional endogenous factors may be responsible. This hypothesis was tested in a defined clinical trial. Data have shown that, despite dose designation (mg/kg or units/kg) each LMWH followed a distinct TFPI release profile, and an instantaneous increase of TFPI antigen level. It was also shown that sequential compression devices affect the release of TFPI.

These new ideas of the nature of prophylactic action of LMWH have not been considered during RPR studies with enoxaparin. However, some results from these studies (e.g., relative resistance to 20mg enoxaparin of patients with cancer) may be better explained with the new than the old concept of initiation of coagulation. The relative resistance of cancer patients might be due to a procoagulant activity of cancer tissue and TFPI release. The concept including TFPI may also explain the rarity of major hemorrhagic episodes after enoxaparin and low-dose heparin prophylaxis of DVT.

Maximum anti-Factor Xa activity occurs 3-5 hours after subcutaneous injection of 20mg or 40mg. Following a 40mg dose significant anti-Factor Xa activity persists in plasma for about 12h. Tests of blood coagulation such as aPTT (standard for heparin) are not applicable for assessment of enoxaparin. Maybe a future assay of TFPI will bring more practical and accurate measurement of enoxaparin activity.

With regards to safety, a drug induced hemorrhage is of major consideration. Small painless hematomas at the injection site were detected in 9/12 (75%) healthy subjects who participated in the pharmacokinetic study (Vol. 2-1-167). Residence time and elimination were significantly longer in elder subjects. Enoxaparin prolonged aPTT below 1.5 controls.

Enoxaparin shares with low-dose heparin the adverse events: hemorrhagic episodes (more minor than major) and thrombocytopenia (rare). Other adverse events are less specific.

For more information see NDA#20-164(Suppl. No.001/02/08)

5.0 DESCRIPTION OF CLINICAL DATA SOURCE

Before submitting this Supplement, RPR has completed two studies ENOX 491001 and PK-537. Both were randomized, double-blind, two-group clinical trials, in which patients undergoing hip surgery, after completion of 14 (ENOX) or 9 (PK-537) days enoxaparin prophylaxis (40mg,sq,od), were randomized to continue with enoxaparin for additional 21 days, or to receive placebo. A total of 441 patients was randomized into enoxaparin (221 patients) and the placebo group (220 patients). The total study period was five weeks, and a follow-up period of three months was vaguely requested after study completion. In the ENOX study the second phase entered only patients who did not have DVT detected by venography. In the PK-537 study the second phase entered patients who did not have DVT demonstrated by clinical signs. At the end of both studies, venography was performed to all patients, and frequency of DVT was considered as "study failure" or the primary study outcome. These studies will be discussed in details further in this review (Table 2-3).

In addition, RPR has another treatment duration clinical trial. This is Study No. RP 54563-307 entitled "A double-blind, placebo controlled clinical trial comparing the efficacy and safety of prolonged outpatient enoxaparin and placebo therapies in the prevention of venous thromboembolic diseases in patients undergoing elective primary hip or knee replacement." This study compares enoxaparin prophylaxis of 40mg, qd, for 21 days beyond an initial _____ day-period with enoxaparin 30 mg BID. The primary endpoint will be the incidence of symptomatic or asymptomatic venous thrombotic disease. This study completed patient recruitment on January 26, 1996. Study results will be available during the third quarter of 1996 (Table 2-3).

Volume 8 contains publications referenced in the submission. They were reviewed and used when appropriate.

Other studies used for this review are summarized on Table 2-3. The list includes four supportive studies (PK-523, ENOX-884, PK-525, and PK-526), and two related studies (PK-567, and PK-568) submitted with the Supplement No. 008 of the same NDA.

Table 2-3

RPR LOVENOX DEVELOPMENT PROGRAM AND HIP SURGERY

STUDY	ENOXAPARIN	CTRL	DURATION days	DVT% all-treated patient	PE-number all-treated patient
PIVOTAL STUDIES					
ENOX 491001 single center, two phases. II phase: randomized, double-blinded, placebo controlled	phase I: 30mg q12h phase II: 40mg qd	phase II: Saline	phase 1: 14 phase 2: 21 total duration: 35	Plan:13%▶2% p:20.2% e: 6.7% d: p=0.008 failure:13.4%	0
PK-537 single center, two phases. II phase: randomized, double-blinded, placebo controlled	phase I: 30mg q12h phase II: 40mg qd	phase II: Saline	phase 1: 9±2 phase 2: 21±2 total duration: 30	Plan:30%▶13% p:34.4% e:16% d: p: failure:34.4%	2 (placebo)
SUPPORTIVE STUDIES					
PK-523 multicenter (Canada), randomize, double-blind, active control, two groups	30 MG Q12H	Calcium heparin 7,500 IU q12h	14	No FUP	E:17 H:19
ENOXAPARIN-884 multicenter (Canada), randomized, double-blind, placebo controlled	30 mg/0.3mL q12h patients:50	saline 0.3 mL q12h patients:50	14	NO FUP	E:10 P:46 E:1 P:2
PK-525 Multicenter (US), open-label, randomized, 2 doses of enoxaparin vs heparin	30 mg BID patients 195 40 mg QD patients 203	heparin 5,000 IU TID patients 209	7	NO FUP	30:5 40:15 hep:12 0 0
PK-526 multicenter (US), dose-ranging	10 mg qd pts: 40 mg qd pts: 199	30 mg q12h pts: 208	7	NO FUP	10:25 40:14 30:11 0 0
RELATED STUDIES					
PK-567 Multicenter, randomized, double-blind, active-control, two groups major abdominal surgery (cancer)	40 mg, qd pts:555	heparin, 5,000 IU TID pts: 560	10±2	3 months	10.1 FUP 1.1 11.3 FUP 1.3 0 death 2tf (4) FUP 2 death 3 tf (22) 2 death 0 tf (7) FUP 1 death 4 tf (27)

PK-568 Multicenter, randomized, double-blind, active-control, two groups colorectal surgery (includes 485 with cancer)	40 mg, qd pts: 673	heparin 5,000 IU TID pts: 674	10±2	6 weeks	7.1 FUP 1 pt (0.14)	6.7 FUP 2 pt (0.3)	1 death 1 FUP 0 death 3 tf (10)	1 death 1 FUP 0 death 0 tf (2)
STUDIES IN PROGRESS								
RP 54563 randomized, double-blind, placebo controlled	phase I: 40mg,qd, and 30mg,q12h phase II: 40mg,qd		phase I:7-10 phase II: 21					

Pivotal studies are submitted with supplement S010; Supprotive studies have been submitted with the original NDA submission for hip surgery; Related studies are submitted with Suplement S008; and Study in Progress is mentioned in Supplement S010.