CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-287/S-032

Name: Fragmin® (Dalteparin Sodium) Injection

Sponsor: Pharmacia & Upjohn

Approval Date: December 10, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-032

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-032

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-032

Pharmacia & Upjohn Company
Attention: Gregory A. Brier
Senior Regulatory Manager
7000 Portage Road
Kalamazoo, MI 49001

Dear Mr. Brier

Please refer to your supplemental new drug application dated February 7, 2003, received February 10, 2003, 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 2, June 6 and December 5 and 10 (2 telefacsimilies), 2003.

This supplemental new drug application provides for the use of Fragmin® (dalteparin sodium) injection for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and submitted labeling (package insert submitted December 10, 2003).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper 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-032." Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Gastrointestinal and Coagulation Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Diane Moore, Regulatory Project Manager, at (301) 827-7476.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joyce Korvick

12/10/03 06:35:49 PM

for Dr. Robert Justice

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-032

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 preassembled with a passive needle guard device, and multiple-dose vials. With reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard, each syringe contains either 2500, 5000, 7500, or 10,000 anti-Factor Xa international units (IU), equivalent to 16, 32, 48, or 64 mg dalteparin sodium, respectively. Each vial contains either 10,000 or 25,000 anti-Factor Xa IU per 1 mL (equivalent to 64 or 160 mg dalteparin sodium, respectively), for a total of 95,000 anti-Factor Xa IU per vial.

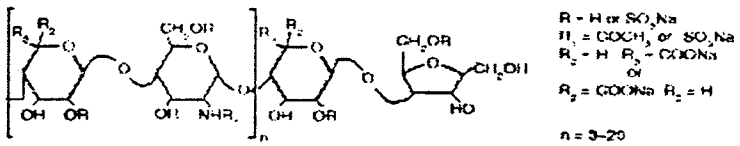
Each prefilled syringe also contains Water for Injection and sodium chloride, when required, to maintain physiologic ionic strength. The prefilled syringes are preservative free. Each multiple-dose vial also contains Water for Injection and 14 mg of benzyl alcohol per mL as a preservative. The pH of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

< 3000 daltons	3.0-15.0%
3000 to 8000 daltons	65.0-78.0%
> 8000 daltons	14.0-26.0%

Structural Formula



CLINICAL PHARMACOLOGY

Dalteparin is a low molecular weight heparin with antithrombotic properties. It acts by enhancing the inhibition of Factor Xa and thrombin by antithrombin. In man, dalteparin potentiates preferentially the inhibition of coagulation Factor Xa, while only slightly affecting clotting time, e.g., activated partial thromboplastin time (APTT).

Pharmacodynamics:

Doses of FRAGMIN Injection of up to 10,000 anti-Factor Xa IU administered subcutaneously as a single dose or two 5000 IU doses 12 hours apart to healthy subjects do not produce a significant change in platelet aggregation, fibrinolysis, or global clotting tests such as prothrombin time (PT), thrombin time (TT) or APTT. Subcutaneous (s.c.) administration of doses of 5000 IU bid of FRAGMIN for seven consecutive days to patients undergoing abdominal surgery did not markedly affect APTT, Platelet Factor 4 (PF4), or lipoprotein lipase.

Pharmacokinetics:

Mean peak levels of plasma anti-Factor Xa activity following single s.c. doses of 2500, 5000 and 10,000 IU were 0.19 ± 0.04, 0.41 ± 0.07 and 0.82 ± 0.10 IU/mL, respectively, and were attained in about 4 hours in most subjects. Absolute bioavailability in healthy volunteers, measured as the anti-Factor Xa activity, was 87 ± 6%. Increasing the dose from 2500 to 10,000 IU resulted in an overall increase in anti-Factor Xa AUC that was greater than proportional by about one-third.

Peak anti-Factor Xa activity increased more or less linearly with dose over the same dose range. There appeared to be no appreciable accumulation of anti-Factor Xa activity with twice-daily dosing of 100 IU/kg s.c. for up to 7 days.

The volume of distribution for dalteparin anti-Factor Xa activity was 40 to 60 mL/ 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 hours.

Following intravenous doses of 40 and 60 IU/kg, mean terminal half-lives were 2.1 ± 0.3 and 2.3 ± 0.4 hours, respectively. Longer apparent terminal half-lives (3 to 5 hours) 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 hours, i.e. considerably longer than values observed in healthy volunteers, therefore, greater accumulation can be expected in these patients.

CLINICAL TRIALS

Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction:

In a double-blind, randomized, placebo-controlled clinical trial, patients who recently experienced unstable angina with EKG changes or non-Q-wave myocardial infarction (MI) were randomized to FRAGMIN Injection 120 IU/kg every 12 hours subcutaneously (s.c.) or placebo every 12 hours s.c. In this trial, unstable angina was defined to include only angina with EKG changes. All patients, except when contraindicated, were treated concurrently with aspirin (75 mg once daily) and beta blockers. Treatment was initiated within 72 hours of the event (the majority of patients received treatment within 24 hours) and continued for 5 to 8 days. A total of 1506 patients were enrolled and treated; 746 received FRAGMIN and 760 received placebo. The mean age of the study population was 68 years (range 40 to 90 years) and the majority of patients were white (99.7%) and male (63.9%). The combined incidence of the double endpoint of death or myocardial infarction was lower for FRAGMIN compared with placebo at 6 days after initiation of therapy. These results were observed in an analysis of all-randomized and all-treated patients. The combined incidence of death, MI, need for intravenous (i.v.) heparin or i.v. nitroglycerin, and revascularization was also lower for FRAGMIN than for placebo (see Table 1).

