

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020287/S008

Trade Name: FRAGMIN

Generic Name: DALTEPARIN SODIUM INJECTION

Sponsor: PHARMACIA and UPJOHN

Approval Date: 03/30/99

**INDICATION(s): FOR PROPHYLAXIS OF DEEP VEIN
THROMBOSIS (dvt), WHICH MAY LEAD TO
PULMONARY EMBOLISM, IN PATIENTS
UNDERGOING HIP REPLACEMENT SURGERY**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 020287/S008

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020287/S008

APPROVAL LETTER



NDA 20-287/S-008

Food and Drug Administration
Rockville MD 20857

Pharmacia & Upjohn
Attention: James H. Chambers
7000 Portage Road
Kalamazoo, Michigan 49001-0199

MAR 30 1999

Dear Mr. Chambers:

Please refer to your supplemental new drug application dated April 16, 1997, received April 17, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin® (dalteparin sodium injection).

We acknowledge receipt of your submissions dated May 9, June 11 and 12, August 13, November 21, 1997, and February 25, March 19, September 8, and November 6, 1998. Your submission of November 6, 1998 constituted a complete response to our April 15, 1998 action letter.

This supplemental new drug application provides for the use of Fragmin® for prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism, in patients undergoing hip replacement surgery.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-287/S-008." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Karen Oliver, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

/s/

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Package Insert Text

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020287/S008

PRINTED LABELING

FRAGMIN®
dalteparin sodium injection

For Subcutaneous Use Only

SPINAL/EPIDURAL HEMATOMAS

When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (also see WARNINGS, Hemorrhage and PRECAUTIONS, Drug Interactions).

DESCRIPTION

FRAGMIN Injection (dalteparin sodium injection) is a sterile, low molecular weight heparin. It is available in single-dose, prefilled syringes and a multiple-dose vial. With reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard, each syringe contains 2500 (16 mg dalteparin sodium) or 5000 (32 mg dalteparin sodium) anti-Factor Xa international units (IU) in 0.2 mL. Each 9.5 mL vial contains 10,000 (64 mg dalteparin sodium) anti-Factor Xa IU per 1 mL, for a total of 95,000 anti-Factor Xa IU per vial.

Each prefilled syringe also contains Water for Injection and sodium chloride, when required, to maintain physiologic ionic strength. The prefilled syringes are preservative free. Each multiple-dose vial also contains Water for Injection and 14 mg of benzyl alcohol per mL as a preservative. The pH of both formulations is 5.0 to 7.5.

Dalteparin sodium is produced through controlled nitrous acid depolymerization of sodium heparin from porcine intestinal mucosa followed by a chromatographic purification process. It is composed of strongly acidic sulphated polysaccharide chains (oligosaccharide, containing 2,5-anhydro-D-mannitol residues as end groups) with an average molecular weight of 5000 and about 90% of the material within the range 2000-9000. The molecular weight distribution is:

The volume of distribution for dalteparin anti-Factor Xa activity was 40 to 60mL/ kg. The mean plasma clearances of dalteparin anti-Factor Xa activity in normal volunteers following single intravenous bolus doses of 30 and 120 anti-Factor Xa IU/kg were 24.6 ± 5.4 and 15.6 ± 2.4 mL/hr/kg, respectively. The corresponding mean disposition half-lives are 1.47 ± 0.3 and 2.5 ± 0.3 hr.

Following intravenous doses of 40 and 60 IU/kg, mean terminal half-lives were 2.1 ± 0.3 and 2.3 ± 0.4 hrs, respectively. Longer apparent terminal half-lives (3 to 5 hrs) are observed following s.c. dosing, possibly due to delayed absorption. In patients with chronic renal insufficiency requiring hemodialysis, the mean terminal half-life of anti-Factor Xa activity following a single intravenous dose of 5000 IU FRAGMIN was 5.7 ± 2.0 hrs, i.e. considerably longer than values observed in healthy volunteers, therefore, greater accumulation can be expected in these patients.

CLINICAL TRIALS

Abdominal Surgery:

FRAGMIN Injection, administered once daily beginning prior to surgery and continuing for 5 to 10 days after surgery, has been shown to prevent deep vein thrombosis (DVT) in patients at risk for thromboembolic complications (see INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION). Data from two double-blind randomized controlled clinical trials performed in patients undergoing major abdominal surgery, summarized in the following tables, show that FRAGMIN 2500 IU was superior to placebo and similar to heparin in preventing DVT (see Tables 1 and 2).

Table 1
Efficacy of FRAGMIN in Abdominal Surgery

Indication	Dosing Regimen	
	<u>FRAGMIN</u> 2500 IU qd s.c.	<u>Placebo</u> qd s.c.
All Treated Abdominal Surgery Patients	102	102
Treatment Failures in Evaluable Patients		
Total Thromboembolic Events	4/91 (4.4%) ¹	16/91 (17.6%)
Proximal DVT	0	5/91 (5.5%)
Distal DVT	4/91 (4.4%)	11/91 (12.1%)
PE	0	2/91 (2.2%) ²

1 p-value versus placebo = 0.008

2 Both patients also had DVT, 1 proximal and 1 distal

Table 2
Efficacy of FRAGMIN in Abdominal Surgery

Indication	Dosing Regimen	
	<u>FRAGMIN</u> 2500 IU qd s.c.	<u>Heparin</u> 5000 U bid s.c.
All Treated Abdominal Surgery Patients	195	196
Treatment Failures in Evaluable Patients		
Total Thromboembolic Events	7/178 (3.9%) ¹	7/174 (4.0%)
Proximal DVT	3/178 (1.7%)	4/174 (2.3%)
Distal DVT	3/178 (1.7%)	3/174 (1.7%)
PE	1/178 (0.6%)	0

¹ p-value versus heparin = 0.74

Data from a double-blind randomized controlled trial show that FRAGMIN 5000 IU once daily is more effective than FRAGMIN 2500 IU once daily in preventing DVT in patients undergoing abdominal surgery with malignancy (see Table 3).

Table 3
Efficacy of FRAGMIN in Abdominal Surgery Patients with Malignancy

Indication	Dosing Regimen	
	<u>FRAGMIN</u> 2500 IU qd s.c.	<u>FRAGMIN</u> 5000 IU qd s.c.
All Treated Abdominal Surgery Patients	696	679
Treatment Failures in Evaluable Patients		
Total Thromboembolic Events	99/656 (15.1%) ¹	60/645 (9.3%)
Proximal DVT	18/657 (2.7%)	14/646 (2.2%)
Distal DVT	80/657 (12.2%)	41/646 (6.3%)
PE		
Fatal	1/674 (0.1%)	1/669 (0.1%)
Non-fatal	2	4

¹ p-value = 0.001

Hip Replacement Surgery:

In an open-label randomized study, FRAGMIN 5000 IU administered once daily subcutaneously (s.c.) was compared to warfarin sodium, administered orally, in patients undergoing hip replacement surgery. Treatment with FRAGMIN was initiated with a 2500 IU dose s.c. within 2 hours before surgery, followed by a 2500 IU s.c. dose the evening of the day of surgery. Then, a dosing regimen of FRAGMIN 5000 IU s.c. once daily was initiated on the first postoperative day. The first dose of warfarin sodium was given the evening before surgery, then continued daily at a dose adjusted for INR 2.0-3.0. Treatment in both groups was then continued for 5 to 9 days postoperatively. The incidence of total DVT, as determined by evaluable venography, was significantly lower for the group treated with FRAGMIN compared to patients treated with warfarin sodium (28/192 vs 49/190; p=0.006) [see Table 4].

Table 4
Efficacy of FRAGMIN in Hip Replacement Surgery

Indication	Dosing Regimen	
	<u>FRAGMIN</u> 5000 IU qd ¹ s.c.	<u>Warfarin Sodium</u> qd ² oral
All Treated Hip Replacement Surgery Patients	271	279
Treatment Failures in Evaluable Patients		
DVT, Total	28/192 (14.6%) ³	49/190 (25.8%)
Proximal DVT	10/192 (5.2%) ⁴	16/190 (8.4%)
PE	2/271 (0.7%)	2/279 (0.7%)

- 1 The daily dose on the day of surgery was divided: 2500 IU was given two hours before surgery and again in the evening of the day of surgery.
- 2 Warfarin dosage was adjusted to maintain a prothrombin time index of 1.4 to 1.5, corresponding to an International Normalized Ratio (INR) of approximately 2.5.
- 3 p-value = 0.006
- 4 p-value = 0.185

In a second study (single-center, double-blind) of 136 patients undergoing hip replacement surgery, FRAGMIN 5000 IU once daily s.c. starting the evening before surgery, was compared to heparin 5000 U s.c. tid, starting the morning of surgery. Treatment in both groups was continued for up to 9 days postoperatively. In the intent-to-treat analysis, the incidence of proximal DVT was significantly lower for patients treated with FRAGMIN compared to patients treated with heparin (6/67 vs 18/69; p=0.010). Further, the incidence of pulmonary embolism detected by lung scan was also significantly lower in the group treated with FRAGMIN (9/67 vs 19/69; p=0.032).

INDICATIONS AND USAGE

FRAGMIN Injection is indicated for prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism:

- In patients undergoing hip replacement surgery;
- In patients undergoing abdominal surgery who are at risk for thromboembolic complications. Patients at risk include those who are over 40 years of age, obese, undergoing surgery under general anesthesia lasting longer than 30 minutes, or who have additional risk factors such as malignancy, or a history of deep venous thrombosis or pulmonary embolism.

CONTRAINDICATIONS

FRAGMIN Injection is contraindicated in patients with known hypersensitivity to the drug, active major bleeding, or thrombocytopenia associated with positive *in vitro* tests for anti-platelet antibody in the presence of FRAGMIN.

Patients with known hypersensitivity to heparin or pork products should not be treated with FRAGMIN.

WARNINGS

FRAGMIN Injection is not intended for intramuscular administration.

FRAGMIN cannot be used interchangeably (unit for unit) with unfractionated heparin or other low molecular weight heparins.

FRAGMIN should be used with extreme caution in patients with history of heparin-induced thrombocytopenia.

Hemorrhage:

FRAGMIN, like other anticoagulants, should be used with extreme caution in patients who have an increased risk of hemorrhage, such as those with severe uncontrolled hypertension, bacterial endocarditis, congenital or acquired bleeding disorders, active ulceration and angiodysplastic gastrointestinal disease, hemorrhagic stroke or shortly after brain, spinal or ophthalmological surgery.

Spinal or epidural hematomas can occur with the associated use of low molecular weight heparins or heparinoids and neuraxial (spinal/epidural) anesthesia or spinal puncture, which can result in long-term or permanent paralysis. The risk of these events is higher with the use of indwelling epidural catheters or concomitant use of additional drugs affecting hemostasis such as NSAIDs (see boxed WARNING and ADVERSE REACTIONS, Ongoing Safety Surveillance.

As with other anticoagulants, bleeding can occur at any site during therapy with FRAGMIN. An unexpected drop in hematocrit or blood pressure should lead to a search for a bleeding site.

Thrombocytopenia:

In clinical trials, thrombocytopenia with platelet counts of $< 50,000/\text{mm}^3$ and $< 100,000/\text{mm}^3$ occurred in $< 1\%$ and $< 1\%$, respectively, of patients undergoing abdominal surgery or hip replacement surgery. In clinical practice, rare cases of thrombocytopenia with thrombosis have also been observed.

Thrombocytopenia of any degree should be monitored closely. Heparin-induced thrombocytopenia can occur with the administration of FRAGMIN. The incidence of this complication is unknown at present.

Miscellaneous:

The multiple-dose vial of FRAGMIN contains benzyl alcohol as a preservative. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. Because benzyl alcohol may cross the placenta, FRAGMIN preserved with benzyl alcohol should not be used in pregnant women. (See PRECAUTIONS, Pregnancy Category B., Nonteratogenic Effects.)

PRECAUTIONS

General:

FRAGMIN Injection should not be mixed with other injections or infusions unless specific compatibility data are available that support such mixing.

FRAGMIN should be used with caution in patients with bleeding diathesis, thrombocytopenia or platelet defects; severe liver or kidney insufficiency, hypertensive or diabetic retinopathy, and recent gastrointestinal bleeding.

If a thromboembolic event should occur despite dalteparin prophylaxis, FRAGMIN should be discontinued and appropriate therapy initiated.

Drug Interactions:

FRAGMIN should be used with care in patients receiving oral anticoagulants and/or platelet inhibitors because of increased risk of bleeding.

Laboratory Tests:

Periodic routine complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with FRAGMIN. No special monitoring of blood clotting times (e.g., APTT) is needed.

When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) are relatively insensitive measures of FRAGMIN activity and, therefore, unsuitable for monitoring.

Drug/Laboratory Test Interactions:

Elevations of Serum Transaminases:

Asymptomatic increases in transaminase levels (SGOT/AST and SGPT/ALT) greater than three times the upper limit of normal of the laboratory reference range have been reported in 1.7 and 4.3%, respectively, of patients during treatment with FRAGMIN. Similar significant increases in transaminase levels have also been observed in patients treated with heparin and other low molecular weight heparins. Such elevations are fully reversible and are rarely associated with increases in bilirubin. Since transaminase determinations are important in the differential diagnosis of myocardial infarction, liver disease and pulmonary emboli, elevations that might be caused by drugs like FRAGMIN should be interpreted with caution.

Carcinogenicity, Mutagenesis, Impairment of Fertility:

Dalteparin sodium has not been tested for its carcinogenic potential in long-term animal studies. It was not mutagenic in the *in vitro* Ames Test, mouse lymphoma cell forward mutation test and human lymphocyte chromosomal aberration test and in the *in vivo* mouse micronucleus test. Dalteparin sodium at subcutaneous doses up to 1200 IU/kg (7080 IU/m²) did not affect the fertility or reproductive performance of male and female rats.

Pregnancy: Pregnancy Category B.

Teratogenic Effects:

Reproduction studies with dalteparin sodium at intravenous doses up to 2400 IU/kg (14,160 IU/m²) in pregnant rats and 4800 IU/kg (40,800 IU/m²) in pregnant rabbits did not produce any evidence of impaired fertility or harm to the fetuses. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects:

Cases of "Gasping Syndrome" have occurred when large amounts of benzyl alcohol have been administered (99 - 404 mg/kg/day). The 9.5 mL multi-dose vial of FRAGMIN contains 14 mg/mL of benzyl alcohol.

Nursing Mothers:

It is not known whether dalteparin sodium is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FRAGMIN is administered to a nursing mother.

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Hemorrhage:

The incidence of hemorrhagic complications during treatment with FRAGMIN Injection has been low. The most commonly reported side effect is hematoma at the injection site. The incidence of bleeding may increase with higher doses; however, in abdominal surgery patients with malignancy, no significant increase in bleeding was observed when comparing FRAGMIN 5000 IU to either FRAGMIN 2500 IU or low dose heparin.

In a study comparing FRAGMIN 5000 IU once daily to FRAGMIN 2500 IU once daily in patients undergoing surgery for malignancy, the incidence of bleeding events was 4.6% and 3.6%, respectively (n.s.). In a study comparing FRAGMIN 5000 IU once daily to heparin 5000 IU twice daily, the incidence of bleeding events was 3.2% and 2.7%, respectively (n.s.) in the malignancy subgroup.

Abdominal Surgery:

Table 5 summarizes bleeding events that occurred in clinical trials which studied FRAGMIN 2500 and 5000 IU administered once daily to abdominal surgery patients.

Table 5
Bleeding Events in Abdominal Surgery

Indication	FRAGMIN vs Heparin				FRAGMIN vs Placebo		FRAGMIN vs FRAGMIN	
	Dosing Regimen				Dosing Regimen		Dosing Regimen	
	FRAGMIN 2500 IU qd s.c.	Heparin 5000 U bid s.c.	FRAGMIN 5000 IU qd s.c.	Heparin 5000 U bid s.c.	FRAGMIN 2500 IU qd s.c.	Placebo qd s.c.	FRAGMIN 2500 IU qd s.c.	FRAGMIN 5000 IU qd s.c.
Abdominal Surgery								
Postoperative Transfusions	26/459 (5.7%)	36/454 (7.9%)	81/508 (15.9%)	63/498 (12.7%)	14/182 (7.7%)	13/182 (7.1%)	89/1025 (8.7%)	125/1033 (12.1%)
Wound Hematoma	16/467 (3.4%)	18/467 (3.9%)	12/508 (2.4%)	6/498 (1.2%)	2/79 (2.5%)	2/77 (2.6%)	1/1030 (0.1%)	4/1039 (0.4%)
Reoperation due to Bleeding	2/392 (0.5%)	3/392 (0.8%)	4/508 (0.8%)	2/498 (0.4%)	1/79 (1.3%)	1/78 (1.3%)	2/1030 (0.2%)	13/1038 (1.3%)
Injection Site Hematoma	1/466 (0.2%)	5/464 (1.1%)	36/506 (7.1%)	47/493 (9.5%)	8/172 (4.7%)	2/174 (1.1%)	36/1026 (3.5%)	57/1035 (5.5%)

Hip Replacement Surgery:

Table 6 summarizes: 1) all major bleeding events and, 2) other bleeding events possibly or probably related to treatment with FRAGMIN, warfarin, or heparin in clinical trials of hip replacement surgery.

Table 6
Bleeding Events in Hip Replacement Surgery

Indication	FRAGMIN vs Warfarin Sodium		FRAGMIN vs Heparin	
	Dosing Regimen		Dosing Regimen	
	FRAGMIN 5000 IU qd s.c. (n = 274 ²)	Warfarin Sodium ¹ oral (n = 279)	FRAGMIN 5000 IU qd s.c. (n = 69 ⁴)	Heparin 5000 U tid s.c. (n = 69)
Major Bleeding Events ³	7/274 (2.6%)	1/279 (0.4%)	0	3/69 (4.3%)
Other Bleeding Events ⁵				
Hematuria	8/274 (2.9%)	5/279 (1.8%)	0	0
Wound Hematoma	6/274 (2.2%)	0	0	0
Injection Site Hematoma	3/274 (1.1%)	NA	2/69 (2.9%)	7/69 (10.1%)

- 1 Warfarin sodium dosage was adjusted to maintain a prothrombin time index of 1.4 to 1.5, corresponding to an International Normalized Ratio (INR) of approximately 2.5.
- 2 Includes three treated patients who did not undergo a surgical procedure.
- 3 A bleeding event was considered major if: 1) hemorrhage caused a significant clinical event, 2) it was associated with a hemoglobin decrease of ≥ 2 g/dL or transfusion of 2 or more units of blood products, 3) it resulted in reoperation due to bleeding, or 4) it involved retroperitoneal or intracranial hemorrhage.
- 4 Includes two treated patients who did not undergo a surgical procedure.
- 5 Occurred at a rate of at least 2% in the group treated with FRAGMIN 5000 IU once daily.

