11.3 APPENDIX 3: STUDY 529

1. LIST OF PARTICIPANTS

LIST OF PARTICIPATING COUNTRIES, CENTERS, INVESTIGATORS AND NUMBER OF PATIENTS ASSIGNED.

Country	Center	Investigator	Number of Patients			
			Heparin	Enoxaparin		Combined
				qd	bid	
Australia	Royal Melbourne Hospital Department of Hematology Parkville VIC	Dr. Andrew Grigg	4	8	4	161
	Royal Brisbane Hospital Brisbane QLD	Dr. John Rowell	5	5	4	14
Austria	Wilhelminenspital Der Stadt Vienna	Dr Hugo Partsch	5	6	7	18
Belgium	A Z Stuivenberg 2060 Antwerpen	Dr. Hendrik Discart	0	1	0	1
	AZ Sint-Jan 8000 Brugge	Dr Marco Lanckneus	0	0	1	1
Denmark	University of Copenhagen Coagulation Laboratory 2900 Hellerup	Dr. Jorn Dalsgaad	?			
		Dr. Nielsen	5	2	3	10
	Bisperbjerg Hospital 2400 Copenhagen	Dr. Andrea Landorph	6(1)	5	4(1)	15(2)
France	Hopital Bellevue Service de Medicine Interne 42055 Saint Etienne	Dr. Herve Decousus	2	2	0	4
	Clinic Saint Vincent 25022 Besancon	Dr. Rene Faivre	?			
	Hopital Morvan Service Sebileau 29285 Brest	Dr. Dominique Mottier	3(1)	2	4	9(1)
	Hopital Antoine Beclere 92141 Clamart	Dr. Gerald Simonneau	14	13 (1)	14	41(1)
	Hopital Laenec 75007 Paris	Dr. Herve Sors	6(2)	7	6	19(2)
Hungary	Hospital of the County Borsod 3501 Miskolc	Dr. Istvan Vaci	5	4	6	15
Ireland	Beamont Hospital Department of Haematology Dublin 9	Dr. John Rory O.Donnell	2(1)	1	0	3(1)
Israel	Tel-Aviv Sourasky Medical center Department of Hematology 64239 Tel-Aviv	Dr. Amiram Eldor	6	6	7	19

	Chaim Sheba Medical Center National hemophilia Center 52621 Tel-Hashomer	Dr. David Varon	4	6	5	15
Italy	Universita Cattolica del Sacro Cuore Istituto di Semeiotica Medica-Division di Ematologia. 00168 Roma RM	Dr. Bruno Bizzi	0	0	1	1
	Universita di Milano - Ospedale Maggiore. Centro Emofilia e Trombosi 20122 Milano	Dr. Pier Mannucci	6	4	4	14
Netherlands	Canisus Wilhelmina Ziekenhuis 6532 Nijmegen	Dr. Sven Jannsen	3	4	5	12-
	Academic Hospital Nijmengen 6525 Nijmegen	Dr. Irena Smale-Novakova	5	3	3	11
Norway	Aker Hospital Medical department 0514 Oslo	Dr. Ulrich Abildgaard	15(1)	13	14 (1)	42(2)
	Ulleval Hospital Medical Department 0407 Oslo	Dr. Per Morten Sandset	15	14	16 (1)	45(1)
Poland	Academy of Medicine Department of Hematology 61-833 Poznan	Dr. Krystina Zawilska	3	3	2	8
Spain	Hospital de Cruces Haematology Department Bilbao	Dr. Juana Chacon	0	0	1	1
	Hospital Germans Trias i Pujol Barcelona	Dr. Manuel Monreal	6	8	7	21
	Hospital Ramon Y Cajal Madrid	Dr. Jose Navaro	?			
	Hospital Valle de Hebron Barcelona	Dr. Maria Villar	5(1)	3	5	13(1)
Sweden	Helsingborg Hospital Department of Medicine S-251 87 Helsingborg	Dr. Stig Bornhov	7	6(1)	7	20(1)
	Central Hospital Department of Medicine S-351 85 Vaxjo	Dr. Hans Larsson	7	9(1)	7	23(1)
	University hospital Department of Medicine S-221 85 Lund	Dr. Carl-Gustav Olsson	20(2)	22 (1)	22 (1)	64(4)
United Kingdom	Addenbrooke's Hospital Haematology department Cambridge	Dr. Trevor Baglin	4	2	4	10
	St Georges Hospital Haematology Department London	Dr. David Bevan	0	0	1	1