Table 1
Efficacy of FRAGMIN in the Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction

Indication	Dosing Regimen	
	FRAGMIN 120 IU/kg/12 hr s.c.	Placebo q 12 hr s.c.
All Treated Unstable Angina and Non-Q-Wave MI Patients	746	760
Primary Endpoints – 6 day timepoint Death, MI	13/741 (1.8%)[1]	36/757 (4.8%)
Secondary Endpoints – 6 day timepoint Death, MI, i.v. heparin, i.v. nitroglycerin, Revascularization	59/739 (8.0%)[1]	106/756 (14.0%)

[1] p-value = 0.001

In a second randomized, controlled trial designed to evaluate long-term treatment with FRAGMIN (days 6 to 45), data were also collected comparing 1-week (5 to 8 days) treatment of FRAGMIN 120 IU/kg every 12 hours s.c. with heparin at an APTT-adjusted dosage. All patients, except when contraindicated, were treated concurrently with aspirin (100 to 165 mg per day). Of the total enrolled study population of 1499 patients, 1482 patients were treated; 751 received FRAGMIN and 731 received heparin. The mean age of the study population was 64 years (range 25 to 92 years) and the majority of patients were white (96.0%) and male (64.2%). The incidence of the combined triple

endpoint of death, myocardial infarction, or recurrent angina during this 1-week treatment period (5 to 8 days) was 9.3% for FRAGMIN and 7.6% for heparin (p=0.323).

Prophylaxis of Deep Vein Thrombosis in Patients Following Hip Replacement Surgery:
In an open-label randomized study, FRAGMIN 5000 IU administered once daily s.c. was compared with 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 dose s.c. 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 to 3.0. Treatment in both groups was then continued for 5 to 9 days postoperatively. Of the total enrolled study population of 580 patients, 553 were treated and 550 underwent surgery. Of those who underwent surgery, 271 received FRAGMIN and 279 received warfarin sodium. The mean age of the study population was 63 years (range 20 to 92 years) and the majority of patients were white (91.1%) and female (52.9%). The incidence of deep vein thrombosis (DVT), any vein, as determined by evaluable venography, was significantly lower for the group treated with FRAGMIN compared with patients treated with warfarin sodium (28/192 vs 49/190; p=0.006) [see Table 2].

Table 2
Efficacy of FRAGMIN in the Prophylaxis of Deep Vein Thrombosis Following Hip Replacement Surgery

Indication	Dosing Regimen	
	FRAGMIN 5000 IU qd[1] s.c.	Warfarin Sodium 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 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.
3 p-value = 0.006
4 p-value = 0.185

In a second single-center, double-blind study of patients undergoing hip replacement surgery, FRAGMIN 5000 IU once daily s.c. starting the evening before surgery, was compared with heparin 5000 U s.c. tid, starting the morning of surgery. Treatment in both groups was continued for up to 9 days postoperatively. Of the total enrolled study population of 140 patients, 139 were treated and 136 underwent surgery. Of those who underwent surgery, 67 received FRAGMIN and 69 received heparin. The mean age of the study population was 69 years (range 42 to 87 years) and the majority of patients were female (58.8%). In the intent-to-treat analysis, the incidence of proximal DVT was significantly lower for patients treated with FRAGMIN compared with patients treated with heparin

(6/67 vs 18/69; p=0.012). 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).

A third multi-center, double-blind, randomized study evaluated a postoperative dosing regimen of FRAGMIN for thromboprophylaxis following total hip replacement surgery. Patients received either FRAGMIN or warfarin sodium, randomized into one of three treatment groups. One group of patients received the first dose of FRAGMIN 2500 IU s.c. within 2 hours before surgery, followed by another dose of FRAGMIN 2500 IU s.c. at least 4 hours (6.6 ± 2.3 hr) after surgery. Another group received the first dose of FRAGMIN 2500 IU s.c. at least 4 hours (6.6 ± 2.4 hr) after surgery. Then, **both** of these groups began a dosing regimen of FRAGMIN 5000 IU once daily s.c. on postoperative day 1. The third group of patients received warfarin sodium the evening of the day of surgery, then continued daily at a dose adjusted for INR 2.0 to 3.0. Treatment for all groups was continued for 4 to 8 days postoperatively, after which time all patients underwent bilateral venography.

In the total enrolled study population of 1501 patients, 1472 patients were treated; 496 received FRAGMIN (first dose before surgery), 487 received FRAGMIN (first dose after surgery) and 489 received warfarin sodium. The mean age of the study population was 63 years (range 18 to 91 years) and the majority of patients were white (94.4%) and female (51.8%).

Administration of the first dose of FRAGMIN after surgery was as effective in reducing the incidence of thromboembolic events as administration of the first dose of FRAGMIN before surgery (44/336 vs 37/338; p=0.448). Both dosing regimens of FRAGMIN were more effective than warfarin sodium in reducing the incidence of thromboembolic events following hip replacement surgery.

Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery in Patients at Risk for Thromboembolic Complications:
Abdominal surgery 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 vein thrombosis or pulmonary embolism.

FRAGMIN administered once daily s.c. beginning prior to surgery and continuing for 5 to 10 days after surgery, was shown to reduce the risk of DVT in patients at risk for thromboembolic complications in two double-blind, randomized, controlled clinical trials performed in patients undergoing major abdominal surgery. In the first study, a total of 204 patients were enrolled and treated; 102 received FRAGMIN and 102 received placebo. The mean age of the study population was 64 years (range 40 to 98 years) and the majority of patients were female (54.9%). In the second study, a total of 391 patients were enrolled and treated; 195 received FRAGMIN and 196 received heparin. The mean age of the study population was 59 years (range 30 to 88 years) and the majority of patients were female (51.9%). As summarized in the following tables, FRAGMIN 2500 IU was superior to placebo and similar to heparin in reducing the risk of DVT (see Tables 3 and 4).

Table 3
Efficacy of FRAGMIN in the Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery

Indication	Dosing Regimen	
	FRAGMIN 2500 IU qd s.c.	Placebo 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 = 0.008
[2] Both patients also had DVT, 1 proximal and 1 distal

Table 4
Efficacy of FRAGMIN in the Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery

Indication	Dosing Regimen	
	FRAGMIN 2500 IU qd s.c.	Heparin 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 = 0.74

In a third double-blind, randomized study performed in patients undergoing major abdominal surgery with malignancy, FRAGMIN 5000 IU once daily was compared with FRAGMIN 2500 IU once daily. Treatment was continued for 6 to 8 days. A total of 1375 patients were enrolled and treated; 679 received FRAGMIN 5000 IU and 696 received 2500 IU. The mean age of the combined groups was 71 years (range 40 to 95 years). The majority of patients were female (51.0%). The study showed that FRAGMIN 5000 IU once daily was more effective than FRAGMIN 2500 IU once daily in reducing the risk of DVT in patients undergoing abdominal surgery with malignancy (see Table 5).