Six of the patients treated with FRAGMIN experienced seven major bleeding events. Two of the events were wound hematoma (one requiring reoperation), three were bleeding from the operative site, one was intraoperative bleeding due to vessel damage, and one was gastrointestinal bleeding. None of the patients experienced retroperitoneal or intracranial hemorrhage nor died of bleeding complications.

Thrombocytopenia: See WARNINGS: Thrombocytopenia.

Other:

Allergic Reactions:

Allergic reactions (i.e., pruritus, rash, fever, injection site reaction, bullous eruption) and skin necrosis have occurred rarely. A few cases of anaphylactoid reactions have been reported.

Local Reactions:

Pain at injection site, the only non-bleeding event determined to be possibly or probably related to treatment with FRAGMIN and reported at a rate of at least 2% in the group treated with FRAGMIN, was reported in 4.5% of patients treated with FRAGMIN 5000 IU qd vs 11.8% of patients treated with heparin 5000 U bid in the abdominal surgery trials. In the hip replacement trials, pain at injection site was reported in 12% of patients treated with FRAGMIN 5000 IU qd vs 13% of patients treated with heparin 5000 U tid.

Ongoing Safety Surveillance:

Since first international market introduction in 1985, there have been 5 reports of epidural or spinal hematoma formation with concurrent use of dalteparin sodium and spinal/epidural anesthesia or spinal puncture. No cases have been reported in the United States since approval in 1994. Four of the 5 patients had post-operative indwelling epidural catheters placed for analgesia or received additional drugs affecting hemostasis. The hematomas caused long-term or permanent paralysis in four of the cases (one complete, three partial paralyses). The fifth patient experienced temporary paraplegia but made a full recovery. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

OVERDOSAGE

Symptoms/Treatment:

An excessive dosage of FRAGMIN Injection may lead to hemorrhagic complications. These may generally be stopped by the slow intravenous injection of protamine sulfate (1% solution), at a dose of 1 mg protamine for every 100 anti-Xa IU of FRAGMIN given. A second infusion of 0.5 mg protamine sulfate per 100 anti-Xa IU of FRAGMIN may be administered if the APTT measured 2 to 4 hours after the first infusion remains prolonged. Even with these additional doses of protamine, the APTT may remain more prolonged than would usually be found following administration of conventional heparin. In all cases, the anti-Factor Xa activity is never completely neutralized (maximum about 60 to 75%).

Particular care should be taken to avoid overdosage with protamine sulfate. Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulfate, it should be given only when resuscitation techniques and treatment of anaphylactic shock are readily available. For additional information, consult the labeling of Protamine Sulfate Injection, USP, products. A single subcutaneous dose of 100,000 IU/kg of FRAGMIN to mice caused a mortality of 8% (1/12) whereas 50,000 IU/kg was a non-lethal dose. The observed sign was hematoma at the site of injection.

DOSAGE AND ADMINISTRATION

Abdominal Surgery:

In patients undergoing abdominal surgery with a risk of thromboembolic complications, the recommended dose of FRAGMIN Injection is 2500 IU administered by subcutaneous (s.c.) injection once daily, starting 1 to 2 hours prior to surgery and repeated once daily for 5 to 10 days postoperatively (See INDICATIONS AND USAGE).

In patients undergoing abdominal surgery associated with a high risk of thromboembolic complications, such as malignant disorder, the recommended dose of FRAGMIN is 5000 IU s.c. the evening before surgery, then once daily for 5 to 10 days postoperatively. Alternatively, in patients with malignancy, 2500 IU of FRAGMIN can be administered s.c. 1 to 2 hours before surgery followed by 2500 IU s.c. 12 hours later, and then 5000 IU once daily for 5 to 10 days postoperatively.

Hip Replacement Surgery:

In patients undergoing hip replacement surgery, the recommended first dose of FRAGMIN is 2500 IU administered by s.c. injection within 2 hours before surgery and the second dose of 2500 IU s.c. in the evening of the day of surgery (at least 6 hours after the first dose). If surgery is performed in the evening, omit the second dose on the day of surgery. Starting on the first postoperative day, the recommended dose of FRAGMIN is 5000 IU administered by s.c. injection once daily. Alternatively, 5000 IU of FRAGMIN can be administered the evening before surgery, followed by 5000 IU once daily, starting in the evening of the day of surgery. Up to 14 days of treatment was well tolerated in controlled clinical trials, where the average duration of treatment was 5 to 10 days postoperatively.

Dosage adjustment and routine monitoring of coagulation parameters are not required if the dosage and administration recommendations specified above are followed.

Administration:

FRAGMIN is administered by subcutaneous injection. It must not be administered by intramuscular injection.

Subcutaneous injection technique: Patients should be sitting or lying down and FRAGMIN administered by deep subcutaneous injection. FRAGMIN may be injected in a U-shape area around the navel, the upper outer side of the thigh or the upper outer quadrangle of the buttock. The injection site should be varied daily. When the area around the navel or the thigh is used, using the thumb and forefinger, you **must** lift up a fold of skin while giving the injection. The entire length of the needle should be inserted at a 45 to 90 degree angle.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

FRAGMIN Injection is available in the following strengths and package sizes:

0.2 mL single-dose prefilled syringe, affixed with a 27-gauge x 1/2 inch needle. Package of 10:

2500 anti-Factor Xa IU NDC 0013-2406-91

5000 anti-Factor Xa IU NDC 0013-2426-91

9.5 mL multiple-dose vial:

10,000 anti-Factor Xa IU/mL NDC 0013-2436-06

(95,000 anti-Factor Xa IU/vial)

Storage

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

Rx only

U.S. Patent 4,303,651

Manufactured for: Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA

By: Vetter Pharma-Fertigung
Ravensburg, Germany
(prefilled syringes)

Pharmacia & Upjohn AB
Stockholm, Sweden
(multiple-dose vial)

(Copy code) Revised _____

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020287/S008

MEDICAL REVIEW(S)

APR 15 1998

1

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

NDA #20-287/S-008

SUBMISSION: Efficacy and Safety Supplement for New Indication

DRUG: FRAGMIN Injection (Dalteparin Sodium)

CLASS: Antithrombotic: Low Molecular Weight Heparin

INDICATIONS: Prophylaxis of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) in patients undergoing hip replacement surgery.

SPONSOR: Pharmacia & Upjohn Company, Kalamazoo, MI

SUBMISSION DATE: 4-17-1997

DUE DATE: 4-16-1998

MEDICAL REVIEWER: Lilia Talarico, M.D.

DATE OF REVIEW: 4-10-1998

APPEARS THIS WAY ON ORIGINAL

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1.0 INTRODUCTION AND BACKGROUND

1.1 Thromboprophylaxis in Hip Replacement Surgery

Patients undergoing orthopedic surgery are at high risk of thromboembolic complications. Without thromboprophylaxis, the incidence of venous thromboembolic events (VTE) has been reported to be in excess of 50%. Non-fatal pulmonary embolism (PE) following orthopedic surgery occur in about 10% of patients; about 2% of PE have fatal outcome. The incidence of PE in the high risk orthopedic population is much higher than the 0.2% incidence of PE complicating major general surgery.

The connection between DVT in the lower extremities involving proximal veins and risk of pulmonary embolization is well established. Prior to the introduction of the Fibrinogen Uptake Test (FUT) as a diagnostic test for DVT in the early seventies, DVT was diagnosed by clinical criteria and confirmed by venography. The use of FUT has allowed to detect clinically asymptomatic DVT with an incidence rate of more ten times the rate of symptomatic DVT. More recent methods for the assessment of DVT include plethysmography, several types of ultrasound (Doppler flow, Duplex ultrasound). However, bilateral ascending phlebography remains the "reference standard" for diagnosis of DVT because of its objectivity even though considerable inter- and intra-variability in VG reading has been acknowledged. The majority of asymptomatic DVT are non-occlusive by VG assessment. However, asymptomatic DVT can also contribute to occurrence of PE. The VG diagnosis of DVT is based on "intraluminal filling defect" found on "at least two phlebogram".

The diagnosis of PE is based on clinical symptoms confirmed by ventilation/perfusion scintigraphy and/or pulmonary angiography (the "reference standard"). Historical data and data used in clinical trials to compare the PE incidence with the prophylactic effect of anticoagulant drugs are based on this diagnostic approach. The use of scintigraphy for screening of asymptomatic patients for PE has greatly increased the incidence of PE because of the detection of "moderate or high probability" PE involving small pulmonary vessels. The future clinical relevance of these asymptomatic PE is still unclear.

Following a better understanding of risk factors for DVT and PE, thromboprophylaxis has been widely used for prevention of asymptomatic DVT following orthopedic and/or other surgery with high risk for PE. Antithrombotic regimens have included heparin and warfarin. The NIH Consensus Conference on Prevention of Venous Thrombosis and Pulmonary Embolism in 1986 issued guidelines (*JAMA*. 1986; 286:745-9) which included the recommendation for the use of low-dose heparin (5000 IU, b.i.d. or t.i.d.).

In high risk surgical procedures, such as orthopedic surgery, thromboprophylaxis with fixed low-dose unfractionated heparin (UH) has been considered inadequate. However, sc administration of heparin at the dose of 5000 IU q8h has been shown to reduce the incidence of VTE in hip replacement surgery to approximately 20% compared to no treatment or to placebo. More effective thromboprophylaxis is achieved with the administration of sc heparin administered at doses adjusted according to APTT.

1.2 Low Molecular Weight Heparin (LMWH) for Perioperative Prophylaxis of DVT and PE

Antithrombotic compounds that have been extensively evaluated over the past decade for thromboprophylaxis in high risk patients are represented by the Low Molecular Weight Heparins (LMWH). LMWHs are fragments of unfractionated heparin (UH) produced by various processes of controlled chemical or enzymatic fractionation of heparin. Similar to UH, LMWHs exert their anticoagulant activity by activating AT-III, however they differ from UH in their relative inhibitory activity against factor Xa and IIa: whereas UH has equivalent anti-Xa and anti-IIa, LMWHs have greater anti-Xa than anti-IIa activity.

LMWHs differ in their manufacturing process, consequently, they differ chemically from each other and are not interchangeable. The MW distribution, mean MW, anti-Xa and anti-IIa activity and the anti-Xa/anti-IIa ratio differ for each LMWH.

LMWHs exhibit pharmacologic characteristics that make them more suitable for thromboprophylaxis than unfractionated heparin, among which, nearly 100% absorption from sc administration and longer duration of activity. LMWHs have better bioavailability and produce a more predictable anticoagulant response than UH. At thromboprophylactic doses, LMWH do not prolong global tests of coagulation such as PT, APTT and ACT, and consequently do not require laboratory monitoring of anticoagulant effect.

There are two major safety concerns regarding the use of LMWH for thromboprophylaxis in surgery: hemorrhagic complications and heparin-induced thrombocytopenia/thrombosis. Major bleeding events, defined on the basis of location (intracranial, neuraxial, retroperitoneal), size (ecchymosis/hematoma ≥ 5 cm diameter), amount of hemoglobin decrease (≥ 2 g/dL), and number of blood transfusions (≥ 2 units), are uncommon with the administration of LMWHs at doses used for thromboprophylaxis.

Heparin-induced thrombocytopenia (HIT) is an immune-mediated adverse event occurring in about 3% of patients receiving heparin for longer than 5-10 days. The *de novo* incidence of HIT is significantly lower in patients receiving LMWH, however, preformed anti-heparin antibodies cross-react with LMWHs in nearly 100% of cases.

Other adverse events reported in patients receiving Fragmin or other LMWH are classified according to COSTART BODY SYSTEM Dictionary.

Three LMWH, including Lovenox (enoxaparin sodium), Normiflo (ardeparin sodium), Fragmin (dalteparin sodium), and one heparinoid compound, Orgaran (danaparoid sodium) are approved in US for thromboprophylaxis in hip or knee replacement surgery or in high risk abdominal surgery.

1.3 Fragmin for Thromboprophylaxis in Hip Replacement Surgery

Fragmin (Dalteparin sodium) is a LMWH composed of acidic sulfated polysaccharide chains produced through controlled nitrous acid depolymerization and chromatographic purification of sodium heparin obtained from porcine intestinal mucosa. Fragmin is a mixture of heparin fragments; approximately 3-15% of the fragments have a MW of less than 3000, 65-78% of the fragments have a MW of 3000-8000, and 14-26% have a MW greater than 8000. The average MW of dalteparin is 5000 D.

At present, Fragmin has been authorized for use in 44 countries all over the world. Approved indications include: thromboprophylaxis, hemodialysis, and treatment of DVT. The first approval was granted in Germany, 1985. Since the first marketing in 1985 to May 1996, it is estimated that approximately 22 million patients worldwide have been treated with Fragmin.

The drug product is approved as single dose syringe (2,500 IU, and 5,000 IU), ampule (2,500 IU, 5,000 IU, 10,000 IU), and vials (4 and 10 mL; multidose).

On 8-6-1992, an NDA (#20-27) was submitted for the US approval of Fragmin for prophylaxis against DVT and PE in high risk patients undergoing general abdominal surgery or hip replacement surgery. In December 1994, Fragmin, at the dose of 2500 anti-Xa U sc qd, was approved for prophylaxis of DVT in patients undergoing abdominal surgery who are at risk of TE complications. Approval for Fragmin for thromboprophylaxis in hip replacement was not granted because one of the two pivotal studies (D-4) was unacceptable and the second study (D-10) was found to be inadequate as single pivotal study.

Fragmin, at the dose of 5000 anti-Xa U once daily sc, was subsequently approved also for thromboprophylaxis in patients undergoing abdominal surgery at high risk of TE complications.

An efficacy supplement (S-008) to NDA 20-287 has been submitted for the approval of Fragmin for the indication "for prophylaxis against DVT which may lead to pulmonary embolism (PE), in patients undergoing hip replacement surgery." The new indication

is supported by two pivotal studies conducted with patients undergoing hip replacement surgery: Study 91-137, a multi-center, warfarin-controlled clinical trial of 580 patients conducted in the U.S. and Study D-10, the single center, heparin-controlled trial of 140 patients conducted in Sweden and submitted in the initial NDA on 8-6-1992.

In addition to the two pivotal trials, other controlled clinical trials submitted in the original NDA (20-287) have been submitted as supportive studies, as well as a meta-analysis of Heparin-controlled Fragmin studies in hip arthroplasty.

Other Studies that support the indication of high risk surgery include "abdominal surgery for patients at risk for thrombosis such as cancer, or history of previous DVT or PE."

The Fragmin dosage regimen for patients undergoing hip replacement surgery is 2500 anti-Xa IU, SC, within 2h prior to surgery and again in the evening of the day of surgery (at least 6h after the first dose). If surgery is performed in the evening, the second dose on the day of surgery is omitted. Starting on the first postoperative day, Fragmin is administered at the dose of 5000 IU SC once daily. Alternatively, the initial dose of 5000 IU once daily can be started in the evening of the day of surgery. In both regimens, treatment is continued throughout the period of postoperative care until the risk of DVT has diminished. Up to 14 days of treatment was well tolerated in clinical trials, where the usual duration of treatment was 5-10 days postoperatively.

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2.0 NDA 20-287/S-008 TABLE of CONTENT

SUPPLEMENT 20-287/S-008 CLINICAL DATA

CONTENT	
Vol.1	Index, Application Summary (Annotated Package Insert, Foreign Marketing History)
Vol.2	Chemistry, Manufacturing and Controls. Part IV. Environmental Assessment.
Vol.3	Samples, Methods Validation and Labeling. Samples. Labeling.
Vol.4	Study 91-137: Clinical Data. Electronic Files (Diskettes in Item 10, Review Copy). A. List of investigators. B. Background/Overview of Clinical Investigations. D. Controlled Clinical Studies. Publication.
Vol.5	Study D-10: Revised Research Report . (p.1-256) Investigational Plan, Statistical Methods Planned, Disposition of Patients Entered, Efficacy Results, Safety Results, Summary and Conclusions, References. Appendix (p.257-575) Protocol and Amendments, Publications, List of Investigators, Statistical Methods and Randomization Codes, Patient Data Listings, Individual Patient data Listing.
Vol.6	Synopses of Other Controlled Hip Replacement Surgery Studies submitted with the same NDA. Study E-4, E-5, E-7 and E-8. E. Uncontrolled Clinical Studies. F. Other Studies and Information. G. Integrated Summary of Effectiveness Data (pivotal, supportive, meta-analysis of LMWH in hip surgery, Study 91-137). Integrated Summary of Safety Data (List of studies. Patient exposure. Hemorrhagic events. Non-hemorrhagic adverse events. Deaths and premature withdrawals. Laboratory data. Study 91-137. I. Drug Abuse & Overdose Information. J. Integrated Summary of Benefits and Risks of the Drug.
Vol.7-9	Statistical Section

Electronic data were submitted only in SAS format. They were available for statistical analysis. No data in electronic form were available in WP or Word formats.

3.0 MATERIAL REVIEWED IN NDA 20-287/S-008

a. Clinical Data

The NDA Supplement was submitted in 32 volumes. The clinical and statistical data from the two pivotal studies and from supportive studies are presented in volumes 1 through 9.

The data from the pivotal study 91-137 were submitted in volume 4 and the data from study D-10 were submitted in volume 5.

The study protocol with amendments were included in Vol.22-24. Case Report Tabulations, Patient Profiles, and Case Report Forms for Patients who Discontinued were submitted in electronic format.

This NDA supplement was reviewed by the Dr. Markovic who submitted a draft review on March 13, 1998. Material from Dr. Markovic's draft review and revised tables of data have been included in the present review.

b. 4-Month Safety Update (Amendment to Supplement S-008).

This update includes new safety data that have become available between 07/01/95 and 02/28/97.

The safety data from this amendment are also included in the Integrated Assessment of Safety.

REVIEW OF THE CLINICAL DATA: PIVOTAL STUDIES

4.0 REVIEW OF STUDY 91-137 (NDA/S Vol.4)

Title: An open, randomized study evaluation the thromboprophylactic efficacy of low molecular weight heparin (Fragmin®) vs. warfarin in total hip replacement.

Indication: Prophylaxis of DVT in patient undergoing total hip replacement.