	Freemam Hospital Haematology department Newcastle Upon Tyne	Dr. Patrick Kesteven	15	14	13	42
	University Hospital of Wales Department of radiology Cardiff	Dr. Andrew Mayne	?			
		Wood	4	6	6	16
U.S.A.	Overlook Hospital Medical Arts center Summit, NJ	Dr. Yale Arkel	?			
	Sarasota Memorial Hospital Clinical Research Center Sarasota, FL	Dr. Lameel Audeh	0	4	4	8
	Duke University Medical Center Durham, NC	Dr. Scott Berkowitz	1	0	0	1
	University of Texas Medical branch Gavaston, TX	Dr. David Bessman	0	1	1	2
	University of Kansas Medical Center Kansas City, KS	Dr. David Bodensteiner	0	1	1	2
	St Francis Hospital, Cancer Center Hem/Onc Section Hartford, CT	Dr. Robert Bona	2	2	0	4
U.S.A.	Seattle VA Medical center Div. Hematology/Oncology Seattle, WA	Dr. Thomas Chauncey	?			
	Hahneman University Medical center Pulmonary Critical Care Philadelphia, PA	Dr. Bruce Davidson	3	4(1)	1	8(1)
	Scripps Clinic & Research Foundation Chest and Critical Care Medicine La Jolla, CA	Dr. Darlene Elias	10	9(1)	11 (1)	30(2)
	Highland Clinic Sheverport, LA	Dr. Roan Flenniken	?			
	New England Medical Center Boston, MA	Dr. Bruce Furie	0	0	1	1
	Loyola University Medical Center Maywood, Il	Dr. John Godwin	1	0	2	3
	Individual investigator Columbia, SC	Dr. M. Francisco Gonzales	2	1(1)	2	5(1)
	Baylor College of Medicne Houston, TX	Dr. Arnold Gorin	?			
	Individual investigator Portland, OR	Dr. Stephen Jones	2	2	3	7
	Individual investigator Washington, DC	Dr. Craig Kessler	?			

	University of Colorado Health Sci.Ctr. Department opf Vascular Surgery Denver, CO	Dr. William Krupski	8	9	10 (1)	27(1)
	VA Lakeside Hospital Chocago, Il	Dr. Hau Kwaan	7(1)	8(1)	7	22(2)
	Individual investigator San Antonio, TX	Dr. Roger Lyons	4	7(1)	5	16(1)
	University of Rochester Med.Ctr. Hematology Unit Rochester, NY	Dr. Victor Marder	1	1	1	3
	Rush Presbiterian St. Lukes Med. Ctr. Chicago, Il	Dr. Rajalaxami Mckenna	2	2	3	7
	Thomas Jefferson University Philadelphia, PA	Dr. Geno Merli	3	3	2	8
	Upstate Clinical Research Greer, SC	Dr. John Milas	2	2	4	8
	Medical College of Georgia, Department of Surgery Augusta, GA	Dr. Robert Nesbit	1	0	5	6
	St. louis University Health Ctr. Division of Pulmonary and Occupational Medicine St. Louis, MO	Dr. Jill Ohar	5(1)	2(1)	3(1)	10(3)
	Individual investigator Morristown,NJ	Dr. Mark Oliver	3	2	6	11
	Individual investigator Bridgeville, Il	Dr. Phillip Painter	6	5(1)	5(1)	16(2)
	Lousiana State University Med. Ctr. Pulmonary and Critical Care Medicine Shreveport, LA	Dr. D. Keith Payne	?			
	UMDNJ-R.W.Johnson Medical Scholl New Brunswick, NJ	Dr. Claire Phillip	?			
	Hennepin County Medical Center Minneapolis, MN	Dr. Tanja Repka	2	4(1)	2	8(1)
	University of Utah Medical Center, Hematology-Oncology Division Salt Lake City, UT	Dr. George Rodgers	9	10	9	28
	Medical University of South Carolina Charelston, SC	Dr. Gerald Silvestri	?			
	Dan Rudy Cancer Center Nashville, TN	Dr. John Strupp	1	2(1)	3	6(1)
	Texas A&M University College of Medicine, Scott and White Clinic Temple, TX	Dr. Arthur A. Trowbridge	13	13	11	37
	VAH-James A Haley Pulmonary and Critical Care Tampa, FL	Dr. Frank Walsh	3	3	3	9