Table 5
Efficacy of FRAGMIN in the Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery

Indication	Dosing Regimen	
	FRAGMIN 2500 IU qd s.c.	FRAGMIN 5000 IU qd s.c.
All Treated Abdominal Surgery Patients[1]	696	679
Treatment Failures in Evaluable Patients		
Total Thromboembolic Events	99/656 (15.1%)[2]	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] Major abdominal surgery with malignancy
[2] p-value = 0.001

Prophylaxis of Deep Vein Thrombosis in Medical Patients at Risk for Thromboembolic Complications due to Severely Restricted Mobility During Acute Illness:
In a double-blind, multi-center, randomized, placebo-controlled clinical trial, general medical patients with severely restricted mobility who were at risk of venous thromboembolism were randomized to receive either FRAGMIN 5000 IU or placebo s.c. once daily during Days 1 to 14 of the study. The primary endpoint was evaluated at Day 21, and the follow-up period was up to Day 90. These patients had an acute medical condition requiring a projected hospital stay of at least 4 days, and were confined to bed during waking hours. The study included patients with congestive heart failure (NYHA Class III or IV), acute respiratory failure not requiring ventilatory support, and the following acute conditions with at least one risk factor occurring in >1% of treated patients: acute infection (excluding septic shock), acute rheumatic disorder, acute lumbar or sciatic pain, vertebral compression, or acute arthritis of the lower extremities. Risk factors include > 75 years of age, cancer, previous DVT/PE, obesity and chronic venous insufficiency. A total of 3681 patients were enrolled and treated: 1848 received FRAGMIN and 1833 received placebo. The mean age of the study population was 69 years (range 26 to 99 years), 92.1% were white and 51.9% were female. The primary efficacy endpoint was defined as at least one of the following within Days 1 to 21 of the study: asymptomatic DVT (diagnosed by compression ultrasound), a confirmed symptomatic DVT, a confirmed pulmonary embolism or sudden death.

When given at a dose of 5000 IU once a day s.c., FRAGMIN significantly reduced the incidence of thromboembolic events including verified DVT by Day 21 (see Table 6). The prophylactic effect was sustained through Day 90.

Table 6
Efficacy of FRAGMIN in the Prophylaxis of Deep Vein Thrombosis in Medical Patients with Severely Restricted Mobility during Acute Illness

Indication	Dosing Regimen	
	FRAGMIN 5000 IU q.d., s.c.	**Placebo q.d. s.c.**
All Treated Medical Patients During Acute Illness	1848	1833
Treatment failure in evaluable patients (Day 21)[1] DVT, PE, or sudden death	42/1518 (2.77 %)[1,2]	73/1473 (4.96 %)
Total thromboembolic events (Day 21)	37/1513 (2.45 %)	70/1470 (4.76%)
Total DVT	32/1508 (2.12 %)	64/1464 (4.37%)
Proximal DVT	29/1518 (1.91 %)	60/1474 (4.07%)
Symptomatic VTE	10/1759 (0.57 %)	17/1740 (0.98 %)
PE	5/1759 (0.28 %)	6/1740 (0.34 %)
Sudden Death	5/1829 (0.27%)	3/1807 (0.17%)

[1]Defined as DVT (diagnosed by compression ultrasound at Day 21 + 3), confirmed symptomatic DVT, confirmed PE or sudden death.
[1,2]p-value = 0.0015

INDICATIONS AND USAGE

- FRAGMIN Injection is indicated for the prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin therapy (as described in CLINICAL TRIALS, Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction).

- FRAGMIN is also indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE):
  - ◊ In patients undergoing hip replacement surgery;
  - ◊ In patients undergoing abdominal surgery who are at risk for thromboembolic complications;
  - ◊ In medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

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 undergoing regional anesthesia should not receive FRAGMIN for unstable angina or non-Q-wave myocardial infarction due to an increased risk of bleeding associated with the dosage of FRAGMIN recommended for unstable angina and non-Q-wave myocardial infarction.

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 $<100,000/mm^3$ and $<50,000/mm^3$ occurred in <1% and <1%, respectively. 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 vials of FRAGMIN contain 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, platelet inhibitors, and thrombolytic agents because of increased risk of bleeding (see **PRECAUTIONS, Laboratory Tests**). Aspirin, unless contraindicated, is recommended in patients treated for unstable angina or non-Q-wave myocardial infarction (see **DOSAGE AND ADMINISTRATION**).

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/m^2) 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/m^2) in pregnant rats and 4800 IU/kg (40,800 IU/m^2) 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 multiple-dose vials of FRAGMIN contain 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.

Geriatric Use
Of the total number of patients in clinical studies of FRAGMIN, 5204 patients were 65 years of age or older and 2123 were 75 or older. No overall differences in effectiveness were observed between these subjects and younger subjects. Some studies suggest that the risk of bleeding increases with age. Postmarketing surveillance and literature reports have not revealed additional differences in the safety of FRAGMIN between elderly and younger patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised, particularly in geriatric patients with low body weight (<45 kg) and those predisposed to decreased renal function (see also **CLINICAL PHARMACOLOGY** and **General** and **Drug Interactions** subsections of **PRECAUTIONS**)."

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 trial 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 trial comparing FRAGMIN 5000 IU once daily to heparin 5000 U twice daily, the incidence of bleeding events was 3.2% and 2.7%, respectively (n.s.) in the malignancy subgroup.

Unstable Angina and Non-Q-Wave Myocardial Infarction:
Table 7 summarizes major bleeding events that occurred with FRAGMIN, heparin, and placebo in clinical trials of unstable angina and non-Q-wave myocardial infarction.

Table 7
Major Bleeding Events in Unstable Angina and Non-Q-Wave Myocardial Infarction

Indication	Dosing Regimen		
Unstable Angina and Non-Q-Wave MI	**FRAGMIN** 120 IU/kg/12 h s.c.[1]	**Heparin** i.v. and s.c.[2]	**Placebo** q 12 hr s.c.
Major Bleeding Events[3, 4]	15/1497 (1.0%)	7/731 (1.0%)	4/760 (0.5%)

1 Treatment was administered for 5 to 8 days.
2 Heparin i.v. infusion for at least 48 hours, APPT 1.5 to 2 times control, then 12,500 U s.c. every 12 hours for 5 to 8 days.
3 Aspirin (75 to 165 mg per day) and beta blocker therapies were administered concurrently.
4 Bleeding events were considered major if: 1) accompanied by a decrease in hemoglobin of ≥2 g/dL in connection with clinical symptoms; 2) a transfusion was required; 3) bleeding led to interruption of treatment or death; or 4) intracranial bleeding.