Study Drugs: Test Drug: Fragmin 2500 IU (Batch Nos.DXN 1 85,94046A01) 2h before surgery followed by 2500 after 12 hours and 5000 IU (Batch Nos.DXN 186, DXN 241, 94032A02) q.d. afterwards.
Control drug: Warfarin, dose adjusted for INR 2.0-3.0. The treatment was continued for up to 9 days following surgery.

Study Dates: 05/19/92 to 03/30/95. Date of Report: 03/31/96

Investigators: Multicenter (n=8, all in the U.S.).

Adjudicator: Blinded radiologist who evaluated the venograms from all study sites (S.Totterman, M.D., Radiologists. Univ. of Rochester Med. Cnt.).

4.1 STUDY OBJECTIVES

- A. The primary objective was to compare the incidence of verified postoperative DVT after unilateral total hip replacement [THR] in patients receiving fragmin vs. warfarin.
- B. Secondary objectives of the study were to:
1. Compare the incidence of postoperative verified proximal DVT within approximately one week after surgery.
 2. Compare the incidence of postoperative verified pulmonary embolism (PE) in patients with suggestive clinical findings within approximately one week after surgery.
 3. Compare the incidence of clinical thromboembolic events (verified DVT and/or PE) within about one week post-operatively.
 4. Compare the incidence of clinical thromboembolic events within the follow-up period (5-7 weeks post-op).
 5. Evaluate the safety parameters such as bleeding during and after surgery, re-operation due to bleeding, surgically or spontaneously evacuated wound hematoma, other bleeding complications, blood transfusion requirements, and hemoglobin, hematocrit, and platelet count.

4.2 SYNOPSIS OF STUDY 91-137

Study 91-137 was designed and completed in the U.S. to serve as a pivotal trial for the approval of fragmin for prophylaxis of DVT/PE in patients undergoing hip replacement surgery.

The objective of the study was to demonstrate that fragmin is safe and superior to warfarin for thromboprophylaxis in hip replacement surgery.

The study enrolled 580 patients at eight centers in the U.S. The patients were randomly assigned to either Fragmin (2500 IU prior to operation, followed by 2500 IU after operation, and 5000 IU daily for 5-9 days) or Warfarin (first dose night before surgery, followed by the same dose the day of surgery, and then dosed to maintain INR approximately about 2.5). Per protocol population included 192 Fragmin patients and 190 warfarin patients.

At the end of the study (day 5-9) all patients were examined by a bilateral ascending venography. Venograms (VG) were evaluated for thrombosis by radiologists and by an adjudication committee blinded for study drug allocation. The primary efficacy endpoint, DVT was found in 28/192 (15%) patients on Fragmin, and 49/190 (26%) patients on Warfarin treatment. This difference was significant ($p=0.006$).

Patients in the Fragmin group had more hemorrhagic episodes than those in the Warfarin group (F=30/274 or 10.9%; W=12/279 or 4.3%). At least two patients in the Fragmin group had major hemorrhage and discontinued the study. Non-hemorrhagic adverse events were comparable in the two treatment groups. Eight Fragmin and six Warfarin patients had at least one platelet count value below 100,000/mm³. No case of HIT was reported. No deaths were reported.

The study 91-137 demonstrated that Fragmin reduced the risk of postoperative DVT compared to warfarin, however, this benefit carried a moderate risk of perioperative hemorrhage.

4.3 SUMMARY OF THE INVESTIGATIONAL PLAN

a. Study Design

The study was multicenter (n=8), randomized, open-label, assessor blinded, parallel group, active treatment controlled clinical trial. Five hundred-eighty (580) enrolled patients were randomly assigned by a central coordinating center to receive either Fragmin (288 patients) or Warfarin (292 patients).

Patients treated with Fragmin received 2500 IU sc within two hours prior to surgery. This dose was repeated in the evening the day of the surgery. Fragmin was continued with 5000 IU sc every morning thereafter for 7±2 days of study.

Patients treated with Warfarin received the first dose in the evening before surgery followed by the second equal dose (5 or 7.5 mg) the evening after surgery. Thereafter, daily doses of Warfarin were adjusted to maintain a prothrombin time index (PTI) of 1.4-1.5 or INR approximately 2.5. Warfarin was given for the same time as Fragmin (7±2 days).

Bilateral ascending phlebography was performed 7±2 days after surgery. Efficacy assessment included incidence of DVT and PE. Venograms were assessed by an independent radiologist who had no knowledge of the treatment groups. Patients who presented clinical signs or symptoms suggestive of acute PE, were subject to perfusion/ventilation scintigraphy and/or pulmonary angiography for confirmation of diagnosis.

Patients were evaluated for safety starting preoperatively and through the 5-7 week follow-up period. Patients were monitored for bleeding, clinically observed and reported adverse events, and events which would result in premature withdrawal from the trial.

b. Choice of Control Group

The active control drug, Warfarin, is approved for prophylaxis of DVT and PE in general, but not specifically for the indication of this trial. However previous clinical experience has established the efficacy of warfarin compared to no treatment, therefore, study 91-137 was accepted as pivotal study. Furthermore, the study was designed to show superiority of Fragmin over Warfarin.

c. Study Population

Patients scheduled for hip replacement were screened for eligibility in order to allow enrollment of 580 patients to enter the study.

d. Randomization

Patients were randomly assigned to one of two treatment regimens by central randomization. Random numbers were provided to each center.

Within two weeks prior to surgery, the investigator called the Randomization Center either at the Strong Memorial Hospital, Rochester, NY, or the [REDACTED]

[REDACTED] Patients were allocated a consecutive patients number and treatment (Fragmin or Warfarin) in the order of entering the study.

e. Study Medication

Test Drug: Dalteparin was provided in single dose syringes for sc injection, containing either 2,500 IU/0.2 mL, or 5,000 IU/0.2 mL. For morning operations, dalteparin (2,500 IU) was administered 2h prior to surgery and in the evening of the same day (2,500 IU), but at least six hours after the preoperative injection. For evening surgery (4.00 pm and later), the evening dose was not given. All patients received 5,000 IU the first postoperative day, and 5-9 following days.

ELIGIBILITY CRITERIA

Inclusion Criteria

1. Male and female patients 18 years or older.
2. Scheduled for unilateral total hip replacement surgery within two weeks after randomization.
3. Written informed consent.

Exclusion Criteria

1. Previously undergone surgery in this study.
2. Simultaneous participation in another study involving investigational drug.
4. Renal insufficiency (serum creatinine ≥ 1.7 mg/dL).
5. Liver insufficiency (abnormal prothrombin time).
6. Documented bleeding, e.g., gastrointestinal, within three months prior to surgery.
7. Defect hemostasis, e.g., thrombocytopenia or ongoing anticoagulant treatment.
8. Cerebral hemorrhage within three months prior to surgery.
9. Eye, ear or CNS surgery within one month prior to surgery.
10. Known hypersensitivity to heparin, LMWH or contrast media.
11. Severe hypertension (diastolic pressure ≥ 120 mm Hg).
12. Septic endocarditis.
13. Weight less than 90 pounds.
14. Known pregnancy or breast feeding.
15. Positive pregnancy test in woman of reproductive potential.
16. Patients who are expected to be unable to follow instructions given in connection to the study.

Control Drug: The first warfarin dose was weight adjusted. Patients ≤ 125 lb (57 kg) received 5 mg. Those >125 lb (57 kg) received 7.5 mg. The initial fixed, weight adjusted dose was given on the evening before surgery and the evening after surgery. Thereafter, daily dose was adjusted according to individual response to maintain an INR of approximately 2.5. Duration of therapy 7 \pm 2 Days after surgery.

Venography was mandatory for all patients on Day 8 or earlier if clinical symptoms of an outcome were present. Patients with positive venography were treated at the discretion of the physician. For patients with negative venography, anticoagulant therapy was discontinued.

Concomitant use of ASA, NSAID, dextran or compression stockings was not allowed.

f. Efficacy and Safety Variables

● Efficacy

- 1) The primary efficacy variable was the incidence of a venous thromboembolic event (VTE), defined as objectively confirmed DVT, PE, death by thromboembolism, or any combination, in the Per-Protocol patient population (P-P), within one week following surgery.
- 2) The secondary efficacy variables were:
 - the incidence of VTE in the All-Treated patient population (all randomized patients who were operated on and received any study medication) within one week following surgery, and
 - the incidence of clinically symptomatic VTE within the follow-up period of 5-7 weeks after surgery.

● Criteria for efficacy endpoints

DVT: DVT was diagnosed if a constant filling defect was present in more than one VG projection. DVT was classified as distal (calf veins) or proximal (popliteal and more proximal veins).

PE: Two criteria were used for confirmation of PE:

- a positive pulmonary angiogram, and
- high clinical probability together with high probability lung scan.

● *Safety*

Hemorrhage (bleeding) was considered the primary safety variable. The following variables were assessed and recorded on CRF for statistical analysis of safety:

- 1) Bleeding evaluated as a composite endpoint including:
 1. Perioperative blood loss (mean in mL) - estimation by anaesthetist.
 2. Postoperative blood loss (mean in mL) - measurement of blood loss in drains.
 3. Blood transfusion requirements (number of patients requiring transfusion) - information from the Blood Bank.
 4. Plasma substitute - type and amount.
 5. Reoperation due to bleeding.
 6. Surgically or spontaneously evacuated wound hematoma.
 7. Other bleeding complications.
- 2) Allergic Reactions.
- 3) Adverse Events including the two primary efficacy variables (DVT and PE), the primary safety variable (bleeding), and Non-Hemorrhagic Adverse Events.
 1. Bleeding was assessed as a composite variable including the following WHO-ART terms: Hemorrhage, Wound Hematoma, GI Bleeding, Bleeding, Ecchymosis at Wound and Injection Site.
 2. Non-hemorrhagic adverse events were summarized by WHO-ART Body System and by WHO-ART Preferred Term within body system.
- 4) Analyses of Subsets of Patient Population/Sub-Group:
 - . Elderly vs. Young
 - . Males vs. Females
 - . Patients with Body Weight <80 kg vs. ≥80 kg.
 - . Patients with Risk Factors ≥2 vs. <2.
 - . Primary Operation vs. Revision Surgery.
- 5) Withdrawals/Dropouts. The following reasons were considered for withdrawal: allergic reaction, serious intercurrent illness, verified DVT/PE, patient request, and canceled operation.

All events were presented by their frequency and distribution parameters in tables. In some instances different statistical methods were used. Conclusions were based on statistical significance ($\alpha=0.05$; power 95%).

● **Laboratory Tests**

Laboratory Analysis.

- Change from baseline for: Hemoglobin, Hematocrit, Platelets
- Baseline: Hemoglobin, hematocrit, platelets, PT, creatinine.
- Daily: PT for patients on warfarin
- Ad hock: Anti-Xa, PT, APTT, hemoglobin, platelet count.
- End of study: Platelet count, hemoglobin.

g. Disposition of Study Patients

Information was obtained for the following parameters:

- Demographics: Gender, age (<65), race, body weight.
- Risk Factors: type of operation, duration of anesthesia and operation, previous VTE, cancer, trauma, varicose veins and postphlebitic syndrome, CV disease.
- Exposure to Study Medication, Concomitant Medication
- Dropouts, Protocol Violations
- Study Discontinuation
- Deaths

4.4 STATISTICAL METHODS

a. Statistical Analyses of Efficacy and Safety

The statistical analyses are outlined in the following table.

OUTCOME		ENDPOINT	POPULATION	STATISTICAL METHOD
Efficacy	Primary	VTE: DVT, PE or death due to TE events	Per-Protocol	two-sided t-test, $\alpha=0.05$
	Secondary	VTE: DVT, PE or death due to TEc event	All-Treated	
		Symptomatic VTE (5-7 weeks)	All-treated	
Safety		Hemorrhage and Adverse Events	All-treated	

From Protocol Plan: Statistics and Medical Data (Vol.4, 8/1/238)

The statistical plan was changed and Cochran-Mantel-Haenzel Test was used by the sponsor.

b. Sample Size

The sample size was calculated based on 25% failure rate (incidence of VTE) for warfarin, and 15% failure rate for Fragmin. A sample size of at least 250 patients per treatment group was required for a 10% treatment difference with a power of 80% using a two-tailed test at the 5% level of significance. Considering a drop-out rate of about 15%, a total of 580 patients was included to provide at least 500 evaluable patients.

4.5 STUDY RESULTS

4.5.1 Data Sets Analyzed

a. Patients Disposition

All-treated population consisted of patients operated and who received at least one dose of study medication. Per protocol population consisted of patients who were operated, dosed, and had an evaluable venogram. Only the All-Treated and Per-Protocol (P-P) populations were used in the statistical analysis. P-P population was used for primary efficacy analysis. All-treated population was used for safety analyses.

A total of 580 patients were randomized in the study in order to have 500 evaluable patients. Approximately 5% of randomized patients did not enter the study because they either were not operated or not dosed. Approximately one third of the All-Treated patients (30.5%) did not have evaluable VG and were excluded from the P-P population. Consequently, the primary efficacy analysis was performed without the prestated power of 80% due to the reduction of the P-P population. The disposition of the study patients is summarized in the following table.

Patient Disposition		Number of Patients	
		Fragmin	Warfarin
Randomized		288	292
ITT	Included in ITT analysis (all-treated);	271	279
	Excluded: Total	17	13
	No VG Never dosed, No operation,	14	13
	VG Dosed but Surgery canceled, No	3	0
P-P	Included in P-P analysis;	192 (66.6%)	190 (65.1%)
	Excluded: Total	96 (33.4%)	102 (34.9%)
	Never dosed, No operation, No VG	14	13
	VG Dosed but Surgery canceled, No	3	0
	Dosed but No VG	53	70
	Dosed but VG misplaced or missing	7	8
	Dosed but VG not evaluable	19	11

From Tables :Vol 4, p8-1-62, and p.8-1-63

Approximately 10% of patients were withdrawn from the study. The reasons for withdrawal are summarized in the following table.

PATIENTS WHO COMPLETED THE STUDY. REASON FOR WITHDRAWAL.

		Fragmin (n=288)	Warfarin (n=292)
Randomized/Completed		288/262	292/270
Withdrawn	Total	26	22
	Adverse Event	3	3
	Intercurrent Illness	1	1
	DVT/PE	1	1
	Patient Request	7	4
	Operation Canceled	10	7
	Other	4	6

From Table Patient Disposition (Vol.4, p8-1-77)

b. Compliance (Protocol Violations)

Five patients were excluded because of protocol violation: renal insufficiency at baseline [E=2/W=1], hypersensitivity to heparin [F=1], body weight <90 lbs [F=1]).

Another protocol violation was represented by the practice of local investigators to use lower dose of warfarin than specified in the protocol.

A total of 163 patients (85%) of P-P population treated with Fragmin met dosing compliance. One hundred-eighty-two (182) patients (96%) treated with warfarin met compliance criteria. Therefore, the population of patients who were operated on, received dose medication as planned, and had evaluable VGs was even smaller than the P-P population as defined by the sponsor. In either case, neither treatment groups reached the calculated sample size needed for the pre-determined sample power.

c. Demographics

There were no imbalances between the two treatment groups for demographics, patients characteristics, underlying conditions, surgical and anesthesia characteristics, and risk factors for VTEs.

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d. Duration of Treatment

The majority of patients received treatment as specified in the protocol pre-operatively, on the day of surgery and post-operatively for five days (Day 1-5). The number of patients receiving the study drugs decreased from Day 6 and by Day 10 only a few patient were receiving the study drugs. No significant difference was found between treatment groups.

4.5.2 Efficacy Assessment

1. Primary Efficacy Analysis

The primary efficacy endpoint was the incidence of DVT in the P-P population as assessed on VG by an independent blinded radiologist. The results are summarized below:

PRIMARY EFFICACY ENDPOINT: RATES OF VERIFIED DVT AND SUPERFICIAL VEINS THROMBOSIS IN P-P POPULATION*.

DVT Location	Fragmin		Warfarin		P-value
	N=192	%	N=190	%	
Any Deep Vein Thrombosis (total DVT)	28	14.6	49	25.8	0.006*
Risk Ratio-Odds Ratio@	28/164=0.17		49/141=0.35		OR:0.48
Any Superficial Vein Thrombosis**	23	11.9	43	22.6	0.005*
Superficial and deep venous thrombosis	51	26.5	92	48.4	<0.001*
Distal DVT (Calf): Total	21	10.9	43	22.6	0.005*
Proximal DVT (Leg): Total	10	5.2	16	8.4	0.185
Popliteal	2	1	7	4	
Superf. Thigh.	4	2	9	5	
DVT Thigh	4	2	1	1	

From Table: Vol.4, p.8/1/71-72. * Significant difference.

** Superficial vein category (not in the protocol) was analyzed aside of categories any vein, proximal and distal. Some DVT may have been counted in more than one location.

Significant difference was found in the incidence of primary efficacy variable: the 'any DVT' category due to the difference found in 'distal DVT'. A slight numerical difference in favor of Fragmin was found for the proximal DVT which was not statistically significant.

The net reduction in DVT rates in the Fragmin group was 11.2%.

2. Secondary Efficacy Analysis

The following analyses were performed to support the primary efficacy data.

a. All-treated patient population Analysis - VG Data.

- Treatment failures included all patients with a positive venogram. The incidence of DVT was 10% (30/288) in the Fragmin group vs. 18% (53/292) in the warfarin group.
- Treatment failures included all patients with a positive VG or no evaluable VG (*worst case scenario*). The incidence of DVT was 39% for Fragmin vs. 49% for warfarin treated patients.
- Treatment failures included all patients with a positive venogram plus an estimated proportion of patients with no evaluable venogram (*censored scenario*). The incidence of DVT was 16% for Fragmin vs. 24% for warfarin treated patients.

All three analyses demonstrated that there was a statistically significant difference in favor of Fragmin.

b. Patients with symptomatic DVT.

The data are summarized in the following table.

PATIENTS WITH CLINICAL SYMPTOMS OF DVT

DVT diagnosis	Fragmin		Warfarin		p-value
	N=288	%	N=292	%	
Symptomatic DVT	23	7.9	13	4.4	<0.001; F ≤ W
Venography Performed:	23	100	13	100	
Positive	3	13.0	1	7.7	
Negative	13	56.5	9	69.2	
Not known	7	30.4	3	23.0	

From Table EF137-3.2 and 9.4.3 Patients with Clinical Symptoms/Signs of DVT (Vol.4, p. 8/1/76)

A discordance between clinical symptoms of DVT and VG confirmation was noted for 36 patients (F=23/W=13) with clinical signs or symptoms of VTE. DVT was not confirmed on ascending bilateral venography in 13 and 9 respectively. Three DVTs documented by VG were clinically symptomatic in the Fragmin group compared to one in the warfarin group.

c. Patients with symptomatic PE and scan confirmed PE.