	St. Elizabeth Medical Ctr of Boston Division of Clinical Research Boston, MA	Dr. Robert Weinstein	0	2	2	4
	University of Oklahoma Health Sci Ctr. Oklahoma City, OK	Dr. Thomas L. Whitsett	1	1	2	4
	Loma Linda University Med Ctr Loma Linda, CA	Dr. Gregory Wise	5(1)	3	4	12(1)
	Washington University Medical School St. Louis, MO	Dr. Rodger D. Yusen	7	9	10 (1)	26(1)

2. STUDY 529: NARRATIVES FOR PATIENTS WHO DIED

1. A patient (pt#04020) with cecal adenocarcinoma and hemicolectomy received 4-day heparin treatment for iliac vein stenosis due to external compression. Venography was inadequate. On day 5 a CAT confirmed progression of rectal cancer. She died on day 51 due to tumor progression (MS). No autopsy was performed.

2. A patient (pt#06058) with diabetes mellitus and ulcerated legs due to peripheral arterial insufficiency, received 5-day heparin treatment for proximal DVT (external iliac vein) and "intermediate" probability for PE. On day 37 he was admitted because of gangrene of the right foot (infected ulcer). On day 71 he developed rectal hemorrhage and died the same day. No autopsy was performed.

3. A patient (pt#06159) with breast cancer with cerebral and pulmonary metastases received 7-day heparin treatment for proximal DVT and high probability asymptomatic PE. She died on day 29 due to tumor progression. No information on autopsy.

4. A patient (pt#20013) with previous DVT and stage IV adenocarcinoma of the uterus received 7-day heparin for bilateral proximal thrombosis and intermediate probability for PE. She died at home on day 50 due to cancer progression. No autopsy was performed.

5. A patient (pt#20056) with diabetes mellitus, congestive heart failure and chronic obstructive pulmonary disease received 3-day heparin treatment for a symptomatic proximal DVT and intermediate probability PE. On day 3 he experienced PE, discontinued study medication and received an inferior vena cava filter. Continued with warfarin. On day 54 he developed pneumonia, major upper gastrointestinal bleeding and perforated viscous. He died the next day. No autopsy was performed. The hemorrhage in this case is probably due to **uncontrolled warfarin** use.

6. A patient (pt#20559) with varicose veins, obstructive pulmonary disease and congestive heart failure received 5-day heparin treatment for popliteal DVT and high probability PE. She remained in hospital for pulmonary recovery. On day 11 she developed DIC and drop of Hgb for 2.9 g/dL. Ventilation support was ceased and she died the next day. This death was attributed to pneumonia, DIC and PE.

7. A patient (pt#20560) with diabetes mellitus, previous cerebrovascular accident and congestive heart failure received 6-day heparin treatment for proximal DVT (including iliac) and high probability PE. She died on day 86 due to another cerebrovascular accident and PE.

8. A patient (pt#20853) with metastatic prostate cancer on chemotherapy and history of asthma, received 3-day heparin treatment due to chronic proximal thrombosis. On day 80 he died due to progressive pulmonary disease. No autopsy was performed.

9. A patient (pt#20957) with lymphoma on chemotherapy received 3-day heparin treatment for proximal DVT and high probability PE. Venography was inadequate and the patient was discontinued from heparin. On day 16 he developed GO hemorrhage and progressive lymph nodes. Lymphoma progression was confirmed by cervical node biopsy. He died on day 31 due to respiratory failure from tracheal obstruction by recurrent non-Hodgkin lymphoma.

10. A patient (pt#01004) with bronchogenic adenocarcinoma received 9-day enoxaparin (E1) treatment for bilateral proximal DVT and high probability PE. On day 75 he experienced symptomatic extension of thrombosis to external iliac veins, and he was treated with enoxaparin and elevated warfarin. He died on day 87 due to tumor progression. Autopsy was not performed.

11. A patient (pt#01044) chronic cardiac failure and chronic pulmonary disease, with clinical signs for PE (17 days duration) received 2-day enoxaparin treatment for proximal DVT and high probability PE. The treatment was discontinued due to worsening: severe bradicardia ending with cardiac arrest. Autopsy was performed and only pulmonary edema was confirmed. PE was considered to be associated cause of death.