***Hip Replacement Surgery*:**
Table 8 summarizes: 1) all major bleeding events and, 2) other bleeding events possibly or probably related to treatment with FRAGMIN (preoperative dosing regimen), warfarin sodium, or heparin in two hip replacement surgery clinical trials.

Table 8
Bleeding Events Following Hip Replacement Surgery

Indication	FRAGMIN vs Warfarin Sodium		FRAGMIN vs Heparin	
	Dosing Regimen		Dosing Regimen	
Hip Replacement Surgery	**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.

In the third hip replacement surgery clinical trial, the incidence of major bleeding events was similar in all three treatment groups: 3.6% (18/496) for patients who started FRAGMIN before surgery; 2.5% (12/487) for patients who started FRAGMIN after surgery; and 3.1% (15/489) for patients treated with warfarin sodium.

Abdominal Surgery:
Table 9 summarizes bleeding events that occurred in clinical trials which studied FRAGMIN 2500 and 5000 IU administered once daily to abdominal surgery patients.

Table 9

Bleeding Events Following Abdominal Surgery

Indication	FRAGMIN vs Heparin Dosing Regimen				FRAGMIN vs Placebo Dosing Regimen		FRAGMIN vs FRAGMIN Dosing Regimen	
Abdominal Surgery	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.
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%)

Medical Patients with Severely Restricted Mobility During Acute Illness:
Table 10 summarizes major bleeding events that occurred in a clinical trial of medical patients with severely restricted mobility during acute illness.

Table 10
Bleeding Events in Medical Patients with Severely Restricted Mobility During Acute Illness

Indication	Dosing Regimen	
Medical Patients with Severely Restricted Mobility	**FRAGMIN 5000 IU q.d., s.c.**	**Placebo q.d., s.c.**
Major Bleeding Events[1] at Day 14	8/1848 (0.43%)	0/1833 (0%)
Major Bleeding Events[1] at Day 21	9/1848 (0.49%)	3/1833 (0.16%)

[1] A bleeding event was considered major if: 1) it was accompanied by a decrease in hemoglobin of ≥ 2 g/dL in connection with clinical symptoms; 2) intraocular, spinal/epidural, intracranial, or retroperitoneal bleeding; 3) required transfusion of ≥ 2 units of blood products; 4) required significant medical or surgical intervention; or 5) led to death.

Three of the major bleeding events that occurred by Day 21 were fatal, all due to gastrointestinal hemorrhage (two patients in the group treated with FRAGMIN and one in the group receiving placebo). Two deaths occurred after Day 21: one patient in the placebo group died from a subarachnoid hemorrhage that started on Day 55, and one patient died on day 71 (two months after receiving the last dose of FRAGMIN) from a subdural hematoma.

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 nine reports of epidural or spinal hematoma formation with concurrent use of dalteparin sodium and spinal/epidural anesthesia or spinal puncture. Five of the nine patients had post-operative indwelling epidural catheters placed for analgesia or received additional drugs affecting hemostasis. The hematomas caused long-term or permanent paralysis (partial or complete) in seven of these cases. One patient experienced temporary paraplegia but made a full recovery, and one patient had no neurological deficit. 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

Unstable Angina and Non-Q-Wave Myocardial Infarction:

In patients with unstable angina or non-Q-wave myocardial infarction, the recommended dose of FRAGMIN Injection is 120 IU/kg of body weight, but not more than 10,000 IU, subcutaneously (s.c.) every 12 hours with concurrent oral aspirin (75 to 165 mg once daily) therapy. Treatment should be continued until the patient is clinically stabilized. The usual duration of administration is 5 to 8 days. Concurrent aspirin therapy is recommended except when contraindicated.

Table 11 lists the volume of FRAGMIN, based on the 9.5 mL multiple-dose vial (10,000 IU/mL), to be administered for a range of patient weights.

Table 11
Volume of FRAGMIN to be Administered by Patient Weight, Based on 9.5 mL Vial (10,000 IU/mL)

Patient weight (lb)	<110	110 to 131	132 to 153	154 to 175	176 to 197	≥198
Patient weight (kg)	<50	50 to 59	60 to 69	70 to 79	80 to 89	≥90
Volume of FRAGMIN (mL)	0.55	0.65	0.75	0.90	1.00	1.00

Hip Replacement Surgery:

Table 12 presents the dosing options for patients undergoing hip replacement surgery. The usual duration of administration is 5 to 10 days after surgery; up to 14 days of treatment with FRAGMIN have been well tolerated in clinical trials.

Table 12

Dosing Options for Patients Undergoing Hip Replacement Surgery

Timing of First Dose of FRAGMIN	Dose of FRAGMIN to be Given Subcutaneously			
	10 to 14 Hours Before Surgery	Within 2 Hours Before Surgery	4 to 8 Hours After Surgery [1]	Postoperative Period [2]
Postoperative Start	---	---	2500 IU [3]	5000 IU qd
Preoperative Start - Day of Surgery	---	2500 IU	2500 IU [3]	5000 IU qd
Preoperative Start - Evening Before Surgery [4]	5000 IU	---	5000 IU	5000 IU qd

1 Or later, if hemostasis has not been achieved.
2 Up to 14 days of treatment was well tolerated in controlled clinical trials, where the usual duration of treatment was 5 to 10 days postoperatively.
3 Allow a minimum of 6 hours between this dose and the dose to be given on Postoperative Day 1. Adjust the timing of the dose on Postoperative Day 1 accordingly.
4 Allow approximately 24 hours between doses.

Abdominal Surgery:
In patients undergoing abdominal surgery with a risk of thromboembolic complications, the recommended dose of FRAGMIN is 2500 IU administered by s.c. injection once daily, starting 1 to 2 hours prior to surgery and repeated once daily postoperatively. The usual duration of administration is 5 to 10 days.

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 postoperatively. The usual duration of administration is 5 to 10 days. 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 postoperatively. The usual duration of administration is 5 to 10 days.