The data are summarized in the following table.

PATIENTS WITH CLINICAL SYMPTOMS OF PE WITH AND W/O LUNG SCAN CONFIRMATION

PE diagnosis	Fragmin:288	%	Warfarin: 292	%	p-value
cPE (clinical symptoms)	13	4.5	6	2.1	<0.01 F ≤ W
PE confirmed by lung scan	2	0.69	2	0.68	z=0.0145
PE rejected by lung scan	10		3		
Lung scan not available	1		1		

From Tables EF137-4.1 and 4.2 (Vol.4, pp. 8/1/160-1).

A discrepancy between clinical symptoms and lung scan diagnosis was noted, however, the distribution of patients with scan confirmed PE and patients with missing lung scan data was identical in both groups.

d. Subgroup Analyses. Incidence of DVT in All-treated

- Elderly (>65) vs. Young (65≤). More DVT occurred in the older population (17.5%). The incidence was lower with Fragmin than with warfarin (F=13%/W=22%).
- Males vs. Females. More DVT occurred in female patients and in the warfarin group. This difference was not significant.
- Patients stratified by weight category (<80 kg vs.>80 kg). Fragmin treated patients weighing more than 80 kg had higher incidence of DVT.
- Patients with ≥2 risk factors vs. patients with <2 risk factors. Patients with two and more risk factors had significantly higher incidence of DVT (F=14% vs.9%/W=23% vs.16%). Fragmin was superior to warfarin.
- Warfarin therapeutic level stratified by positive and negative VG. Less DVT occurred in patients with PT 1.2 - 1.4 (INR 2.0 - 3.0); more DVT occurred in patients with lower or higher therapeutic level of warfarin. The majority of patients with negative VG had higher PT (>1.4) or INR (>3.0).

4.5.3 Safety Evaluation

Patients who received at least one dose of study medication were assessed for safety. Patients were monitored for bleeding, adverse events and abnormal laboratory data during the treatment period from Day 0 (pre- and post-surgery) to Day 9 (venography and discharge). During a follow-up observational period of 5-7 weeks after hospital discharge, safety information for VTE and AE was collected.

1. Hemorrhagic Events (Primary safety endpoint)

Thirty (30) Fragmin patients and twelve (12) Warfarin patients experienced one or more hemorrhagic events; this difference was statistically significant ($p=0.003$, Fisher's Exact Test). Some patients had more than one bleeding episode. One Fragmin patient (#8035) was re-operated to stop the bleeding.

The incidence of patients with hemorrhage, and site of bleeding are summarized in the following table.

HEMORRHAGIC EVENTS		Fragmin	Warfarin	p=value
Number of patients treated		274	279	
Total patients with hemorrhagic events*		30 (10.9%)	12 (4.3%)	0.003 (Fisher's Exact)
Hemorrhagic events	Hematuria@	10	8	
	Wound Hematoma	7	2	
	GI Bleed (total)	6	3	
	Operative Site/Wound	3	0	
	Wound Drainage/Hemovac	2	1	
	Re-operation due to bleeding	1	0	

From Table: Reported Hemorrhagic Adverse Events (Vol.4, p.8/1/82), and Tables AE137-3.1-3.2. *Some patients may have more than one episode. @ Some patients had urinary catheter installed.

a. Blood Loss

The mean blood loss on the day of surgery was $1,381 \pm 908$ mL for the Fragmin and $1,376 \pm 850$ mL for the warfarin group. During 1-8 days post-op., mean blood loss for the Fragmin group (219 ± 183 mL), and for the Warfarin group (225 ± 161) were similar. The two treatment groups did not differ with respect to blood loss on day of surgery ($p=0.57$) or postoperatively ($p=0.26$).

b. Patients Receiving Blood Transfusion

The number of patients receiving blood transfusion on the day of surgery was comparable between the two treatment groups (F=187 or 69.0% versus W=182 or 65.2%). However, more patients in the Fragmin group received blood transfusion in the subsequent days (F=184 or 67.8% versus W=124 or 44.5%; $p<0.001$).

c. Bleeding in Subsets of Population

There was no difference between treatment groups in any evaluation. However, patients who had revision surgery experienced more blood loss and required more blood transfusions than those who had primary operation; patients with two and more risk factors had higher blood loss and required more blood transfusion, and more wound hematomas occurred in Fragmin treated patients with 2 and more risk factors. Body weight, Gender, and Age did not show any difference in bleeding events.

2. Non Hemorrhagic Adverse Events.

Non Hemorrhagic AEs by Body System and Preferred Term (WHO-ART Dictionary)

ADVERSE EVENTS		Fragmin		Warfarin	
		N=288	%	N=292	%
Dosed		274	100	279	100
Patients with at least 1 event		250	91.2	248	88.9
Skin & Appendages	Total	39	14	47	17
	Pruritus	21	8	26	9
	Rash	14	5	16	6
Musculo-Skeletal	Postop. pain	210	77	215	77
CNS+Peripheral nerv.system	Total	59	22	63	
	Dizziness	26	9	26	9
	Hypertonia	13	5	7	3
	Hyperesthesia	12	4	8	3
Vision	Total	4	1	4	1
Hearing/ Vestibular	Total	1	0	0	0.0
Psychiatric	Total	53	19	47	17
	Insomnia	38	14	37	13

GI System	Total	146	53	147	53
	Nausea	72	26	71	25
	Constipation	49	18	47	17
	Nausea/Vomiting	30	11	37	13
Liver & Biliary	Total	1	0	0	0.0
Metabolic & Nutrition	Total	37	14	31	11
	Hypokalemia	30	11	28	10
Endocrine	Total	1	0	0	0.0
CV General	Total	37	14	37	13
Myo Endo Valve	Total	4	1	2	1
Heart Rate/Rhythm	Total	19	7	21	8
	Tachy/Bradycardia	14	6	9	3
Vascular	Total	0	0.0	1	0
Respiratory	Total	39	14	29	10
	Pharyngitis	9	3	12	4
	Dyspnoea	9	3	3	1
Platelet, Bleeding, Clotting	Total	13	5	13	5
	Purpura	7	3	7	3
	Thrombocytopenia	3	1	0	0.0
	Thrombosis	1	0	3	1
Urinary System	Total	33	12	22	8
	UTI	20	7	11	4
Body as a Whole	Total	174	64	165	59
	Wound drainage	135	49	124	44
	Oedema legs	45	16	40	14
	Pain	15	9	32	12
Application Site	Total	6	2	3	1
	Skin necrosis	3	1	2	1
	Local reaction	0	0.0	1	0
Resistance Mechanism	Total	11	4	8	3
	Infection	5	2	5	2

From Table AE137-4.2

a. Most frequent non-hemorrhagic Adverse Events

NON-HEMORRHAGIC EVENTS	Fragmin	Warfarin
Postoperative pain	210	215
Fever	135	124
Nausea	72	71
Constipation	49	47
Oedema legs	45	40
Insomnia	38	37
Nausea/Vomiting	30	37
Hypokalaemia	30	28
Dizziness	26	26
Pruritus	21	26

From Table AE137-4.3

b. Adverse Events Leading to Discontinuation

Eight patients were withdrawn (F=4 / W=4) due to AEs. One Fragmin patient (F#1162) was withdrawn on study Day 6 because of GI bleeding, one because of MI, one for postop. ileus, and one for naso-gastric tube bleeding. One Warfarin patient was withdrawn due to UA, one to chest pain, one to ileus, and one for revision surgery, Major bleedings lead to study discontinuation in two Fragmin patients.

c. Deaths

No deaths were reported during the study period.

3. Clinical Laboratory Evaluation

Laboratory Data: There was no difference between the two treatment groups with respect to the change from baseline in all three parameters of hemoglobin, hematocrit, and platelet count. However, in the Fragmin group hemoglobin was reduced by 25% (from 13 to 10 g/dL) while in the warfarin group the reduction was 15% (from 13 to 11 g/dL).

Thrombocytopenia: Eight Fragmin and 6 warfarin patients had at least one platelet count below 100,000/mm³. No cases of HIT or HITTS were reported.

4. Summary of Safety Analyses

Patients treated with Fragmin for prophylaxis of DVT and PE following hip surgery, had three times more probability to experience any hemorrhage. The majority of these events were minor and did not require medical intervention.

4.6 CONCLUSIONS

Although open-label, study 91-137 was adequate and well controlled. The data support the efficacy of Fragmin for prophylaxis of DVT (detected by VG) in patients undergoing THR. The proposed regimen of Fragmin for DVT prophylaxis appeared to be safe.

5.0 REVIEW OF STUDY D-10 (NDA/S vol. 5)

Study Title: Comparison of Fragmin and Unfractionated Heparin in prophylaxis of deep vein thrombosis and pulmonary embolism in total hip replacement.

Principal Investigator: B. Eriksson, M.D., Ostra Hospital, Gothenburg, Sweden

Study Period: The study was started in 1986 and completed in 1988. Date of the initial study report: 5-22-89; date of revised report: 3-18-96.

Study Drugs: Fragmin syringes 5, 000 IU = DxN 123, DxN 133
Heparin (KabiVitrum) syringes 5, 000 IU= DxN 120, DxN 131
Placebo syringes (NaCl 0.9%)= DxN 121, DxN 121-52, DxN 132.
Single dose syringes of 0.2 mL = 5,000 IU of Fragmin, Heparin 5.000 IU or placebo were used in the study.

5.1 OBJECTIVE OF THE STUDY

The objective of the study was to investigate the difference in prophylactic effect of low-dose heparin and Fragmin on postoperative VTE in elective hip replacement surgery. Safety was assessed for bleeding complication and transfusion requirements of each treatment group.

5.2 STUDY SYNOPSIS

This is a 1996 amended version of the D-10 study that was conducted in Sweden from 1986 to 1989. Study D-10 was initially reviewed at the time of the NDA 20-287 submission of 8-6-1992 and will be only summarized here. At the time of the NDA submission,

the study was considered to be marginally acceptable as pivotal study because of the selection of a suboptimal regimen (sc heparin) as comparator. The study was, however considered adequate to provide supportive evidence for the indication of Fragmin for thromboprophylaxis in hip replacement surgery.

The original study included 130 patients undergoing elective hip replacement surgery randomized to receive either fragmin 5000 IU sc qd starting the evening before surgery (N=65) or standard heparin 5000 IU sc tid (N=65) starting the morning before surgery.

DVTs were assessed by bilateral VG and PEs were diagnosed by perfusion/ventilation scintigraphy. Both procedures were performed about two weeks postoperatively.

Safety was assessed by measurement of blood loss, need of transfusion and recording adverse events.

There was no significant difference between the two treatment groups regarding the overall incidence of DVT (F=30.6% / H=40.3%; numerical difference not statistically significant). The frequency of proximal thrombosis was significantly lower in the fragmin group (F=5 / H=11). The frequency of PE was also significantly reduced in the fragmin group (total PE: F=12.7% / H=31.7%; p=0.011). The overall reduction of VTE in the Fragmin group was significant (p=0.033) due to the reduction of PE.

The revised D-10 study enrolled 140 patients (randomized to fragmin 70, and heparin 70). The overall incidence of DVT was not significantly different between treatment groups (29.9% in the Fragmin group and 39.1% in the heparin group), however, the incidence rates of proximal DVT and femoral DVT were significantly lower in the fragmin group (9.0% versus 26.1% for proximal DVT and 7.5% versus 18.8% for femoral vein DVT; p=0.006). There was a significant difference of incidence of clinically silent PE detected by scan (13.4% in the Fragmin group versus 27.5% in the heparin group; p=0.032).

Total blood loss and transfusion requirements were not significantly different in the two groups. A total of 20 patients reported hemorrhage (F=4, all mild / H=16, 1 severe, 15 mild). There was no significant difference of the incidence of other adverse events between treatment groups. Thrombocytopenia was not reported in either group.

5.3 SUMMARY OF THE INVESTIGATIONAL PLAN

a. Study Design

This was a single center, randomized, double-blind, two parallel groups, active treatment controlled clinical trial. A total of 136 patients undergoing hip replacement received Fragmin (N=67) or low-dose heparin (N=69) in randomized blocks of ten patients.

Fragmin and heparin were given subcutaneously for 10 days.

Efficacy was evaluated by bilateral ascending VG and pulmonary scans about two weeks after surgery. In case of death, thromboembolic events (VTE) were diagnosed by autopsy if performed.

The safety monitoring included blood loss and transfusion requirements after surgery and the decrease from baseline of hemoglobin levels at day 7 postoperatively. Platelet count was also recorded. Other complications such as wound infections, allergic reactions, pain and hematoma at the injection site were specifically looked for. The patients had a follow-up period of six weeks postoperatively.

b. Control Group

Low-dose heparin was the comparator regimen chosen in the study. The regimen of low-dose heparin administered sc is not approved for thromboprophylaxis in orthopedic surgery, but it has been widely used in the past for this indication. Furthermore, study D-10 was designed to show superiority of Fragmin vs. sc Heparin.

c. Study Population

Patients undergoing elective hip replacement surgery at one center were enrolled in the study. Eligibility criteria included hip surgery and age above 40. Exclusion criteria were history of bleeding or recent serious bleeding events, renal insufficiency, hypersensitivity to heparin, recent treatment with other anticoagulants. The patients were randomized to each treatment groups using block size of 10.

d. Effectiveness Variables

- Incidence of venous thromboembolic event (VTE) was defined as occurrence of DVT, PE or death by thromboembolism.

- VTE was confirmed by one of the following:
 - DVT diagnosed by venography (VG) 2 weeks after surgery.
 - Clinical signs of DVT, verified by VG at any time during drug prophylaxis.
 - PE diagnosed by lung scintigraphy about 2 weeks after surgery.
 - Clinical signs of PE documented by lung scintigraphy at any time during the study period.
 - Clinical signs of VTE and/or PE verified at any time between the 2 weeks VG/lung scan examinations and the six weeks follow-up visit.
 - Autopsy verified DVT of PE.

VGs were analyzed twice by two experienced radiologists. Proximal DVT included thromboses of the femoral and iliac veins. Thromboses of the muscular veins, tibial and fibular veins and popliteal veins were defined as distal DVT.

Perfusion lung scans were performed immediately before the VG; ventilation scans and chest radiography were performed on the following day in every patient, except for patients with normal perfusion scans. Only high probability scans was classified as PE. The scans were evaluated blindly by an expert reader.

e. Safety Variables:

- Hemorrhage: The following were recorded in all patients:
 - Blood loss during operation estimated by the anesthetist (mL).
 - Post-operative blood loss measured daily from suction drain bottles.(mL)
 - Transfusion requirements in blood units.(changed to mL)
 - Hemoglobin level at baseline and one week postoperatively.
- Platelet count was measured postoperatively and one week after surgery.
- Adverse Events
 - Hemorrhagic: Excessive bleeding, wound hematoma, hematoma at site of injection, reoperation due to bleeding.
 - Non-Hemorrhagic: Deep and superficial wound infections. Pain at the injection site; Allergic reactions.
- Anti-Xa, t-PA and PAI-1 activity and antigen were analyzed.

f. Disposition of Patients

The following information was collected at baseline or during the study:

- Demographics.
- Risk Factors for thromboembolism following hip replacement, including:
 - Time between the first dose and surgery
 - Factors related to the surgical procedure: anesthesia, prosthesis, dextran-70 during surgery.
- Concomitant Medication, particularly ASA and NSAIDs within seven days prior to operation.
- Dropouts, Protocol Violations, Study Discontinuation.
- Deaths.

5.4 Statistical Methods

a. Statistical Analyses of Efficacy and Safety

The proportions of DVT, PE and both in each of the treatment groups were compared using the two-tailed Fisher's exact test. Two-sided 95% CI were calculated for the difference of proportions.

Statistical analyses were applied to the safety variables blood loss and transfusion volumes. The change of hemoglobin level from Day -1 to Day- 7 was also analyzed. The Wilcoxon rank sum (non-parametric test) was chosen for the comparison of treatments.

b. Sample Size

The original sample size of 120 patients was based on the expected rate of VTE of 45% for heparin and 20% for Fragmin (two-sided $\alpha = 0.05$ and power 80%). An interim analysis was performed when 2/3 of patients had been included because the observed high frequency of VTE in the fragmin group. The level of significance was decreased from 5% to 4.7%, and the sample size was increased by 20 patients per group because of the interim analysis.

5.5 STUDY RESULTS

5.5.1 Patient Disposition

The number of patients for each study populations were as follows:

- Randomized (ITT):	140	F=70	H=70
- All-treated patient population:	136	F=67	H=69
- Per-protocol population:	129	F=65	H=64
- Evaluable patient population:	125	F=63	H=62

The All-treated patient population was defined as the operated patients who had received at least one dose of study medication.

One hundred twenty-nine (129) patients completed the study as scheduled. Eight patients discontinued the study because of patient wish (2 heparin patients); poor compliance (1 Fragmin, 2 heparin); therapy failure (1Fragmin); adverse event (2 Heparin). The Per-Protocol (P-P) population included 129 patients (92.8% of ITT population). The evaluable patient population included a total of 125 patients (F=63/H=62).

There was no significant difference between treatment groups with regard to baseline demographics and risk factors.

5.5.2 Efficacy Assessment

Efficacy analyses were performed on the all-treated patient and in the Per-Protocol patient populations.

a. Primary Efficacy Results

1) Incidence of VTE

The primary efficacy variable was incidence of VTE (DVT, PE or death by TE). Only one patient died during the treatment period (pt#1051) and autopsy revealed no thrombosis.

The efficacy data for the All-treated population are summarized in the following table.

INCIDENCE OF VTE. ALL-TREATED PATIENT POPULATION

Event	Fragmin		Heparin	
	N=67	%=100	N=69	%=100
Missing	4	6.0	7	10.1
DVT or sPE	20	29.9	27	39.1
DVT only (VG)	11	16.4	8	11.6
sPE only (lung scan)	1	1.5	2	2.9
DVT and sPE	8	11.9	17	24.6

From Table Thromboembolism 9C1.1 and 9C1.2 (Vol.5, pp.8/2/120-21).

The overall incidence rate of VTE (DVT/PE) in both treatment groups was 34.6%. This rate was higher than expected due mostly to the high incidence of PE diagnosed by lung scans. In this study, popliteal DVT were considered distal DVT.