12. A patient (pt#04042) with alcoholic liver disease and sigmoid colectomy fro adenomas 5 years ago, esophageal varices with gastrointestinal hemorrhage, received 2-day enoxaparin (E1) treatment for bilateral proximal thrombosis (symptomatic for 3 weeks) and intermediate probability for PE. Study drug was discontinued because of high creatinine (deviation of protocol). Warfarin continued. On day 32 he experienced severe Go hemorrhage. Endoscopy revealed esophageal varices and oral anticoagulation was stopped permanently. On day 35 he experienced a cardiopulmonary arrest and died. Autopsy was performed and revealed an upper gastrointestinal hemorrhage from esophageal varices together with liver cirrhosis and pulmonary edema.

13. A patient (pt#04099) with old gastrectomy due to perforated ulcer, atrial fibrillation after MI and endogenous depression received 6-day enoxaparin (E1) treatment for bilateral proximal DVT and intermediate probability for PE. Therapy was interrupted because of INR of 4.6 and unchanged signs of DVT. On day 30 subcutaneous heparin was substituted for warfarin because of high INR. On day 47 he died because of left ventricular failure. Autopsy confirmed severe coronary atheroma, and recurrent MI.

14. A patient (pt#06022) with GI carcinoma with hepatic metastases received enoxaparin (E1) treatment for symptomatic DVT and very low probability of PE. On day 15 she developed signs of superficial thrombophlebitis in the opposite leg. Venography showed extension of the primary DVT. Enoxaparin was reinstituted from day 16 to 20, and replaced with dalteparin. On day 26 she experienced a major gastrointestinal hemorrhage (3 units of blood transfusion). She died on day 62 due to tumor progression. No autopsy was performed.

15. A patient (pt#20016) with diabetes mellitus and hepatitis C, who had hip replacement surgery five weeks prior to admission received enoxaparin (E1) for an inconclusive DVT (confirmed at autopsy). She died on day 4 from cardiac arrest. A massive retroperitoneal hemorrhage was found to be the cause of this death.

16. A patient (pt#20052) with mediastinal adenocarcinoma and squamous cell lung carcinoma with recent radiotherapy, was admitted because of symptomatic proximal DVT (confirmed on venography) and low probability for PE. He received 8-day enoxaparin (E1). On day 23 he was re-hospitalized for hemiparesis due to advancing carcinoma. He died on day 78 from tumor progression.

17. A patient (pt#20063) with colon carcinoma on chemotherapy, received 4-day enoxaparin treatment for acute DVT and low probability for PE. On day 7 therapy was discontinued because of high INR of 8.3. Warfarin was reinstated on day 19, but on day 26 she had INR 18.0 and a major gastrointestinal hemorrhage (4 units packed red cells). She died on day 29. No autopsy was performed.

18. A patient (pt#20148) with mastectomy 1988 for breast cancer, and two months symptomatic DVT received enoxaparin (E1) for proximal DVT and high probability PE. INR was difficult to stabilize due to hepatic metastases. On day 22 she was re-hospitalized for respiratory distress, and died on day 23 due to tumor progression. No autopsy was performed.

19. A patient (pt#20855) with metastatic lung cancer received 7-day enoxaparin (E1) treatment for proximal DVT. On day 89 he died due to tumor progression. No autopsy was performed.

20. A patient (pt#21023) with CLL and recent chemotherapy/radiation received 7-day enoxaparin (E1) treatment for acute DVT with high probability PE. End of therapy confirmed no change of DVT and worsening of PE. On day 34 she developed symptoms of vena cava thrombosis. She died on day 70 due to leukemia progression. No autopsy was performed.

21. A patient (pt#01056) with previous DVT, prostatic adenoma, ischemic heart disease (hypertension) and epistaxis due to heparin prior to randomization, received 6-day enoxaparin for acute DVT with low probability PE. He was found dead in his bed at home on day 85. This sudden death has not been subjected to autopsy.

22. A patient (pt#02040) with chronic obstructive pulmonary disease received enoxaparin (E2) for acute symptomatic bilateral DVT (left leg on venography) with intermediate probability for PE. On day 10 he was re-hospitalized due to recurrence of DVT. Another recurrence appear on day 23 (thrombus in common iliac veins). On day 64 a new deep vein thrombosis was found in the opposite leg. On day 92 he experienced severe chest pain (old PE). On day 105 a neck biopsy confirmed adenocarcinoma of unknown origin (lymph node metastasis). He died the same day. Autopsy was not performed.

23. A patient (pt#04025) with metastatic uterine carcinoma received 4-day enoxaparin (E2) for acute bilateral DVT with high probability for PE. Therapy was ceased because of the improvement. On day 12 she died due to respiratory failure. Autopsy was not performed.