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

Medical Patients with Severely Restricted Mobility During Acute Illness:
In medical patients with severely restricted mobility during acute illness, the recommended dose of FRAGMIN is 5000 IU administered by s.c. injection once daily. In clinical trials, the usual duration of administration was 12 to 14 days.

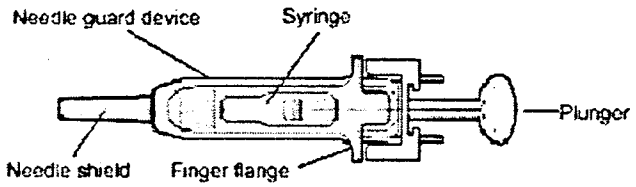
Administration:
FRAGMIN is administered by subcutaneous injection. It must not be administered by intramuscular injection.

Subcutaneous injection technique: Patients should be sitting or lying down and FRAGMIN administered by deep s.c. injection. To ensure delivery of the full dose, do not expel the air bubble from the prefilled syringe before 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.

After first penetration of the rubber stopper, store the multiple-dose vials at room temperature for up to 2 weeks. Discard any unused solution after 2 weeks.

Instructions for using the prefilled single-dose syringes preassembled with passive needle guard devices:



Fixed dose syringes: Hold the syringe assembly by the open sides of the device. Remove the needle shield. Insert the needle into the injection area as instructed above. Depress the plunger of the syringe while holding the finger flange **until the entire dose has been given**. The needle guard will **not** be activated unless the **entire** dose has been given. Remove needle from the patient. Let go of the plunger and allow syringe to move up inside the device until the entire needle is guarded. Discard the syringe assembly in approved containers.

Graduated syringes: Hold the syringe assembly by the open sides of the device. Remove the needle shield. With the needle pointing up, prepare the syringe by expelling the air bubble and then continuing to depress the plunger ~~down~~ to the desired dose or volume, discarding the extra solution in an appropriate manner. Insert the needle into the injection area as instructed above. Depress the plunger of the syringe while holding the finger flange **until the entire dose remaining in the syringe has been given**. The needle guard will **not** be activated unless the **entire** dose has been given. Remove needle from the patient. Let go of the plunger and allow syringe to move up inside the device until the entire needle is guarded. Discard the syringe assembly in approved containers.

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 and preassembled with UltraSafe Passive™ Needle Guard* devices.
Package of 10:

2500 anti-Factor Xa IU	NDC 0013-2406-91
5000 anti-Factor Xa IU	NDC 0013-2426-91

0.3 mL single-dose prefilled syringe, affixed with a 27-gauge x 1/2 inch needle and preassembled with UltraSafe Passive™ Needle Guard* devices.
Package of 10:

7500 anti-Factor Xa IU	NDC 0013-2426-01

1.0 mL single-dose graduated syringe, affixed with a 27-gauge x 1/2 inch needle and preassembled with UltraSafe Passive™ Needle Guard* devices.
Package of 10:

10,000 anti-Factor Xa IU	NDC 0013-5190-01

3.8 mL multiple-dose vial:

25,000 anti-Factor Xa IU/mL (95,000 anti-Factor Xa IU/vial)	NDC 0013-5191-01

9.5 mL multiple-dose vial:

10,000 anti-Factor Xa IU/mL (95,000 anti-Factor Xa IU/vial)	NDC 0013-2436-06

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

Rx only

U.S. Patent 4,303,651

* UltraSafe Passive™ Needle Guard is a trademark of Safety Syringes, Inc.

Manufactured for: Pharmacia & Upjohn Company
A subsidiary of Pharmacia Corporation
Kalamazoo, MI 49001, USA

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

Pharmacia N.V./S.A.
Puurs, Belgium
(multiple-dose vial)

[Updated version control code] [Updated revision date]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-287/S-032

SUMMARY REVIEW

Division Director Summary Review of a Supplemental New Drug Application

NDA: 20-287/S-032
Drug: Fragmin® (dalteparin sodium) Injection
Applicant: Pharmacia and Upjohn
Date: December 3, 2003

This supplemental new drug application seeks approval of dalteparin for the indication of prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness. Dalteparin is already approved for the following indications:

- "FRAGMIN Injection is indicated for the prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin therapy..."
- "FRAGMIN is also indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE):
  - In patients undergoing hip replacement surgery;
  - In patients undergoing abdominal surgery who are at risk for thromboembolic complications."

Summary of Safety and Effectiveness

The application is supported by a single, prospective, randomized, double-blind, parallel group, placebo-controlled, multicenter study (the PREVENT study). To be eligible, general medical patients must have had recent (≤ 3 days) restricted mobility defined as confinement to bed during waking hours and must have been hospitalized for NYHA Class III or IV heart failure, acute respiratory failure not requiring ventilatory support, or other acute medical conditions associated with one or more predefined risk factors for VTE. Patients were randomized (1:1) to dalteparin 5000 IU or placebo once a day s.c. during Days 1 to 14. The primary efficacy endpoint was defined as at least one of the following within Days 1 to 21: asymptomatic DVT (diagnosed by compression ultrasound), a confirmed symptomatic DVT, a confirmed PE or sudden death. A total of 3681 patients were randomized and treated (1848 dalteparin and 1833 placebo). The mean age was 69 years, 92% were white and 52% were female. The major reasons for hospitalization were NYHA heart failure (52%), acute respiratory failure (30%), and acute infectious disease (37%). A total of 2991 patients were evaluable for the primary endpoint (1518 dalteparin and 1473 placebo). Fragmin significantly reduced the incidence of thromboembolic events by Day 21 (Table 1).

Adverse events were reviewed in detail by Dr. Ruyi He. The most significant drug-related adverse event was major bleeding. A bleeding event was considered major if (1) it was accompanied by a decrease in hemoglobin of ≥ 2 g/dL in connection with clinical

symptoms; (2) it was intraocular, spinal/epidural, intracranial, or retroperitoneal bleeding; (3) it required transfusion of ≥ 2 units of blood products; (4) it required significant medical or surgical intervention; or (5) it led to death. Major bleeding events by Day 14 and Day 21 were greater in the dalteparin arm than in the placebo arm (Table 2). Three of the major bleeding events that occurred by Day 21 were fatal, all were due to gastrointestinal hemorrhage. Two patients were in the dalteparin group and one was in the placebo group. Two deaths from bleeding events occurred after Day 21. One patient in the dalteparin group died on Day 71 (2 months after the last dose of dalteparin) of a subdural hematoma and one patient in the placebo group died from a subarachnoid hemorrhage that started on Day 55.