The incidence of DVT in the P-P population and the DVT sites are summarized in the following table.

INCIDENCE OF DVT PER LOCATION. PER-PROTOCOL PATIENT POPULATION

DVT		Fragmin		Heparin		p-value
		N=67	%	N=69	%	
DVT total		19	28.4	25	36.2	
Proximal	Total	6	9.5	18	26.1	0.010*
	Femoral	5	7.5	13	18.8	0.006*
Distal	Total	13	20.6	7	11.2	z=0.838
	Popliteal	1	1.5	2	2.9	N.S.

From Table: 9C1.6 (Vol.5, pp.8/2/129-30).

These data show that fragmin was superior to low-dose heparin for the incidence of proximal (femoral) DVT.

2) Incidence of sPE

The incidence rates of PE detected by lung scans are summarized in the following table.

INCIDENCE OF SCAN PE (sPE). ALL-TREATED PATIENT POPULATION

Pulmonary Embolism	Fragmin		Heparin		p-value
	N=67	%	N=69	%	
Missing Data	2	3.0	7	10.1	N.A.
sPE	9	13.4	19	27.5	0.032

The high incidence of PE in this study is due to the detection by routine lung scans. A statistically significant difference was noted between sPE in Fragmin and Heparin groups.

3) Primary efficacy variable statistical analysis

The results are summarized in the following Table.

SUMMARY OF TEST RESULTS: PRIMARY ANALYSIS OF EFFICACY. EVALUABLE PATIENT POPULATION

Event	Fragmin		Heparin		Fisher's Exact 2-tailed test
	N = 65	%	N = 62	%	
Total VTE	20	31.7%	27	43.5%	0.199
DVT	19	30.1%	25	41.6%	0.194
sPE	9	13.8%*	19	30.6%*	0.032*
Proximal DVT (femoral)	6	9.5%*	18	30.0%*	0.006*
95% Confidence intervals (95% CI)					
Event	Fragmin		Heparin		Difference
VTE	0.21, 0.45		0.31, 0.57		-0.05, 0.29
DVT	0.19, 0.43		0.29, 0.55		-0.05, 0.28
sPE	0.07, 0.25		0.20, 0.44		0.03, 0.31*
Proximal DVT (femoral)	0.04, 0.20		0.19, 0.43		0.07, 0.34*

* = Significant difference. PE diagnosed by lung scans.

Both statistical methods, the Fisher's Exact test and the CI demonstrated a statistically significant difference between treatment groups for sPE and proximal DVT.

5.5.3 Safety Assessment

Safety was evaluated as:

- Extent of Exposure
- Adverse Events (hemorrhage, infection, other)
- Study Discontinuation and Deaths.
- Change of Clinical Laboratory values.

Statistical analyses were applied to the safety variables blood loss and transfusion requirements.

1. Extent of Exposure

On the average, 98.6% patients were exposed for 96% of days of therapy with 95% total active dose or placebo and with 94.8% of planned injections. There was no statistically significant difference between study treatments with regard to study drug exposure. The mean duration of therapy was 10.6 ± 1.9 days for the Fragmin group and 9.6 ± 1.7 days for the heparin group.

The number of patients exposed to the first injection of study medication close to the time of operation (fragmin <6 h preop. or heparin <1.5 h preop.) was similar in the two groups.

2. Hemorrhage

Hemorrhage was analyzed as BLOOD LOSS and TRANSFUSION VOLUMES used. The data are summarized in the following table.

BLOOD LOSS AND TRANSFUSION REQUIREMENTS. ALL-TREATED POPULATION

Parameter		Fragmin, N=67	Heparin, N=69	p-value
Blood Loss (mL)	median (range)	1280 (410 - 3190)	1400 (870 - 8950)*	0.0076
Transfusion (mL/U)	median (range)	900 (450 - 4500)	1350 (450 - 9450)	0.0002

From Table: Analysis of Adverse Events, Vol.5, p.8/2179. * = mostly because of loss during operation

Compared to the heparin group, there was significantly less total blood loss in the fragmin group, as well as a significantly less need for transfusion. It is of note, however, that the difference in transfusion requirement is enhanced by the method of assessment, i.e., mL of blood transfused rather than units of blood or packed RBC transfused, or proportion of patients transfused.

No difference was noted between the two treatment groups for risk factors for bleeding (i.e., use of ASA or other NSAIDs). However, five patients received heparin close to the surgical operation.

3. Adverse Events

Adverse events other than bleeding were rare. Total hemorrhagic events occurred in 4 patients in the Fragmin group (all mild) and in 15 patients in the heparin group (1 event was severe).

In the heparin group, four heparin patients experienced wound infection, one patients experienced cerebral infarction and three had hip luxation.

The statistical analysis of the overall incidence of adverse events showed significant difference in favor of patients receiving fragmin (p=0.007).

Serious AE, AE leading to discontinuation, and Clinical Laboratory Results did not show treatment differences.

Only one patient died in the fragmin group.

5.6 CONCLUSION

Study D-10 was initially reviewed at the time of the NDA 20-287 submission on 8-6-1992. Although at that time the study was planned and submitted as an adequate and well controlled clinical trial, it was considered to be marginally acceptable as single pivotal study because of the selection of a suboptimal regimen (sc heparin) as comparator and because the second pivotal study in hip replacement surgery (D-4) was unacceptable. Study D-10 was, however considered adequate to provide supportive evidence for the indication of Fragmin for thromboprophylaxis in hip replacement surgery when combined with the pivotal study 91-137.

Study D-10 indicates that Fragmin was superior to Heparin in prophylaxis of proximal DVT (mostly in the perioperative hip region) and of PE (as detected by lung scans). No statistically significant difference was observed between treatment groups for the incidence of symptomatic DVT and/or PE.

Compared to other studies, the observed incidence of VTE and DVT in study D-10 was high in both treatment groups (F=31.7%/H=43.5% for VTE and F=30.1%/H=41.6% for DVT). This finding was attributed to the increased sensitivity of the methods of detection of thrombosis used: ascending VG which visualized thrombosis in superficial and deep proximal veins of the hip region and mandatory lung scans in asymptomatic patients.

Safety, assessed as hemorrhagic and non-hemorrhagic adverse events, was comparable between two treatment groups.

6.0 INTEGRATED SUMMARY OF EFFICACY

A total of 1,244 hip replacement patients were enrolled in 6 studies. All received anticoagulation before surgery according to various dose regimens and schedules of administration. Five regimens of Fragmin, two regimens of Heparin and one of Warfarin were used in the clinical trials. The regimens are summarized below.

APPEARS THIS WAY ON ORIGINAL

STUDY DRUG REGIMENS

Fragmin:

- 2500 U 2h before surgery followed by 2500 U within 24h, then 5000 U q.d. for 5-9 days. 292 patients treated in study 91-137
- 5000 U in the evening before surgery, then 5000 U q.d. for 10 days. 67 patients treated in study D-10
- 2500 U 2h before surgery, 2500 U 12h after surgery, then 2500 U q.d. for 10 days. A total of 205 patients were treated in studies E-4, E-5, and E-8.
- 2500 U 2h before surgery, 2500 U 12h after surgery, then 2500 U q12h for 9-13 days. 41 patients were treated in study E-8.
- 2500 U 2h before surgery followed by 5000 U q.d. for 9-13 days. 42 patients were treated in study E-8.

Heparin:

- 5000 IU 2h before surgery, followed by 5000 IU q12h for the duration of Fragmin therapy. 41 patients were treated in study E-8
- 5000 IU 2h before surgery, followed by 5000 IU t.i.d for the duration of Fragmin therapy. 268 patients were treated in study D-10, E-4, E-5 and E-7.

Warfarin

- Warfarin was the control drug in 288 patients in study 91-137. The initial dose was 5 or 7.5 mg before surgery and within 24 hours after surgery; the dose was subsequently adjusted to maintain INR 2.5.

Anticoagulation was well tolerated for up to 14 days after surgery. In one study (E-7), Warfarin maintenance therapy followed successful prophylaxis.

a. Summary of efficacy of all controlled studies

Efficacy data from several controlled clinical trials were provided to support the claim that Fragmin is superior or equivalent to low-dose Heparin for thromboprophylaxis in patients undergoing hip surgery.

The data from these studies and from the two pivotal trials are summarized in the following Table.

CLINICAL STUDIES TO SUPPORT EFFICACY OF FRAGMIN FOR THROMBOPROPHYLAXIS IN HIP SURGERY

STUDY	DESIGN/PATIENTS	DOSE	EFFICACY	SAFETY
PIVOTAL STUDIES				
91-137 U.S. 05/92-03/95 Hip replacement	Multicenter[8], open-label, randomized, two parallel group: fragmin vs. warfarin. Randomization prior to surgery. Total:580. F:292; W:288	F: 2500 preop. and 2500 within 24 hours, followed by 5000 q.d. W: 5 or 7.5 mg preop and same within 24h, followed by warfarin adjusted to INR 2.5	Endpoint: venography (blinded) after 1-9 days of surgery. ITT and PP. PP-DVT F: 28/192(15%) W:49/190(26%) p=0.006	1. AE⇒disc F:3(1 related) W:3 2. Hemorrhage: F>W majority= minor
D-10 Sweden 11/87-06/89 Hip replacement	Single-center, randomized, double-blind, two parallel group:fragmin vs. heparin sc. Total:136. F:67; H:69	F: 5000. Start evening before surgery H: 5000 t.i.d. Start 2h before surgery	VG and scan day 10 F:20/63(31.7%); H:27/62(43.5%) p=0.199 sPE=H>F p=0.032	blood loss H<F Overall AE H>F
SUPPORTIVE STUDIES. Meta-analysis				
E-4 France 10/85-08/86 Hip replacement	Single center, open-label, randomized, two parallel groups: fragmin vs. heparin Total:80. F:40;H:40	F:2500 2h before surgery, 12h after, and 2500 q.d. for 10 days H:5000 2h before surgery, then q8h	VG, PE-scan DVT after 10 days F:7/40(17.5%) H:4/40(10.0%) p=0.33 PE=5(F=3/H=2)	Blood loss in drainage H>F. Transf: H=F
E-5 Spain 01/88-01/91 Hip replacement	Multicenter (6), open-label, randomized, two parallel group: fragmin vs. heparin Total:229. F:117; H:112	F:2500 2h preop, then q12h for 10-15 days. H: 5000 2h before surgery, then q8h	VG: DVT after 10-15 days F:15/74(20.3%) H:9/68(13.2%) PE=3(H=2/E=1)	Blood loss for 7 days: H=F
E-7 Germany 7/84-4/86 Hip replacement	Single center, open-label, randomized, parallel group: fragmin vs. heparin Total:95. F:48;H:47	F:2500 2h preop, 12h after, and 2500 q.d. for 7 days. H:5000 2h preop, then q8h. FUP: warfarin	Fibrinogen uptake test F:7/48(14.6%) H:7/47(14.9%) Phlebography (only 8) H:3/4; F:0/4	Intraoperative blood loss, required transf. H=F
E-8 France 09/85-04/87 Hip replacement	Single center, open-label, randomized, three parallel group: fragmin 1&2 vs. heparin. Total: 124. F1:42;F2:41;H:41	F1:2500 2h preop., 12h after, then q12h for 9-13 ds. F2: same for 2 days, then 5000 q.d. H:5000 2h preop,q12h.	Fibrinogen uptake test after surgery + end F1:2/38(5.3%) F2:3/39(7.7%) H:4/38(10.5%) No PE	Intraoperative blood loss and transfusion requirements F1=F2=H

F= fragmin; H= heparin; W= warfarin; ITT= intent-to-treat; PP= per-protocol; [8]= number of centers; >= superior to; = = equal to; FUP = follow-up period; AE = adverse event.

Efficacy was assessed as incidence of VTE (DVT, PE, death by thromboembolism, or any combination).

Incidence of DVT was assessed as incidence of symptomatic DVT, or DVT found on venography performed at discharge (Study 91-137, D-10, E-4, E-5, E-7). Fibrinogen uptake test was used in study E-7 (with venography) and E-8.

Incidence of PE was assessed as incidence of symptomatic PE, and of pulmonary microembolism as found on pulmonary scan performed at the end-of-study (Study D-10).

No patient died of thromboembolic complication.

Five fragmin regimens were compared with two heparin and one warfarin regimen for prophylaxis of thromboembolism in hip replacement surgery.

Overall efficacy assessment in those studies was based on rejecting the null hypothesis of equivalence between Fragmin and the control drug regimen for postoperative prophylaxis of DVT and PE. In comparison with low-dose heparin this hypothesis could not be rejected in E-4, E-7 and E-8 suggesting comparable efficacy of Fragmin and low-dose Heparin. The hypothesis was rejected in D-10 and E-5 suggesting different efficacy. In E-5 a low-dose Heparin regimen was more efficacious than fragmin. In the two pivotal studies 91-137 and D-10, Fragmin was superior, although marginally to Warfarin (91-137) and low-dose heparin (D-10). In D-10 Fragmin was also superior to low-dose Heparin for prevention of pulmonary microembolism (scan-detected PE).

In summary, these studies indicate that Fragmin is either comparable or better (with some exceptions) than the low-dose heparin or warfarin for thromboprophylaxis in patients undergoing hip replacement surgery.

b. Summary of efficacy analyses in two pivotal studies.

The two pivotal studies assessed different efficacy endpoints. In study 91-137 the primary efficacy variable was the incidence of DVT in the per-protocol patient population whereas in study D-10 efficacy was assessed in the all-treated population. The second primary efficacy endpoint in the D-10 study was the incidence of PE as detected by lung scan at the end of the study. DVT in the popliteal vein was considered proximal in 91-137 and distal in D-10. In study 91-137, superficial vein thromboses were also recorded.

In the two pivotal clinical trials, the overall efficacy of Fragmin was superior to that warfarin and heparin respectively.

The efficacy results of each study are summarized in the following table.

Study 91-137PRIMARY EFFICACY ENDPOINT: RATES OF VERIFIED DVT AND SUPERFICIAL VEINS THROMBOSIS IN P-P POPULATION¹.

DVT Location	Fragmin		Warfarin		P=value
	N=192	%	N=190	%	
Any Deep Vein Thrombosis (total DVT)	28	14.6	49	25.8	0.006*
Any Superficial Vein Thrombosis**	23	11.9	43	22.6	0.005*
Superficial and deep venous thrombosis	51	26.5	92	48.4	<0.001*
Distal DVT (Calf): Total	21	10.9	43	22.6	0.005*
Proximal DVT (Leg): Total	10	5.2	16	8.4	0.185

* Significant difference.

** Superficial vein category (not in the protocol). Some DVT may have been counted in more than one location.

Study D-10

SUMMARY OF TEST RESULTS: PRIMARY ANALYSIS OF EFFICACY. EVALUABLE PATIENT POPULATION

Event	Fragmin		Heparin		Fisher's Exact 2-tailed test
	N = 65	%	N = 62	%	
Total VTE	20	31.7%	27	43.5%	0.199
DVT	19	30.1%	25	41.6%	0.194
sPE	9	13.8%*	19	30.6%*	0.032*
Proximal DVT (femoral)	6	9.5%*	18	30.0%*	0.006*

* = Significant difference. PE diagnosed by lung scans.

The secondary efficacy analyses show that fragmin was superior to warfarin in all categories except "proximal" veins, and superior to low-dose heparin in some, but not the "any DVT" category.

Superficial vein thromboses were visualized at the hip region where surgically-related trauma may have contributed to their development. This category of VTE was analyzed separately from DVT in study 91-137, but it was included into assessment of DVT in the study D-10. When superficial vein thromboses were excluded from "any DVT" in study D-10, the percentages of DVT incidence in Fragmin and low-dose Heparin treatment groups were similar to those in study 91-137. The revised statistical analysis of study D-10 confirmed the superiority of the Fragmin regimen.

c. Conclusion on Efficacy

The data provided by the pivotal studies and by the supportive studies (Fragmin vs. heparin or vs. Warfarin) indicate that Fragmin is effective for prophylaxis of postoperative DVT/PE in hip surgery. Based on these data, it can be concluded that the

administration of Fragmin in hip surgery provides protection for patients against postoperative DVT and PE which is at least as effective well as that of the comparator drugs: low-dose Heparin or Warfarin.

7.0 INTEGRATED SUMMARY OF SAFETY

The sponsor has submitted two documents for assessment of Fragmin safety. This supplement (NDA#20-287/S-008) with a cut-off date 04/17/97, and the Safety Update to cover a period from 07/01/95 to 02/28/97. The updated safety data provided in the two documents were compared to the safety data described in the current Fragmin Package Insert.

Prior Safety Updates were submitted November 5, 1993, November 17, 1994, and January 1, 1996, and in NDA #20-287. The most recent 4-Month Safety Alert Report is reviewed separately.

7.1 Summary of Safety Data in Supplement NDA 20-287/S-008.

This submission contains safety information from 11 clinical trials: 91-137, D-10, D-4, D-16, E-4, E-5, E-6, E-7, E-8, E-9 and E-10. Pertinent information for studies, 91-137, D-10, E-4, E-5, E-7 and E-8, were included with the table on page of this review.

A total of 1893 patients were randomized in the 11 trials and 1916 of them (95.6%) were treated. Fragmin was administered to 908 patients, Heparin to 469 patients, Dihydroergotamine with Heparin to 124 patients, Dextran-70 to 50 patients, Warfarin to 288 patients and placebo to 101 patients.

The majority of patients received Fragmin as single daily injection of 5000 U (9730 patients), while others received the same dose split in two daily sc injections of 2500 U.

The safety information for studies D-4, D-16, E-6, E-9, and E-10 are summarized in the following table.

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CLINICAL STUDIES SUBMITTED FOR SAFETY EVALUATION ONLY

STUDY	DESIGN/PATIENTS	DOSE
D-4 Denmark, 6/92 HR or hip fracture	Randomized, double-blind, parallel group, placebo-controlled Pts: 202. F:101. PL101.	F:2,500 pre- and post-op; 5000 for 6 days. Pl: sc for 6 days
D-16 Spain, (1982) Hip fracture	Randomized, double-blind, parallel-group, heparin controlled. Pts:96. F:46. H:44	F:2500 pre-op, 5000 for 9 days. H: 5000 pre-op, 5000 tid for 9 days.
E-6 Germany, HR	Randomized, open-label, parallel group, heparin/DHE Pts:130. F:66.H:64	F:2500 pre- and post-op, 5000 for 8 (7-10) days. H:5000 pre- and post-op 5000 bid for 8 days. DHE:0.5 mg with H.
E-9 Sweden HR	Randomized, open-label, parallel-group dextran-70 control. Pts:101. F:51.Dx:50	F:2500 pre- and post-op 2500 bid for 6 days. Dx (iv): 500 mL pre- and post-op. 500 mL bid.
E-10 Germany Leg surgery+HR	Randomized, open-label, parallel-group, heparin/DHE control Pts:120. F:60.H:60	F:2500 pre- and post-op, 5000 for 10-14 days. H:5000 pre- and post-op, 5000 bid. DHE:0.5mg with H.