24. A patient (pt#04092) with chronic obstructive pulmonary disease received 7-day enoxaparin (E2) treatment for acute proximal DVT. Ventilation perfusion lung scan showed defects in the lung bases due to bronchiectasis. She had pulmonary distress and infection on day 9-45. She collapsed and died at home on day 56. Autopsy revealed pneumonia as cause of death.

25. A patient (pt#06016) with diabetes mellitus, nephrectomy and pancreatic cancer (diagnosed during study) received enoxaparin (E2) for acute bilateral proximal DVT with intermediate probability for PE. He recovered. On day 39 metastatic pancreatic cancer was discovered. He died 6 days later. Autopsy was not mentioned.

26. A patient (pt#20123) with progressive confusion (6 weeks) dysphasia, bilateral extremity weakness, weight loss of 40 pounds during the hospitalization developed bilateral lower extremity pain, swelling and discoloration. Pre-study heparin was given based on ultrasonography. Venography confirmed proximal DVT in right leg. He was randomized on enoxaparin (E2), but the third day the attending physician requested discontinuation because of incoming surgery. He died on day 13 due to respiratory failure (aspiration of gastric material - senile dementia). Probability of PE was considered by the adjudication committee.

27. A patient (pt#20223) with metastatic non small cell lung cancer and intracranial metastases on chemotherapy received 6-day treatment with enoxaparin (E2) for acute proximal DVT and high probability for PE. On day 11 his respiration was compromised and he died the next day. Autopsy was not performed.

28. A patient (pt#20495) with cancer diagnosed during this hospitalization, developed symptomatic DVT and was randomized to enoxaparin (E2). Venography confirmed proximal DVT and very low probability for PE was found on a lung scan. On day 29 he developed new symptoms of DVT. Inferior vena filter was placed on day 32. He died on day 84 due to liver insufficiency (adenocarcinoma progression).

APPENDIX 4

APPENDIX 4:

SAFETY UPDATE (15-Day Alert Report)
(Submission received 07/10/97).

RPR reports increased frequency of deaths (from outside the US) in patients on Lovenox injection. The frequency was recognized on June 11, 1997. The report interval is from January 1, 1996 to December 31, 1996. Data were compared with a similar interval from January 1, 1995 to December 31, 1995.

Lovenox use & Deaths	Period 01/01/95-12/31/95	Period 01/01/96-12/31/96
Drug Use Estimates	59,306,000 units	66,275,000 units
Number of events	3	19
Event Rates	$5.06*10^{-8}$ events/unit	$2.87*10^{-7}$ events/unit

In 1996, a total of 19 deaths compared with 3 in 1995, were reported from sources outside the US. The RPR beleives that the increased frequency is an artifact due to the change of reporting policy by the French Health Authority.

Listing of the cases included in this report is provided in Appendix 1. Among the 19 cited death, six events have been related to "greater than recommended dose of Lovenox." Two others died of cerebral hemorrhage, but information about enoxaparin dose is not available (Table). Other deaths were less clearly related to the use of enoxaparin. For details see the Appendix 1 of the submission.

Case number (GUARD)	Source	Sex	Age	Prior report	Main adverse event	Comment Lovenox dose
FR02-02149	Spontaneous	F	95	Yes	Anemia, hematoma, multivisceral failure	60 mg bid (120 mg daily)
FR02-02045	FHA*	F	93	Yes	Hematoma/ Cerebral hemorrhage	160 mg qd
FR02-06738	FHA	F	85	Yes	Cerebral hemorrhage, Hypertension	90 mg qd
FR02-06738	FHA	M	70	Yes	Cerebral hemorrhage Hypertension	200 mg qd
FR02-06739	FHA	M	72	Yes	Cerebral hemorrhage	200 mg qd
FR02-06747	FHA	F	81	Yes	Cerebrovascular accident	120 mg qd
XA01-00157	HA**	F	67	Yes	Cerebral hemorrhage	May have continued Lovenox
FR02-01168	Spontaneous	?	?	Yes	Meningeal hemorrhage, thrombocytopenia	Insufficient information

Age, cerebral hemorrhage and enoxaparin use in therapeutical dose, are three common denominators of the cited fatal outcomes. From information that is available it is not clear whether enoxaparin was overdosed, or abused. Another possibility, that has not been elaborated by the sponsor, is that a certain group of elderly patients do not tolerate therapeutical doses of enoxaparin as the others. To explore in this direction, the Agency has requested the sponsor to provide a summary information on adverse event in elderly (>65) using enoxaparin in therapeutical doses.