Table 1: Efficacy Summary

	Fragmin 5000 IU q.d., s.c.	Placebo q.d., s.c.
Number of treated patients	1848	1833
Treatment failure in evaluable patients (Day 21)[1]	42/1518 (2.77%)[2]	73/1473 (4.96%)
Total thromboembolic events (Day 21)	37/1513 (2.45%)	70/1470 (4.76%)
Total DVT	32/1508 (2.12%)	64/1464 (4.37%)
Proximal DVT	29/1518 (1.91%)	60/1474 (4.07%)
Symptomatic DVT	10/1759 (0.57%)	17/1740 (0.98%)
PE	5/1759 (0.28%)	6/1740 (0.34%)
Sudden Death	5/1829 (0.27%)	3/1807 (0.17%)

[1]Defined as DVT (diagnosed by compression ultrasound at Day 21-24), confirmed symptomatic DVT, confirmed PE, or sudden death.
[2]p value=0.0015

Table 2: Major Bleeding Events

	Fragmin 5000 IU q.d., s.c	Placebo q.d., s.c.
Major bleeding events at Day 14	8/1848 (0.42%)	0/1833 (0%)
Major bleeding events at Day 21	9/1848 (0.49%)	3/1833 (0.16%)

Medical Officer Review

The medical officer review by Dr. Ruyi He was completed on November 12, 2003. Dr. He recommended approval of the application with labeling changes. He also recommended that the request for a waiver of pediatric studies be granted and that the postmarketing database should be monitored for thrombocytosis to assess the possibility of a direct causal relationship.

Medical Team Leader Memorandum

The medical team leader memorandum by Dr. Kathy Robie-Suh was completed on November 24, 2003. Dr. Robie-Suh recommended that the application should be approved. Because the population studied was similar to that of the enoxaparin MEDENOX trial and because the enoxaparin indication is for patients with "severely restricted mobility" she recommended that "severely" be added to the dalteparin indication.

Statistical Review and Evaluation

The statistical review by Dr. Thomas Permutt was completed on November 12, 2003. Dr. Permutt concluded that "dalteparin was effective in reducing the incidence of venous thrombo-embolic events in immobilized medical patients." Dr. Permutt's review discussed the issues of missing data and the failure of the study to meet its pre-specified p value of 0.001. Regarding missing data, he stated that

> "Although the primary analysis is described as being on the basis of intent to treat, about 20 percent of the patients did not have the ultrasonographic evaluation, or had it but with inconclusive results. Thus, the number of patients with missing data dwarfs the number of events. Some sensitivity analyses were performed. If these patients were treated as not having events, rather than as missing, the denominators were simply inflated, and the results were similar to those in the primary analysis. If they were treated as *having* events, the results were still statistically significant, but only because the number of missing observations in the placebo group exceeded that in the dalteparin group. Obviously the results could not withstand a worst-case analysis with placebo patients imputed as not having events and dalteparin patients as having them."

Regarding the prespecified p value he states that

> "...the interpretation of a significant result at level 0.0015 need not be different if a level of 0.001 was specified in the protocol than if it was not. The results are significant at level 0.0015, for whatever that is worth.
>
> What is worth here, I think, is strong evidence that dalteparin has the purported effect of preventing venous thrombo-embolic events in this population. The primary significance test is supported by evidence of consistent effects by sex, age, and region. The conclusion of efficacy is also supported by evidence of efficacy of dalteparin as an anticoagulant in other populations."

CMC Review

The CMC review by Dr. Ali Al-Hakim was completed on October 28, 2003 and recommended approval. A categorical exclusion for an environmental assessment was found to be satisfactory.

Division of Scientific Investigations Inspection

No inspection was requested.

Advisory Committee Meeting

There was no Advisory Committee Meeting for this application.

Conclusion

I concur that the application should be approved. The applicant has submitted one large, randomized, double-blind, placebo-controlled multicenter trial that demonstrates a highly statistically significant effect on the primary endpoint of treatment failure. The incidence of major bleeding is lower than that observed in studies conducted for the other approved indications. As Dr. Permutt stated, the adequacy of a single trial for approval of the indication is also supported by the consistent effects by sex, age, and region. More importantly, the anticoagulant effects of dalteparin are confirmed by the studies used to support the three approved indications. Since as Dr. Robie-Suh pointed out, the populations in the dalteparin and enoxaparin studies were similar, the language regarding impairment of mobility should be the same in each label.

Recommendation

The application should be approved when the labeling is finalized.

{see appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director, Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Justice
12/3/03 06:16:34 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-032

LABELING REVIEWS

REGULATORY PROJECT MANAGEMENT LABELING
Division of Gastrointestinal and Coagulation Drug Products (DGICDP)

Application Number: NDA 20-287/SE1-032

Name of Drug: Fragmin® (dalteparin sodium, injection)

Sponsor: Pharmacia & Upjohn Company

Materials Reviewed: Package Insert (PI)

Submission Date: February 7, 2003
Receipt Date: February 10, 2003

Background and Summary

Fragmin is a low molecular weight heparin (LMWH) approved December 22, 1994, for use in the prophylaxis of deep venous thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing hip replacement surgery and in patients undergoing abdominal surgery who are at risk for thromboembolic complications and for treatment of unstable angina and non-Q-wave myocardial infarction.

Efficacy Supplement-032 (SE1-032) was submitted on February 7, 2003 (received February 10, 2003) as a prior approval efficacy supplement to add a new indication for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness.

The most recently approved package insert (PI) for Fragmin is Labeling Supplement S-031 submitted January 14, 2003, received January 15, 2003, and approved June 30, 2003. The Final Printed Labeling for S-031 was submitted July 18, 2003, received July 21, 2003, acknowledged and retained November 6, 2003.

Review

The PI proposed for S-032 submitted February 7, 2003, received February 10, 2003, (no identifying number) was compared to the FPL for S-031 submitted July 18, 2003, (received July 21, 2003, acknowledge and retained November 3, 2003) identified as version control code "5R6775 KV0404-13 818 312 008." The proposed labeling for S-032 is identical to the approved labeling acknowledged and retained November 6, 2003, under S-031 except for the following:

I. **TRADENAME** section

The sponsor has not included the name of the firm "Pharmacia" on the line following the drug product tradename and established name Fragmin® (dalteparin sodium injection).