HR= hip replacement. F= fragmin. H= heparin. Pl= placebo. DHE= dihydroergotamine.

The adverse events described in the ISS consist mainly of hemorrhagic events, including:

Blood Loss:

In five studies (91-137, D-4, E-5, E-6, and E-8), mean perioperative blood loss was larger in fragmin treated patients than in controls. However, the difference was calculated in mL and was not statistically significant. In the remaining six studies the opposite was noted. In conclusion, blood loss was almost equal in both treatment groups.

Blood Transfusions:

The majority of patients received transfusion only on the day of surgery. The percent of patients who received transfusion varied among studies from 30%-100% (day of operation), but there was no significant difference between patients in two treatment groups. Mean transfusion requirement was (mean of means) 868.28 ± 473 for Fragmin and 891.96 ± 526 for the control drug treated groups.

Wound Hematoma:

The incidence of wound hematoma was slightly higher in fragmin than in control drug groups in 9 studies. The difference was never significant.

Re-Operation or Evacuation of Hematoma:

This intervention was required in 4 patients, 2 on Dextran, 1 Fragmin and 1 randomized to Heparin.

Hematoma at Injection Site:

In three studies (D-10, E-5, and E-7) once daily Fragmin was compared to BID or tid heparin. In all studies, the incidence of this event was higher in Heparin-treated patients. However, if corrected for frequency of drug administration, Fragmin showed more frequent injection site hematoma. Neither difference reached any statistical significance.

Deaths and Premature Withdrawal due to Adverse Events:

A total of 12 deaths occurred in all studies (F=5, H=4, Pl=3). Ten of them occurred in hip fracture studies. Two deaths occurred in the elective hip surgery (F=1/H=1). None of deaths was related to study medication, except one patient (D-6 study) on heparin who had acute GI bleeding from peptic ulcer (autopsy finding).

A total of 27 withdrawals including 12 deaths was recorded in 11 studies. Four premature withdrawals due to hemorrhagic adverse events occurred in the fragmin treated group. No other withdrawal was clearly related to any study medication.

Laboratory Data:

There were no unexpected or unexplained changes in laboratory values in any of the studies. A postoperative transient reactive increase in platelet count was seen in many patients.

Subset Analyses:

Data regarding blood loss, patients requiring blood transfusions, amount of blood transfused, and patients with adverse hemorrhagic events were examined and compared in elderly vs. young, male vs. female, patients with ≥ 2 vs. < 2 risk factors. The results show some trends (patients with ≥ 2 risk factors). Patients with revision surgery had more blood loss, more transfusion requirements, and hemorrhagic adverse events. No significant difference between treatment groups was found.

Thrombocytopenia:

Thrombocytopenia was reported only in E-5 (8 cases=3/H=5). One heparin patient had HITT. In other studies thrombocytopenia was either non recorded or not reported.

Conclusions on Safety

The data support the safety profile of Fragmin as presented in the original NDA. No changes in the Labeling pertaining to safety information are required based on this NDA Supplement.

7.2 Four-month Safety Update (SE1/008/SU submitted on 8/18/97)

This is the third Safety Update since the original submission of NDA 20-287. It covers a period between 07/01/95 and 02/28/97.

Integrated safety data from 24 trials of thromboprophylaxis (15 in general surgery and 9 in orthopedic surgery) were included in the Safety Update for the period ending on April 30, 1993 and submitted on November 5, 1993.

New safety data from 19 trials that were ongoing at the time of the previous Safety Update, and data from 5 trials that were initiated after this date, are included in this submission. Updated information on serious adverse event is summarized in the following table.

The submission also contains updated information on serious adverse events reported to a central database, an updated post-marketing safety experience in countries where Fragmin has been marketed, and literature reports relevant to the safety of Fragmin.

The new safety data are consistent with those reported in the Safety Updates submitted November 5, 1993, November 17, 1994 and January 11, 1996. No unexpected adverse event occurred and no increased frequency of expected events have been recorded.

APPEARS THIS WAY ON ORIGINAL

Summary of serious Adverse Events from 19 ongoing and 5 new Fragmin trials

INDICATION	STUDY	SAFETY CONCERN
Orthopedic	91-137 (PIVOTAL) 90-065 93-Frag-016	No new concerns
Myocardial infarction	90-044 92-Frag-012	No new concerns
Unstable Coronary Artery Disease	91-115 91-128 95-Frag-025	No new concerns
PTCA	90-014	No new concerns
DVT Treatment	91-030 91-051 91-196	No new concerns
PE Treatment	90-129 91-134	No new concerns
Prolonged Thromboprophylaxis Following Orthopedic Surgery	91-139, 91-064 93-Frag-015 93-Frag-016	No new concerns
Thromboprophylaxis in total knee replacement	91-138	No new concerns
Thromboprophylaxis in pregnancy	92-Frag-008	No new concerns
Other Indications	Tendonitis (90-118, 90-134) Stage II arteriopathy (92-Frag-002) Peripheral bypass for limb ischemia(95-Frag-024) Children undergoing hemodialysis (92-Frag-010). Chronic hemodialysis (92-Frag-013). Medical patients (95-Frag-023)	No new concerns

From: Safety Update (Vol.1, pp.9/1/1-56), and Clinical Trial Synopses (Vol.1, pp.9/1/58-107) . No new concerns = The new information did not add to the already known safety issues covered in the current Labeling.

7.3 Post-Marketing Surveillance

A total of 304 spontaneous adverse event reports had been received prior to February 28, 1997. These reports included 374 adverse events.

Forty-seven new reports were of thrombocytopenia. In four cases other Heparins were given before or concomitantly with Fragmin, and in three cases thrombocytopenia occurred prior to Fragmin. In 15 cases antibodies against heparin-PF4 were documented. Twelve of them were without any previous exposure to heparins.

7.4 Review of Literature

This periodical review includes summary of 39 articles published elsewhere. Original clinical data appeared in 21 articles.

The reports were on thromboprophylaxis in surgery, orthopedic surgery, in stroke, in urologic surgery, in pregnancy, treatment of DVT, treatment of massive PE, in venous access devices; prevention of thrombosis after stent implantation, anticoagulation and MI, effects on hemostasis in by-pass surgery, anticoagulation and unstable CAD, and anticoagulation and hemodialysis.

There were three case reports: 1) cross reactivity of fragmin in heparin-induced HIT, 2) a vertebral fracture in long-term treatment of a female with acute leukemia, and 3) skin necrosis after short-treatment with heparin followed by fragmin in a patients with cancer and massive DVT.

8.0 SUMMARY AND CONCLUSIONS

Fragmin® Injection (dalteparin sodium) is a low-molecular-weight Heparin developed in Europe [REDACTED] twelve years ago first approved in Germany in 1985.

Currently, Fragmin is authorized for use in 44 countries for thromboprophylaxis, hemodialysis, and treatment of DVT. In the U.S., Fragmin is approved for thromboprophylaxis in patients undergoing high risk abdominal surgery.

Since the first approval (Germany, 1995) approximately 22 million patients have been treated with Fragmin.

The current sponsor, Pharmacia & Upjohn, has submitted an NDA efficacy supplement for Fragmin for the new indication of thromboprophylaxis in hip replacement surgery.

Two adequate and well controlled clinical trials (91-137 and D-10) provide substantial evidence that Fragmin is an effective agent for prophylaxis of postoperative DVT and PE in patients undergoing hip replacement surgery. In both trials, Fragmin was found to be superior (although marginally) to warfarin (study 91-137) and low-dose subcutaneous Heparin (study D-10).

According to data presented in this supplement, patients receiving Fragmin may experience more hemorrhagic episodes, and more severe events than patients on Warfarin, but not more than patients on Heparin. The most frequent hemorrhagic adverse event of Fragmin was injection site hematoma.

HIT (heparin induced thrombocytopenia) occurred rarely, one case in the two trials. There was no other adverse event that can be attributed to Fragmin specifically.

All other reported adverse events were those commonly seen postoperatively, and were comparably distributed among the three treatment groups.

The overall safety of Fragmin in both trials was comparable to that of the control drug.

Several (11) studies were added to this supplement to support efficacy and safety of the proposed fragmin prophylaxis in hip surgery. Although Fragmin was given in different regimens, to relatively small number of patients, and in open-label fashion, these studies, together with the pivotal two, support the sponsor's claim.

Notably, no increased frequency of expected adverse events and no new serious and unexpected adverse event emerged from the studies involving more than 900 patients treated with Fragmin in the clinical trials nor from the Safety Update report submitted on 8-18-1997. Major hemorrhage was a rare event, as well as heparin-induced thrombocytopenia.

The efficacy of Fragmin was superior to that of control regimens (low dose Heparin or Warfarin) in two pivotal studies. The claim of Fragmin safety is supported by its tolerability in approximately 1000 patients who received Fragmin for prophylaxis of VTE in orthopedic surgery.

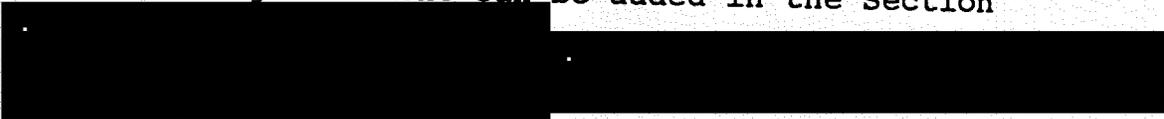
In conclusion, the efficacy and safety data obtained from two pivotal trials 91-137 and D-10 support the conclusion that the risk/benefit for Fragmin for the proposed indication of prophylaxis of DVT and PE in patients undergoing hip surgery is favorable.

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9.0 RECOMMENDATION

Based on the evidence presented in this supplement I would recommend Fragmin to be approvable for the new proposed indication of thromboprophylaxis in hip replacement surgery.

The Labeling for Fragmin® Injection is **APPROVABLE** with the following changes:

- a. The efficacy results of the two pivotal trials of Fragmin in hip replacement must be included in the "Clinical Trial" section.
- b. The following statement can be added in the Section

- c. The sponsor's dosing recommendations should be added in the Section "ADMINISTRATION AND DOSING".

/s/ 

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Center for Drug Evaluation and Research

CC:
NDA 20-287
HFD-180
HFD-10/LTalarico
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020287/S008

CHEMISTRY REVIEW(S)

BEST POSSIBLE COPY

CHEMIST REVIEW #1		1. <u>Organization:</u> HFD-180	2. <u>NDA Number:</u> 20-287
3. <u>Name and Address of Applicant (City & State):</u> Pharmacia & Upjohn 7000 Portage Road Kalamazoo, Michigan 49001-0199		4. <u>AF Number:</u> JUL 22 1997. Supplement(s)	
6. <u>Name of Drug:</u> Fragmin ® Injection		7. <u>Nonproprietary Name:</u> dalteparin sodium	Number: SE1-008 BC Dates: 16 APR 1997 12 JUN 1997
8. <u>Supplement Provides for:</u> a new indication, thromboprophylaxis in patient's undergoing hip replacement surgery.		9. <u>Amendments and Other (Reports, etc.) D.</u>	
10. <u>Pharmacological Category:</u> anti-coagulant	11. <u>How Dispensed:</u> RX <u>XX</u> OTC <u> </u>	12. <u>Related IND/NDA/DMF(s):</u> DMF [REDACTED] DMF [REDACTED] DMF [REDACTED] DMF [REDACTED]	
13. <u>Dosage Form:</u> Injection (SVP)	14. <u>Potency:</u> 2500 IU and 5000 IU (anti-Factor Xa) per 0.2 mL PFS	15. <u>Chemical Name and Structure:</u> See NDA 20-287, Chemistry Review #1.	
		16. <u>Records and Reports:</u>	
		Current <u> </u> Yes <u> </u> No	
		Reviewed <u> </u> Yes <u> </u> No	
17. <u>Comments:</u> S [REDACTED]			
cc: Original NDA 20-287 (S-008) HFD-180/Div/File HFD-180/CSO/KOliver HFD-180/LTalarico HFD-180/JSieczkowski			
Drafted by: Joseph Sieczkowski/7-15-97/WP; c:\wpfiles\chem\S\20287008.1JS Initialed by: E Duffy/ [REDACTED] JS dob DRAFT 7-15-97/F/T 7-17-97 final: [Signature]			
18. <u>Conclusions and Recommendations:</u> From a chemistry viewpoint, it is recommended that the supplement be approved. The R.H. Project Manager should convey to the applicant the acceptability of this application from a chemistry viewpoint.			
19. <u>Reviewer</u>			
Name:	Signature:		Date Completed:
Joseph Sieczkowski, Ph.D.	[REDACTED] JS		7-18-97 July 11, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020287/S008

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT
FOR
FRAGMIN®
(dalteparin sodium)
INJECTION
NDA 20-287/S-008

Division of Gastrointestinal and Coagulation Drug Products
HFD-180
Food and Drug Administration
Center for Drug Evaluation and Research

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-287/S-008
Fragmin® (dalteparin sodium) Injection

A new indication, thromboprophylaxis in patients undergoing hip replacement surgery.

The National Environmental Policy Act of 1969 (NEPA) requires all federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center of Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Fragmin® Injection, Pharmacia & Upjohn Company has prepared an environmental assessment in accordance with 21 CFR 25.31a(b) (5) *True* which evaluates the potential environmental impacts of the manufacture, use, and disposal of the drug product.

In support of their supplemental new drug application (SE1-008), Pharmacia & Upjohn & Upjohn Company has referenced the original EA and provided the following important additional revision to the NDA EA:

A new indication, Fragmin Injection for thromboprophylaxis in patients undergoing hip replacement surgery.

The new EA information does present new information on the manufacture of dalteparin sodium in that dalteparin is a depolymerized heparin (from porcine intestinal mucosa) obtained by sodium nitrite oxidation followed by sodium borohydride reduction. The Fragmin® Injection information remains the same with respect to the formulation.

Approval of the supplemental application will make prophylactic therapy available to a larger group of patients as reflected in the revised indication:

FRAGMIN® Injection is indicated for prophylaxis against deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing hip replacement surgery. FRAGMIN® is also indicated for prophylactic use in abdominal surgery patients at risk for thromboembolic complications.

The drug product will be used in hospital settings for in-patient and out-patient treatment. Disposal is by hospitals as medical waste and returned or damaged product as medical/hazardous waste. The fate and effects of dalteparin sodium remain unchanged from the original EA. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

APPEARS THIS WAY ON ORIGINAL

BEST POSSIBLE

July 18, 1997
DATE

/S/ [Redacted]

PREPARED BY: [Signature]
Joseph Sieczkowski, Ph.D.
Review Chemist
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
Office of New Drug Chemistry II, HFD-820

7/22/97
DATE

/S/ [Redacted]

DIVISION CONCURRENCE:
Eric P. Duffy, Ph.D.
Chemistry Team Leader
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
Office of New Drug Chemistry II, HFD-820

7/26/97
DATE

/S/ [Redacted]

APPROVED: [Signature]
Nancy B. Sager
Environmental Scientist, HFD-357
Center for Drug Evaluation and Research

Attachment:
Environmental Assessment Material Safety Data Sheet (Drug
Substance).
Environmental Assessment FOI version.

FRAGMIN® Injection (NDA 20-287)
Item 3. Chemistry, Manufacturing and Controls
Part IV. Environmental Assessment Report (Revised)

Freedom of Information Document

ENVIRONMENTAL ASSESSMENT REPORT (EA)

This Environmental Assessment is being submitted in accordance with the requirements of 21 CFR 25.31a(b)(5) to accompany Pharmacia & Upjohn Company's (P&U) supplemental New Drug Application (NDA) #20-287 for FRAGMIN® (dalteparin sodium) Injection.

1. DATE

March 1992
Revised: June 1997

2. NAME OF APPLICANT

Pharmacia & Upjohn Company

3. ADDRESS

The mailing address and telephone number of P&U's Kalamazoo site are:

7000 Portage Road
Kalamazoo, Michigan 49001

Corporate telephone number (616) 833-4000

4. DESCRIPTION OF THE PROPOSED ACTION

4.a. Requested Approval

The former Kabi Pharmacia AB filed NDA #20-287 in October 1991 pursuant to Section 505(b) of the Food, Drug and Cosmetic Act for FRAGMIN® (dalteparin sodium) Injection.

The drug substance is packaged in polyethylene bags enclosed in aluminum foil. The drug product will be marketed in the U.S. in single-dose syringes of [REDACTED] with a needle of passivated stainless steel. A needle shield [REDACTED] plunger stopper [REDACTED] and a plunger [REDACTED]

FRAGMIN® Injection (NDA 20-287)
Item 3. Chemistry, Manufacturing and Controls
Part IV. Environmental Assessment Report (Revised)

Freedom of Information Document

The drug product, FRAGMIN (dalteparin sodium) Injection 2500 IU (anti-X_a)/0.2 mL and 5000 IU (anti-X_a)/0.2 mL, will be marketed in the U.S. as 10-packs of single-dose syringes.

4.b Need for Action

• Indication

The original EA dated 1 March 1992 covered the indications of both abdominal surgery and hip replacement surgery; however, the hip replacement surgery indication was later withdrawn from that NDA.

This supplement to NDA #20-287 is intended for hip replacement surgery.

• Action Mode

Please see Item 4, Description of proposed action, p. 406, of the original EA, included as non-confidential Appendix 1. A Finding of No Significant Impact (FONSI) was issued for this EA on 3 March 1993 (copy attached as non-confidential Appendix 2).

4.c Production Locations

• Drug Substance - Sweden

All steps involved in manufacturing, processing, packaging, labeling and control operations of the drug substance are performed by Pharmacia & Upjohn AB at the following sites:

The [REDACTED] drug substance is performed at:

Pharmacia & Upjohn AB
Mariefredsvägen 37
S 645 41 Strängnäs, Sweden

Control laboratories for testing raw materials, packaging materials, intermediates and finished product are located at:

FRAGMIN® Injection (NDA 20-287)
Item 3. Chemistry, Manufacturing and Controls
Part IV. Environmental Assessment Report (Revised)

Freedom of Information Document

Pharmacia & Upjohn AB
Lindhagensgatan 133
S 112 87 Stockholm, Sweden

Pharmacia & Upjohn AB
Nordenflychtsvägen 62
S 112 87 Stockholm, Sweden

The plant site is near the town of Strängnäs, 80 kilometers southwest of Stockholm. This plant is Pharmacia & Upjohn's main facility for production of substances by biochemical and chemical processing.