Oliver

DIVISION FOR GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW
October 8, 1997

NDA#20-164

OCT - 8 1997

Submission: **15-Day Alert Report (NDA 20-164) Lovenox (enoxaparin sodium) injection**

Subject: Increased Frequency of Deaths of Patients on Enoxaparin Therapy Outside the U.S. in 1996.

Received: 09/22/97
Completed: 10/07/97

Action Proposed: NOTED;
INCORPORATED INTO S-015 SAFETY REVIEW;
SPONSOR REQUESTED TO PROVIDE MORE INFORMATION.

Medical Reviewer: Nenad Markovic, M.D.
Review File: ALERT96.R53

Background

This report was forwarded to HFD-180 from the Division of Epidemiology and Surveillance. It was accompanied by the following note: "The company attributes this increased frequency to an "artifact" of reporting. The increased reporting represents greater ascertainment of events. It should not be considered as "artifact."(DK Wysowski).

The submission contains a Cover Letter (Rhone Poulenc Rorer, from July 2, 1997), Appendix 1 (Listing of 19 events), and Appendix 2 (FDA form 3500A's for events in the reporting interval).

REVIEW SUMMARY

This submission is a 15-Day Alert Report by the manufacturer. RPR reports increased frequency of deaths (from outside the US) in patients on Lovenox injection. The frequency was recognized on June 11, 1997. The report interval is from January 1, 1996 to December 31, 1996. Data were compared with a similar interval from January 1, 1995 to December 31, 1995.

Table 1
COMPARISON OF DEATH EVENTS AND DRUG USE BETWEEN EVENT AND CONTROL PERIODS

Lovenox use & Deaths	Control Period 01/01/95-12/31/95	Event Period 01/01/96-12/31/96
Drug Use Estimates	59,306,000 units	66,275,000 units
Number of events	3	19
Event Rates	$5.06*10^{-8}$ events/unit	$2.87*10^{-7}$ events/unit

In 1996, a total of 19 deaths compared with 3 in 1995, were reported from sources outside the US. The RPR believes that the increased frequency is an artifact due to the change of reporting policy by the French Health Authority.

Listing of the cases included in this report is provided in Appendix 1. Among the 19 cited deaths, six events have been attributed to "greater than recommended dose of Lovenox." Two others died of cerebral hemorrhage, but information about enoxaparin dose is not available (Table 2). Other deaths were less clearly related to cerebral hemorrhage or the use of enoxaparin. For details see the Appendix 1 of the submission.

Table 2
DEATH BY CEREBRAL HEMORRHAGE

Case number (GUARD)	Source	Sex	Age	Prior report	Main adverse event	Comment Lovenox dose
FR02-02149	Spontaneous	F	95	Yes	Anemia, hematoma, multivisceral failure	60 mg bid (120 mg daily)
FR02-02045	FHA*	F	93	Yes	Hematoma/ Cerebral hemorrhage	160 mg qd
FR02-06738	FHA	F	85	Yes	Cerebral hemorrhage, Hypertension	90 mg qd
FR02-06738	FHA	M	70	Yes	Cerebral hemorrhage Hypertension	200 mg qd
FR02-06739	FHA	M	72	Yes	Cerebral hemorrhage	200 mg qd
FR02-06747	FHA	F	81	Yes	Cerebrovascular accident	120 mg qd
XA01-00157	HA**	F	67	Yes	Cerebral hemorrhage	May have continued Lovenox
FR02-01168	Spontaneous	?	?	Yes	Meningeal hemorrhage, thrombocytopenia	Insufficient information

The possibility that the increased number of deaths reported in 1996 is the result of the changes in reporting requirements cannot be excluded.

It is of note that age and enoxaparin dose are common denominators of death due to cerebral hemorrhage. From the available information, it is not clear whether enoxaparin was absolutely or relatively overdosed, i.e., whether a certain group of elderly patients do not tolerate therapeutical doses of enoxaparin. To explore this possibility, the Agency has requested the sponsor on October 7, 1997, to provide a summary information of adverse events in a subset of elderly (>65) patients using enoxaparin in therapeutical doses of 150 mg daily and above (i.e., 1 mg/kg/bid for body weight of 75 kg).

This report will be incorporated in the Supplement 015 safety review.

/S/ [redacted]
Nenad Markovic, M.D.

cc:
NDA 20-164
HFD-180
HFD-180/LTalarico
HFD-180/NMarkovic

[redacted] BEST POSSIBLE

/S/ [redacted] 10-8-97