The deletion is editorial and acceptable.

II. **CLINICAL TRIALS** section

Following the subsection entitled, "**Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery in Patients at Risk for Thromboembolic Complications**" the sponsor added the following new subsection:

"**Prophylaxis of Deep Vein Thrombosis in Medical Patients at Risk for Thromboembolic Complications due to Restricted Mobility During Acute Illness:** In a double-blind, multi-center, randomized, placebo-controlled clinical trial, general medical patients with restricted mobility who were at risk of venous thromboembolism were randomized to receive either FRAGMIN 5000 IU or placebo s.c. once daily during Days 1 to 14 of the study. The primary endpoint was evaluated at Day 21, and the follow-up period was up to Day 90. These patients had an acute medical condition requiring a projected hospital stay of at least 4 days, and were confined to bed during waking hours. The study included patients with congestive heart failure (NYHA Class III or IV), acute respiratory failure not requiring ventilatory support,

[redacted]

The prophylactic effect was sustained through Day 90.

Table 6
Efficacy of FRAGMIN in the Prophylaxis of Deep Vein Thrombosis, [redacted] in Medical Patients with Restricted Mobility during Acute Illness

Indication	Dosing Regimen	
	FRAGMIN 5000 IU [redacted] s.c.	Placebo [redacted] s.c.
All Treated Medical Patients During Acute Illness	1848	1833
[redacted]		

The Medical Officer should comment on this addition.

III. **INDICATIONS AND USAGE** section

In the second paragraph, first sentence that begins, "FRAGMIN is also indicated for the prophylaxis of deep vein thrombosis . . ." in the third sentence that reads, "In patients undergoing abdominal surgery who are at risk for thromboembolic complications," the sponsor revised the period at the end of the sentence to a semicolon. The sponsor also followed the third sentence that begins, "In patients undergoing abdominal surgery . . . " with the following sentence: "In medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness."

The proposed sentence adds a new indication to the labeling. The Medical Officer should comment on the addition.

IV. **WARNINGS** section

A. In the **Miscellaneous** subsection, in the first sentence that reads "The multiple-dose vial of FRAGMIN contains . . ." the sponsor added an "s" to the word "vial" to indicate that FRAGMIN is now available in two multiple-dose vials.

The addition is editorial and acceptable.

B. In the **Miscellaneous** subsection, in the third sentence that reads, "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**). . . ." the sponsor has not bolded the phrase "PRECAUTIONS, Pregnancy Category B., Nonteratogenic Effects."

The phrase should be bolded as in the approved labeling contained in S-031.

V. **PRECAUTIONS** section

A. In the **Drug Interactions** subsection, in the first sentence that reads "FRAGMIN should be used with care in patients receiving oral anticoagulants, platelet inhibitors, and thrombolytic agents because of increased risk of bleeding (see **PRECAUTIONS, Laboratory Tests**)," the sponsor did not bold the phrase "**PRECAUTIONS, Laboratory Tests.**"

The phrase should be bolded as in the approved labeling contained in S-031.

B. In the **Nonteratogenic Effects** subsection, in the second sentence that begins "The 9.5 mL multiple-dose vial of FRAGMIN . . ." the sponsor deleted the phrase "9.5 mL," added the letter "s" to the word "vial" and deleted the letter "s" from the word "contains" so that the sentence reads as follows:

"The multiple-dose vials of FRAGMIN contain 14 mg/mL of benzyl alcohol."

The revisions are editorial and acceptable.

C. The sponsor has not included the **Geriatric Use** subsection that follows the **Pediatric Use** subsection in the approved labeling contained in S-011 (submitted August 25, 1998, received August 26, 1998, refused to file September 14, 1998; resubmitted February 4, 1999, received February 8, 1999; amended December 4, 2001, received December 5, 2001; amended December 19, 2001, received December 20, 2001; amended September 12, 2002, received September 13, 2002; amended January 16, 2003, received January 17, 2003, approved February 27, 2003; acknowledge and retained May 12, 2003). The following section should be included in the labeling:

"Of the total number of patients in clinical studies of FRAGMIN, 2765 patients were 65 years of age or older and 897 were 75 or older. No overall differences in effectiveness were observed between these subjects and younger subjects. Some studies suggest that the risk of bleeding increases with age. Postmarketing surveillance and literature reports have not revealed additional differences in the safety of FRAGMIN between elderly and younger patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised, particularly in geriatric patients with low body weight (<45 kg) and those predisposed to decreased renal function (see also **CLINICAL PHARMACOLOGY** and **General** and **Drug Interactions** subsections of **PRECAUTIONS**)."

This section was added in S-011 (approved February June 27, 2003). The sponsor should include this section in the PRECAUTIONS section of the PI.

VI. **ADVERSE REACTIONS** section

A. **Hemorrhage** subsection

1. ***Unstable Angina and Non-Q-Wave Myocardial Infarction*** sub-subsection

a. In the first sentence that begins, "Table 6 summarizes major bleeding . . ." the sponsor replaced the number "6" with the number "7" so that the sentence reads "Table 7 summarizes major bleeding events that occurred with FRAGMIN, heparin, and placebo in clinical trials of unstable angina and non-Q-wave myocardial infarction."

The revision of the Table number realigns the order of the tables because of the addition of the new Table 6 entitled "Table 6 Efficacy of FRAGMIN in the Prophylaxis of Deep Vein Thrombosis, Pulmonary Embolism, or Sudden Death in Medical Patients with Restricted Mobility during Acute Illness." The revision is editorial and acceptable.

b. In the Table entitled "**Major Bleeding Events in Unstable Angina and Non-Q-Wave Myocardial Infarction**" the sponsor revised the Table number from "6" to "7" to include the previously added new Table 6.

The revision is editorial and acceptable.

2. ***Hip Replacement Surgery*** sub-subsection

a. In the first paragraph, the first sentence that begins, "Table 7 summarizes:" the sponsor revised the table number "7" to "8" so that the sentence reads "Table 8 summarizes: 1) all major bleeding events and, 2) other bleeding events possibly or probably related to treatment with FRAGMIN (preoperative dosing regimen), warfarin sodium, or heparin in two hip replacement surgery clinical trials."