The site is [REDACTED]. The areas of buildings are [REDACTED]. The plant consists of approximately [REDACTED] buildings for chemical and biochemical production, storage, utilities, laboratories, offices and waste water treatment. It is located in an industrial area outside the town. The surrounding area is flat and rural.

• Drug Product - Germany

All steps involved in manufacturing, processing, packaging, labeling and in-process controls of the drug product will be performed at Pharmacia & Upjohn's contract manufacturer, [REDACTED]. All analyses specified by the drug product specifications are performed by Pharmacia & Upjohn in Sweden, except for the sterility test and ejectable volume, which are performed at [REDACTED] at the following address:

[REDACTED]

The plant site is located in [REDACTED], a town in southern [REDACTED]. [REDACTED] produces mostly sterile drug products and works exclusively as a contract manufacturer. The manufacturing site is located in an industrial area on the outskirts of the town.

4.d Locations of Use

The ultimate use and disposal of the finished product will be mainly at hospitals, clinics, and consumer dwellings. Finished products will be stored in distribution centers throughout the U.S. prior to transportation for sale at hospitals, clinics, and pharmacies.

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4.e Disposal Sites

Disposal of drug product may result in the form of rejected, expired, or returned goods or from end user disposal of individual units of empty or partly empty finished product containers. Recovery and/or ultimate disposal mechanisms follow:

- Rejected, Expired or Returned Drug Product

Rejected, expired, or returned drug product will be disposed in the on-site permitted incinerator at the P&U Kalamazoo, Michigan site.

- *On-Site Incinerator.* The incinerator is being operated as a Resource Conservation and Recovery Act (RCRA) interim status treatment facility under EPA I.D. #MID000820381 in compliance with 40 CFR 265, Subpart O requirements.

A hazardous waste RCRA Part B/Act 451, Part 111 permit application has been submitted to the Waste Management Division of the Michigan Department of Natural Resources (now the Michigan Department of Environmental Quality, MDEQ) in Lansing, Michigan. The P&U facility is operating under interim status provisions until action is taken on the permit application. MDEQ action on the permit application is expected in 1997. The State air permit issued on July 15, 1980 (#242-80), revised to incorporate the Act 451, Part 111 requirements, was approved on May 26, 1993.

The incinerator is a two-stage system: the primary chamber rotary kiln operates at a minimum of 700°F; the secondary chamber, where final destruction of the product and off-gasses occurs, operates at a minimum of 1,904°F. The incinerator is equipped with a pollution control equipment train designed to remove gaseous and particulate pollutants. The pollution control equipment consists of: a quench section, an acid-gas pre-scrubber, a Venturi scrubber, an entrainment separator, an induced draft fan, and an exhaust stack.

All necessary permits are in place for the manufacture of this product to begin, as an existing interim status facility in accordance with Section 3005(e) of RCRA and Michigan Act 451, Part 111 licensing requirements.

Ash generated as a result of the incineration process is sent to a permitted hazardous waste landfill. At the present time, P&U has available for use the following facilities:

- *Hazardous Waste Landfills:*

- Environmental Quality Co., 1349 South Huron Street, Ypsilanti, MI; Michigan Disposal, Inc., 49350 North I-94 Service Drive, Belleville, MI (treatment) operating license listed under EPA ID No. MID 000 724 831; Wayne Disposal, Inc., 49350 North I-94 Service Drive, Belleville, MI (disposal) operating license listed under EPA ID No. MID 048 090 633;

- Chemical Waste Management of Indiana, Inc., 4636 Adams Center Road, Fort Wayne, IN, operating license listed under Indiana Dept. of Environmental Management (IDEM) Permit No. IND 078911146;

- P&U may use other facilities for such disposal which are suitable for that purpose and are properly permitted.

P&U has contracts with each of these facilities that require the facility to be in compliance with all applicable laws and regulations. The waste stream profile support documentation established with the hazardous waste landfill sites affirm compliance status. All facilities are audited and approved for use by a P&U environmental auditor prior to the first shipment of waste from P&U to the site. In addition, P&U personnel conduct periodic environmental audits of off-site disposal facilities during use of the facilities.

- Discarded Product in Hospital, Clinic Setting, or Consumer Dwelling

- Any discarded product or product containers generated in a hospital or clinic environment will typically be disposed in accordance with applicable Federal, State and local regulations governing hospital wastes.

- Individual empty or partly empty end products disposed by consumers will be handled along with household garbage by the community's solid waste management system and disposed in an approved sanitary landfill. Only minute traces of the active ingredient, dalteparin sodium, would be expected to remain with empty product containers.

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5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT TO THIS PROPOSED ACTION

• **Drug Substance**

The materials used in processing the drug substance, dalteparin sodium, including Chemical Abstracts Service (CAS) No., molecular weight (M.W.), empirical formula, and a brief physical description, are included in confidential Appendix 7. [not included in FOI document]

• **Drug Product**

The material safety data sheet (MSDS) for the drug product, FRAGMIN, is enclosed as non-confidential Appendix 3. The ingredients used in formulating the drug product, FRAGMIN (dalteparin sodium) Injection, including Chemical Abstracts Service (CAS) No., molecular weight (M.W.), empirical formula, and a brief physical description, are included at non-confidential Appendix 4.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

The drug product is not expected to be introduced into the environment through transportation and storage. Product will be shipped in Department of Transportation (DOT) specification packaging. FRAGMIN (dalteparin sodium) Injection is not regulated as a hazardous material under current DOT regulations. Product ready for shipment will be stored in either the manufacturing facility or distribution centers. Both maintain security through limited access.

6.a Substances Expected to be Emitted

A list of substances that may be emitted during the synthesis of the drug substance and drug product are included at confidential Appendix 7 [not included in FOI document] and non-confidential Appendix 4.

6.b Controls Exercised

Certifications from responsible company officials that the drug substance synthesis plant and drug product manufacturing plant are in compliance with, or on an enforceable schedule to be in compliance with, all national, regional, provincial and local environmental laws and regulations and all emission limits, permits and consent decrees are provided in non-confidential Appendices 5 and 6.

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6.c. Rejected, Expired or Returned Drug Product

Section 4. includes a discussion of any rejected, expired or returned drug product that would be disposed through the P&U Kalamazoo, MI site.

6.d Citation of and Statement of Compliance with Applicable Emission Requirements

• Disposal Site - Kalamazoo, MI

The following regulations or standards are cited as applicable to the proposed action:

1. Federal Food, Drug and Cosmetic Act, PL 75-717, as amended, including subsections 306(a) and (b) [debarment].
2. Clean Air Act PL 91-604, as amended.
3. Clean Water Act PL 95-217, as amended.
4. Safe Drinking Water Act PL 93-523.
5. Resources Conservation and Recovery Act of 1976 PL 94-580, as amended.
6. Occupational Safety and Health Act of 1970, as amended.
7. Hazardous Materials Transportation Act of 1975, as amended.
8. Standards from the American National Standards Institute.
9. National Fire Protection Agency Standards.
 - a. National Electrical Code Standards
 - b. Life Safety Requirements
10. Act # 451 of 1994, Michigan Natural Resources and Environmental Protection Act, as amended including:
 - Part 31, Water Resources Protection
 - Part 55, Air Pollution Control
 - Part 111, Hazardous Waste Management
 - Part 115, Solid Waste Management
 - Part 121, Liquid Industrial Waste
 - Part 625, Mineral Wells
11. Act #399 of 1976, Michigan Safe Drinking Water Act, as amended.
12. Act #368 of 1978, Public Health Code.
13. Chapter 28 of the Kalamazoo City Code (Services and Wastewater) as amended by ordinance No. 1190.
14. Michigan Occupational Safety and Health Act of 1970, as amended. (Local regulation applicable to the State of Michigan.)

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- **Emission Requirements.** P&U states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees or administrative orders applicable to the disposal of dalteparin sodium at its facilities in Kalamazoo, Michigan, as well as emission requirements set forth in applicable Federal, State, and local statutes and regulations applicable to the disposal of dalteparin sodium at its facilities in Kalamazoo, Michigan.
- **OSHA Requirements.** P&U certifies that it has comprehensive programs and practices in place addressing all applicable OSHA requirements.

6.e. Discussion of the Effect of Approval on Compliance with Current Emissions

The approval of the FRAGMIN (dalteparin sodium) Injection supplemental NDA will have no effect on the ability of P&U sites to meet their current emission requirements.

6.f. Expected Introduction Concentrations (EIC)

A theoretical EIC for the aquatic environment can be calculated for dalteparin sodium utilizing the following equation and fifth-year production estimates. (See confidential Appendix 8 for the five-year market forecast.) [not included in FOI document]

$$\text{EIC-aquatic (ppm)} = A \times B \times C \times D$$

where:

- A = kg/year production
- B = 1/liters per day entering POTWs*
- C = year/365 days
- D = [REDACTED]

CDER has routinely found that drugs at concentrations [REDACTED] have no significant effect on relevant standard test organisms and therefore are unlikely to have a significant effect on the environment. CDER has also determined that information for environmental assessment format items 7, 8, 9, 10, and 11 will normally not be needed whose expected introduction concentration is [REDACTED]. Since the calculated EIC for FRAGMIN at its highest manufacturing rate in the next five years is [REDACTED] (the actual figures are presented in confidential Appendix

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8) [not included in FOI document], the format items mentioned above have not been included.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

Based on information in CDER's revised guidance document dated November 1995 (see Guidance, Section 14.) wherein FRAGMIN meets the Tier 0 criteria, information for format items 7 through 11 are not included for this document.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

Based on information in CDER's revised guidance document dated November 1995 (see Guidance, Section 14.) wherein FRAGMIN meets the Tier 0 criteria, information for format items 7 through 11 are not included for this document.

9. USE OF RESOURCES AND ENERGY

Based on information in CDER's revised guidance document dated November 1995 (see Guidance, Section 14.) wherein FRAGMIN meets the Tier 0 criteria, information for format items 7 through 11 are not included for this document.

10. MITIGATION MEASURES

Based on information in CDER's revised guidance document dated November 1995 (see Guidance, Section 14.) wherein FRAGMIN meets the Tier 0 criteria, information for format items 7 through 11 are not included for this document.

11. ALTERNATIVES TO THE PROPOSED ACTION

Based on information in CDER's revised guidance document dated November 1995 (see Guidance, Section 14.) wherein FRAGMIN meets the Tier 0 criteria, information for format items 7 through 11 are not included for this document.

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12. LIST OF PREPARERS

The following persons contributed to the preparation of this EA:

Anders Mähl	Environmental Coordinator Environment & Safety, Stockholm Pharmacia & Upjohn AB M.S., Chemical Engineering Professional experience: 27 years
Jeffrey S. Mehring	Manager, Science & Information Environment & Safety Pharmacia & Upjohn Company Ph.D., Agriculture Professional experience: 26 years
Susan I. Shedore	Environment & Safety Environmental Technician Pharmacia & Upjohn Company A.A. Corporate experience: 26 years

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13. CERTIFICATION

The undersigned officials certify that the information presented is true, accurate, and complete to the best of their knowledge.

The undersigned officials certify that the EA summary document and Appendices 1-6 contain non-confidential information and acknowledge that this information will be made available to the public in accordance with 40 CFR § 1506.6.

Randal S. Senger
Randal S. Senger, Associate Director
Environment and Safety
(telephone 616/833-5341)

June 9, 1997
Date

Jeffrey S. Mehring
Jeffrey S. Mehring, Manager
Science and Information
Environment and Safety
(telephone 616/833-4746)

9 JUNE 97
Date

14. REFERENCES

1992 Needs Survey, Report to Congress, EPA 832-R-93-002, September 1993.

Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements. Center for Drug Evaluation and Research, CMC 6, November 1995.

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15. APPENDICES

Non-Confidential

- 1 Original EA for FRAGMIN dated 1 March 1992
- 2 Finding of No Significant Impact (FONSI) dated 3 March 1993 written for original EA for FRAGMIN dated 1 March 1992
- 3 MSDS for the Drug Product, FRAGMIN
- 4 Ingredients Used in Formulating the Drug Product
- 5 Compliance letter - Sweden
- 6 Compliance letter - Germany

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NON-CONFIDENTIAL APPENDICES

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Appendix 1

Original EA dated 1 March 1992

ENVIRONMENTAL ASSESSMENT		Page
Product Fragmin solution for injection 2500 IU (anti-Factor X _a)/0.2 ml, and 5000 IU (anti-Factor X _a)/ 0.2 ml, single dose syringe		Number/Date 1991-10-30
Compiled by date and name HAMA/mg		Replaces number

	VOLUME	PAGE
III. ENVIRONMENTAL ASSESSMENT	1.4	405
APPENDIX	1.4	415
1. Environmental assessment Kabi Pharmacia AB, Strängnäs Decision - No. 502-180/88	1.4	416
Vetter Pharma Fertigung GmbH & Co Kg Statement 1991-10-29	1.4	420
2. Pharmacology-Toxicology Summary	1.4	421
3. Curriculum Vitae of preparers	1.4	469

Environmental assessment for proposed approvals of FDA-regulated products-Format 1 as per 21 CFR 25.31a (b)(5).

Item 1.) Date; March 1, 1992

Item 2.) Applicant Name; Kabi Pharmacia, AB

Item 3.) Address:
Corporate office; Rapskatan 7
S-751 82 Uppsala
Sweden

Division headquarters, R and D, and Manufacturing site;

Lindhagensgatan 133
S-112 87 Stockholm
Sweden

Item 4.) Description of proposed action;

The applicant is requesting approval of its' New Drug Application for the use of a low molecular weight heparin, call Fragmin®, as prophylaxis against thromboembolic complications in the peri- and post operative period of surgery. Because Fragmin acts mainly by accelerating the rate of neutralization of certain activated coagulation factors by antithrombin (other mechanisms may be involved) it is considered an antithrombotic. By its binding to antithrombin it potentiates, preferentially the inhibition of coagulation Factor Xa and only slightly affects thrombin inhibition and clotting time. The antithrombotic effect of fragmin is well correlated to the inhibition of Factor Xa. As such, a single daily injection of 2500IU (anti Factor Xa) of Fragmin can significantly reduce the incidence of thromboembolic complication of general surgery. A single daily injection of a higher dose, 5000IU (anti Factor Xa), significantly reduces thrombosis in orthopedic surgery, and in the surgical treatment of patients with malignant disorders and or other risk factors considered to increase the thrombosis risk. Thus the resultant reduction of thromboembolic complications such as deep vein thrombosis and pulmonary embolisms could lead to reduction in death from these causes as well as from myocardial infarction.

The product will be produced at the following sites in Sweden and Germany;

Manufacturer of Fragmin Drug Substance:

All steps involved in the manufacturing, processing, packaging, labeling and control operations are performed by Kabi Pharmacia AB, Sweden in its' own facilities at the following sites:

The degradation of heparin sodium, isolation and purification of the drug substance is performed at;

Kabi Pharmacia AB, Mariefredsvägen 35, S15200 STRÄNGNÄS, Sweden.

Control laboratories for testing raw materials, packaging materials, intermediates and finished product are located at;

Kabi Pharmacia AB, Lindhagensgatan 133, S11287 STOCKHOLM, Sweden.

Kabi Pharmacia AB, Nordenflychtsvägen 62, S11287 STOCKHOLM, Sweden.

Control laboratories for biological test are located at;

Kabi Pharmacia AB, Franzéngatan 7, S11287 STOCKHOLM, Sweden.

Kabi Pharmacia AB, Kraftvägen 1, S19634 KUNGSÄGEN, Sweden.

Manufacturer of Fragmin Drug Product:

All steps involved in the manufacturing, processing, packaging, labeling and in-process controls are performed at Kabi's contract laboratory, [REDACTED]

[REDACTED] All analyses specified by the Drug Product Specifications are performed by Kabi Pharmacia in Sweden, except for the sterility test and ejectable volume, these are done at Vetter.

Manufacturing facility:

[REDACTED]

Labeling and Packaging:

[REDACTED]

Warehouse for storage of raw materials, packaging materials and finished product is located at:



Control laboratories for testing of raw materials, intermediates and finished products is located at:



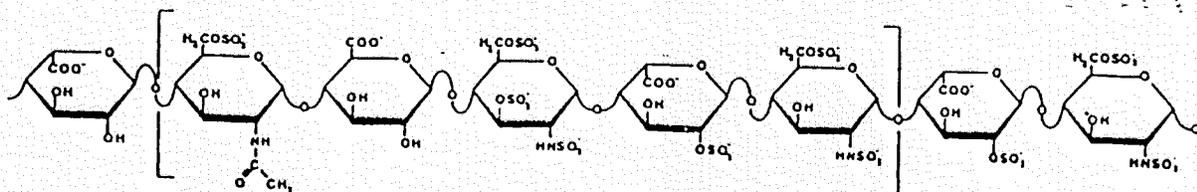
Control laboratories for testing of packaging materials is located at:



The finished product will be shipped to the United States from Kabi Pharmacia, AB, Sweden and marketed for hospital use, by order from a licensed physical and under the direct supervision of a licensed physical. As such the product will therefore be used and disposed of in a hospital setting. Hospitals have processes and procedures in place to deal with use and disposal of hypodermic needles and syringes in compliance with local, state and federal laws and regulations. The environment present and adjacent to various hospitals throughout the United States vary extensively and as such it is not possible to give this information.

Item 5.) Identification of Chemical substances that are the subject of the proposed action;

Low molecular weight heparin is obtained from heparin, a natural occurring substance found in the human body and in animal intestines and lungs in high concentrations. Heparin is obtained from animal tissues by various protein fractionation and purification procedures. Heparin is composed of a polysaccharide built up from disaccharides made up of alternating uronic acid and glucosamine unites. Below is the structure of a heparin octasaccharide sequence that shows most of the variously substituted monosaccharides identified to date. The pentasaccharide sequence in brackets represents the antithrombotic-binding region of heparin. It is also this region that is thought to account for the activity of low molecular weight heparins, namely by binding to antithrombin it potentiates, preferentially the inhibition of coagulation Factor Xa and only slightly affects thrombin inhibition and clotting time.



Low molecular weight heparins, in principal can be produced in two different ways. Either by enrichment of "natural" low molecular material in standard heparin or by depolymerization of heparin. Enrichment procedures involve fractional precipitation of heparin by such substances as ethanol and or chromatographic techniques such as gel filtration. Methods have been developed for controlled chemical depolymerization of heparin. Nitrous acid depolymerization of heparin is used commonly, and is the procedure described in this NDA. Other methods have been tried, such as depolymerization of the benzylic ester of heparin by β -elimination and methods using peroxides. Enzymatic depolymerization of heparin using heparinase is another possible method. Scheme 1 on the following page is an over view of Kabi's production method.

DRUG SUBSTANCE, Low molecular weight heparin, Fragmin®.

Names

INN (WHO list 31), BAN

Dalteparin sodium

Trade name

FRAGMIN® drug substance

Laboratory code and names

- Heparin fragment Kabi 2165
- Low molecular weight heparin
(sodium salt)

Chemical name

Oligo-saccharides derived from heparin, major components are 2-O-sulfo- α -L-idopyranosuronic acid at the non-reducing end and a 6-O-sulfo-2,5-anhydro-D-mannitol at the reducing end of the chain. Average molecular mass, 5000.

Physical, Chemical and Biological characteristics

Description:

An odorless white or yellowish white powder moderately hygroscopic and freely soluble in water.

FRAG/EA/92

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Solubility/Viscosity:

1 gm per ml of water yields a viscosity of 314 mPas.

pH:

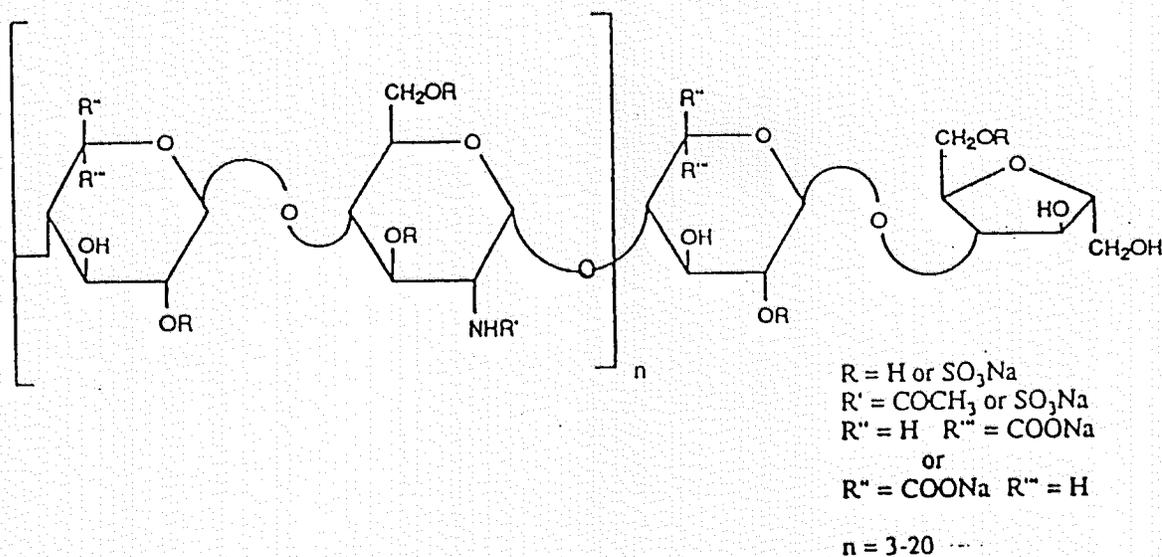
1 % w/w solution of the sodium salt has a pH of 5.0 - 7.5.

Optical rotation:

The specific optical rotation is not less than

$$[\alpha] D^{20} = +35^{\circ} \quad (C = 2.0, \text{ water}).$$

Structural formula:



Molecular formula:

C, H, O, N, and S with variable composition.

Relative molecular mass:

Polydisperse, with about 90 % of the material within 2000 - 9000 and with an average of 5000.

Biological Activity/Potency:

1. Anti-Factor Xa activity (Method of Analysis, H-236)

One International Unit (anti-Factor Xa) of Fragmin corresponds to the activity of one International Unit of the First International Standard for low molecular weight Heparin with respect to inhibition of coagulation Factor Xa in plasma utilizing the chromogenic substrate S-2222.

2. APTT activity (Method of Analysis, F-601)

One International Unit (APTT) of Fragmin corresponds to the activity of one International Unit of the First International Standard for low molecular weight Heparin with respect to its ability to prolong the plasma clotting time as measured by the APTT assay.

3. Coagulation Factor IIa assay (Method of Analysis, S 643)

One International Unit (anti-Factor IIa) of fragmin corresponds to the activity of one International Unit of the First International Standard for low molecular weight Heparin with respect to inhibition of thrombin by purified antithrombin utilizing the chromogenic substrate S-2238.

Specific activity:

The specific activity of Fragmin as measured by the anti-Factor Xa activity is about 160 IU/mg.

The specific activity of Fragmin as measured by the APTT and anti-Factor IIa activity is about 60 IU/mg.

The ratio anti-Factor Xa activity is (IU/mg) per APTT activity (IU/mg) is about 2.6.

Items 6, 7, 9, 10 and 11, namely, - Item 6, Introduction of substances into the environment; Item 7, Fate of emitted substances in the environment; Item 9, Use of resources and energy; Item 10, Mitigation measures; and Item 11, Alternatives to the proposed action, - are addressed in the enclosed document from the Swedish National Franchise Board, decision number Dnr 502-180/88 and a statement from Kabi Pharmacia regarding Vetter Pharma Fertigung, GmbH & Co KG. See appendix, document 1.

Item 8.) Environmental effects of released substances;

This information is partially address in the Swedish National Franchise Board document cited above as well as this New Drug Application Volumes 1.7 to 1.10, - Nonclinical, pharmacology, and toxicology section. See appendix document 2 for summary.

Item 12.) List of preparers;

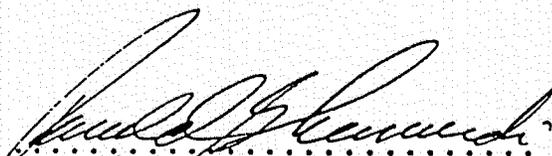
1. Dr. Ronald G. Leonardi, Ph.D.
President, R & R REGISTRATIONS
P.O. Box 262069
San Diego, CA 92196-2069
Curriculum Vitae, see appendix 3.
2. Mr. Claus-Gunnar Meinking
Plant Manager
Kabi Pharmacia AB, Biopharma
S645 41 STRÄNGNÄS, Sweden
Curriculum Vitae, see appendix 3.
3. Mr. Anders Ulfhielm
Vice President, Operations
Kabi Pharmacia AB, Biopharma
S112 87 STOCKHOLM, Sweden
Curriculum Vitae, see appendix 3.

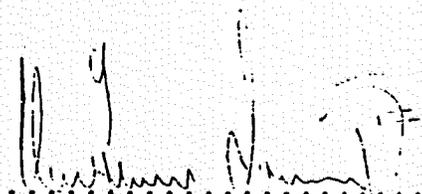
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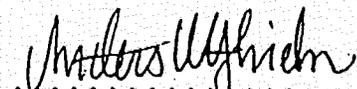
Item 13.) Certification;

The undersigned officials certify that the information presented is true, accurate, and complete to the best of the knowledge of the firm or agency responsible for preparation of the environmental assessment.

DATE.....; Signature(s) and Titles


.....
Dr. Ronald G. Leonardi, Ph.D.
President, R & R REGISTRATIONS


.....
Mr. Claus Gunnar Meinking
Plant Manager
Kabi Pharmacia AB, Biopharma


.....
Mr. Anders Ulfhielm
Vice President, Operations
Kabi Pharmacia AB, Biopharma

Item 14.) References;
Fragmin New Drug Application, enclosed.

Item 15.) Appendices;

1. Environmental assessment statements for 
2. NDA Pharmacology-Toxicology Summary
3. Curriculum Vitae of preparers

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Appendix 2**

FONSI dated 3 March 1993 written for Original EA dated 1 March 1992

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-287

Fragmin (dalteparin sodium)

Injection

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Fragmin, Kabi Pharmacia AB has conducted a number of environmental studies and prepared an environmental assessment (21 CFR 25.31a(a)(5) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Fragmin, a low molecular weight heparin, acts mainly by accelerating the rate of neutralization of certain activated

coagulation factors by antithrombin.

The drug substance is manufactured in Sweden. The drug product is manufactured in Germany. The firm has provided letters from the appropriate government officials with specificity to the drug asserting that manufacture will not have a significant environmental impact. The Agency believes that use and disposal of the drug product will not have significant environmental impact due to the biological nature of the altered heparin molecule.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Any residues of Fragmin or its major metabolites entering the environment as a result of administering the drug to humans are expected to rapidly degrade.

3/3/93
DATE

Phillip G. Vincent

Phillip G. Vincent, Ph. D.
Environmental Assessment Officer
Center for Drug Evaluation and Research

3/3/93
DATE

Charles S. Kumkumian

Charles S. Kumkumian, Ph. D.
Assistant Director (Chemistry)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment: Environmental Assessment
MSDS
FPL

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Appendix 3

MSDS for the Drug Product, FRAGMIN

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Appendix 3

MATERIAL SAFETY DATA SHEET

Revision Date: March 27, 1995
Agent Id#: 53875

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

COMMON NAME: FRAGMIN®
SYNONYMS: Dalteparin Sodium Injection
MOLECULAR FORMULA: Mixture
MANUFACTURER/SUPPLIER: PHARMACIA & UPJOHN
7171 PORTAGE RD
KALAMAZOO, MI 49001-0199
TELEPHONE NUMBERS: (616) 833-5122 - (24 HOURS)
(616) 833-7555 - (8:00 a.m. - 4:30 p.m.)

2. COMPOSITION/INFORMATION ON INGREDIENTS

INGREDIENT 1

COMMON NAME: Water
% BY WEIGHT: 89 - 94 %
CAS NUMBER: 7732-18-5
EXPOSURE LIMIT(S): Not established.

INGREDIENT 2

COMMON NAME: Heparin Sodium
% BY WEIGHT: 5.9 - 11.4 %
CAS NUMBER: 9041-08-1
EXPOSURE LIMIT(S): Not established.
EXPOSURE LIMIT(S) FOR THE MATERIAL: Not established.

INGREDIENT 3

COMMON NAME: Sodium Chloride
% BY WEIGHT: < 1%
CAS NUMBER: 7647-14-5
EXPOSURE LIMIT(S): Not established.

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3. HAZARDS IDENTIFICATION

PRIMARY ROUTE(S) OF EXPOSURE: Inhalation, ingestion, absorption through the skin or accidental needle puncture injury.

EFFECTS OF OVEREXPOSURE:

ACUTE OVEREXPOSURE: Bleeding.

CHRONIC OVEREXPOSURE: Bleeding.

MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE: Bleeding, diathesis.

4. FIRST AID MEASURES

EYES: Rinse with water. Assure adequate flushing by separating the eyelids with fingers. Seek medical attention if irritation persists.

SKIN: Wash with soap and water.

INHALATION: Move to fresh air, rest. Rinse nose and mouth with water. Get medical attention immediately. If breathing becomes difficult, call a physician.

INGESTION: Wash out mouth with water. Give some glasses of water.

5. FIRE FIGHTING MEASURES

FLASH POINT: Not applicable.

LOWER EXPLOSION LIMIT (LEL): Not applicable.

UPPER EXPLOSION LIMIT (UEL): Not applicable.

AUTOIGNITION TEMPERATURE: Not applicable.

EXTINGUISHING MEDIA: Water spray, carbon dioxide, dry chemical powder, or polymer foam as appropriate for surrounding fire and materials.

FIRE-FIGHTING PROCEDURES: Evacuate personnel to safe area. Fire-fighters should use self-contained breathing equipment and protective clothing.

UNUSUAL FIRE OR EXPLOSION HAZARDS: None.

HAZARDOUS COMBUSTION PRODUCTS: Unknown.

6. ACCIDENTAL RELEASE MEASURES

STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED: Use NIOSH/MSHA-approved mask for protection from aerosols. Swab with absorbent wipes, paper towel, cellulose sorbent, vermiculite or the like. Place the absorbent material into a plastic bag and dispose of in accordance with Federal, state and local regulations.

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7. HANDLING AND STORAGE

PRECAUTIONS FOR HANDLING AND STORING: Handle with care. Avoid formation of aerosols. Store in original packing (single dose syringes in cartons) at room temperature.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

RESPIRATORY PROTECTION: Wear suitable respiratory equipment, NIOSH/MSHA-approved for protection from aerosols.

VENTILATION: General.

PROTECTIVE GLOVES: Yes.

EYE PROTECTION: Safety glasses.

OTHER PROTECTIVE EQUIPMENT: Not applicable.

9. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE/PHYSICAL STATE: Clear, colorless or straw-colored solution.

BOILING POINT: The product consists of approximately 90% water. The value is essentially the same as water.

EVAPORATION RATE: The product consists of approximately 90% water. The value is essentially the same as for water.

MELTING POINT: Not applicable.

SOLUBILITY IN WATER: Freely soluble.

SPECIFIC GRAVITY (WATER=1): 1.04

VAPOR DENSITY (air = 1): The product consists of approximately 90% water. The value is essentially the same as for water.

VAPOR PRESSURE: The product consists of approximately 90% water. The value is essentially the same as for water.

VOLATILITY: Product is 89-94% water.

REACTIVITY IN WATER: None.

10. STABILITY AND REACTIVITY

STABILITY: Stable.

PHYSICAL CONDITIONS TO AVOID: None.

INCOMPATIBILITY WITH OTHER MATERIALS: None.

HAZARDOUS DECOMPOSITION PRODUCTS: None.

HAZARDOUS POLYMERIZATION: Will not occur.

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11. TOXICOLOGICAL INFORMATION

ACUTE STUDIES:

INTRAVENOUS LD50 (DOG): 1,000 MG/KG

INTRAVENOUS LD50 (RAT): 354 MG/KG

INTRAVENOUS LD50 (MOUSE): 2,800 MG/KG

ORAL LD50 (MOUSE): > 5,000 MG/KG

INTRAPERITONEAL LD50 (MOUSE): > 2,500 MG/KG

SUBCUTANEOUS LD50 (MOUSE): > 2,500 MG/KG

OTHER STUDIES:

CARCINOGENICITY: Ingredient(s) are not listed as carcinogenic by IARC,
NTP or OSHA.

12. DISPOSAL CONSIDERATIONS

WASTE DISPOSAL METHOD: Mix the material with a combustible solvent and burn in a chemical incinerator equipped with an afterburner and scrubber. Dispose of in accordance with federal, state and local regulations.

13. OTHER INFORMATION

DISCLAIMER: The MSDS information is believed to be correct but should only be used as a guide. Pharmacia & Upjohn disclaims any express or implied warranty as to the accuracy of the MSDS information and shall not be held liable for any direct, incidental or consequential damages resulting from reliance on the information.

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Appendix 4**

Ingredients Used in Formulating the Drug Product

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Ingredients Used in Formulating the Drug Product

Ingredient	CAS No.	M.W.	Formula	Physical Appearance
Dalteparin sodium	9041-08-1	Avg. molecular mass: 5000 D	Not applicable: depolymerization of sodium heparin	White or yellowish-white powder
Sodium chloride*	7647-14-5	58.44	NaCl	White powder
Water	7732-18-5	18.0	H ₂ O	Colorless liquid

*applicable to 2500 IU/0.2 mL, single-dose syringes

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Appendix 5

Compliance Letter - Sweden



Pharmacia & Upjohn

Food and Drug Administration
CDER
Rockville, MD
USA

Strängnäs, June 2, 1997

HABO/LEIL

Pharmacia & Upjohn AB certifies that its manufacturing facilities for the production of dalteparin sodium are in compliance with all local and national environmental laws; are in compliance with, or are on an enforceable schedule to be in compliance with, all emission requirements set forth in all permits; and that approval and subsequent increase in production at the facility are not expected to affect compliance with current emission requirements of compliance with environmental laws.

Yours sincerely,

PHARMACIA & UPJOHN AB
Technical Operations
Plant Strängnäs

A handwritten signature in cursive script, appearing to read 'Börje Haag'.

Börje Haag
Plant Manager

Postal address
Pharmacia & Upjohn AB
Strängnäs Plant
S-645 41 Strängnäs
Sweden

Office address
Mariefredsvägen 37

Telephone
+46 152 273 00

Telefax
+46 152 273 66

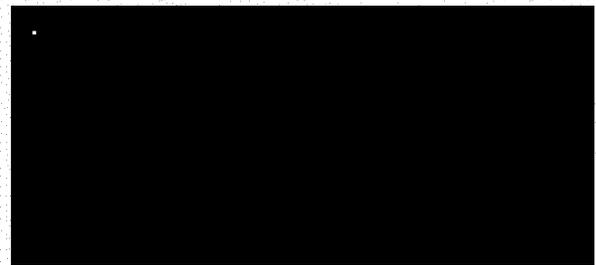
Registered Office: Stockholm. Reg. No.: 556131-9608

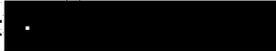
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Appendix 6

Compliance Letter - Germany



Name: 

Food and Drug Administration
CDER
5600 Fishers Lane
ROCKVILLE, MD 20857
U.S.A.



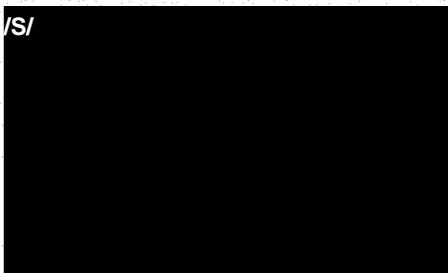
Date: June 3, 1997

Environmental Assessment

 certifies that its manufacturing facilities for the production of **FRAGMIN (dalteparin sodium) Injection**

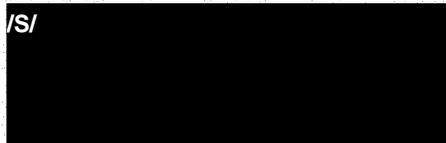
- are in compliance with all local and national environmental laws;
- are in compliance with, or are on an enforceable schedule to be in compliance, with all emission requirements set forth in all permits;
- and that approval and subsequent increase in production at the facility are not expected to affect compliance with current emission requirements or compliance with environmental laws.

/s/



Managing Director

/s/



Director of Regulatory Affairs