The revision was made to include the previously added new Table 6. The revision is editorial and acceptable.

b. In the title of Table 7, the sponsor revised the number from "7" to "8" so that the title reads "Table 8 Bleeding Events Following Hip Replacement Surgery"

The revision was made to include the previously added new Table 6. The revision is editorial and acceptable.

3. *Abdominal Surgery* sub-subsection

   a. In the first sentence that begins "Table 8 summarizes bleeding events . . ." the sponsor revised the number "8" to number "9" so that the sentence reads "Table 9 summarizes bleeding events that occurred in clinical trials which studied FRAGMIN 2500 and 5000 IU administered once daily to abdominal surgery patients."

      The revision was made to include the previously added new Table 6. The revision is editorial and acceptable.

   b. In the title of Table 8, the sponsor revised the number from "8" to "9" so that the title reads "Table 9 Bleeding Events Following Abdominal Surgery"

      The revision was made to include the previously added new Table 6. The revision is editorial and acceptable.

4. *Medical Patients with Restricted Mobility* sub-subsection

   The sponsor added the following section following the ***Abdominal Surgery*** sub-subsection:

   "Table 10 summarizes major bleeding events that occurred in a clinical trial of medical patients with restricted mobility during acute illness.

Table 10
Bleeding Events in Medical Patients with Restricted Mobility

Indication	Dosing Regimen	
Medical Patients with Restricted Mobility	**FRAGMIN 5000 IU ——— s.c.**	**Placebo ——— s.c.**
Major Bleeding Events[1] at Day 14	8/1848 (0.43%)	0/1833 (0%)
Major Bleeding Events[1] at Day 21	9/1848 (0.49%)	3/1833 (0.16%)

[1] A bleeding event was considered major if: 1) was accompanied by a decrease in hemoglobin of ≥ 2 g/dL in connection with clinical symptoms; 2) intraocular, spinal/epidural, intracranial, or retroperitoneal bleeding; 3) required transfusion of ≥ 2 units of blood products; 4) required significant medical or surgical intervention; or 5) led to death.

Three of the major bleeding events that occurred by Day 21 were fatal, all due to gastrointestinal hemorrhage (two patients in the group treated with FRAGMIN and one in the group receiving placebo). Two deaths occurred after Day 21: one patient in the placebo group died from a subarachnoid hemorrhage that started on Day 55,

and one patient died on day 71 (two months after receiving the last dose of FRAGMIN) from a subdural hematoma."

The Medical Officer should comment on this addition.

B. **Other** subsection

1. ***Ongoing Safety Surveillance*** sub-subsection

The sponsor revised the paragraph under "***Ongoing Safety Surveillance***" sub-subsection to update information on postmarketing spontaneous reports of spinal hematomas. The paragraph was revised as follows. Additions are denoted with double underlines and deletions are denoted with ~~strikeout letters~~.

"Since first international market introduction in 1985, there have been ~~six~~ nine reports of epidural or spinal hematoma formation with concurrent use of dalteparin sodium and spinal/epidural anesthesia or spinal puncture. Five of the ~~six~~ nine patients had post-operative indwelling epidural catheters placed for analgesia or received additional drugs affecting hemostasis. The hematomas caused long-term or permanent paralysis (partial or complete) in ~~four~~ seven of these cases. ~~The sixth~~ One patient experienced temporary paraplegia but made a full recovery, and one patient had no neurological deficit. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

The Medical Officer should comment on these revisions.

VII. **DOSAGE and ADMINISTRATION** section

A. **Unstable Angina and Non-Q-Wave Myocardial Infarction** subsection

1. In the second paragraph, first sentence that begins, "Table 9 lists . . ." the sponsor revised the number "9" to the number "11" and added the phrase "based on the 9.5 mL multiple-dose vial (10,000 IU/mL)," after the word "FRAGMIN" so that the sentence reads "Table 11 lists the volume of FRAGMIN, based on the 9.5 mL multiple-dose vial (10,000 IU/mL), to be administered for a range of patient weights.

The revision of the table number realigns the order of the tables because of the addition of the new Table 6 entitled "Table 6 Efficacy of FRAGMIN in the Prophylaxis of Deep Vein Thrombosis, Pulmonary Embolism, or Sudden Death in Medical Patients with Restricted Mobility during Acute Illness" and the new Table 10 entitled "Bleeding Events in Medical Patients with Restricted Mobility." The revision is editorial and acceptable.

2. In Table 9 entitled "Volume of FRAGMIN to be Administered by Patient Weight," the sponsor revised the table number from "9" to "11" and deleted the footnote that

reads "calculated volume based on the 9.5 mL multiple-dose vial (10,000 anti-Factor Xa IU/mL)"

a. **The revision of the table number realigns the order of the tables because of the addition of the new Tables 6 and 10. This is an editorial revision and is acceptable.**

b. **The sponsor added the information in the deleted footnote to the sentence prior to the new Table 11. The sponsor noted in the submission that 1) because the volumes required to obtain the doses for the 9.5 mL vial in the table are much smaller for the 3.8 mL vial, 2) because the increments in the volume for weight differences for the 3.8 mL vial are very small, and 3) because it would be difficult to draw a dose accurately for the 3.8 mL vial unless a 0.5 mL tuberculin syringe is used, they did not add the volumes for the 3.8 mL vial to the table, but decided to emphasize that the volumes are only for the 9.5 mL vial. The Medical Officer should comment on the inclusion and placement of the information.**

B. **Hip Replacement Surgery** subsection

1. In the first paragraph, first sentence that reads "Table 10 presents the dosing options for patients undergoing hip replacement surgery," the sponsor revised the table number from "10" to "12."

   The revision of the table number realigns the order of the tables because of the addition of the new Tables 6 and 10. The revision is editorial and acceptable.

2. In the title of Table 10, the sponsor revised the number from "10" to "12" so that the title reads "Table 12 Dosing Options for Patients Undergoing Hip Replacement Surgery."

   The revision of the table number realigns the order of the tables because of the addition of the new Tables 6 and 10. The revision is editorial and acceptable.

C. **Medical patients with Restricted Mobility** subsection

Following the Abdominal Surgery subsection, the sponsor added the following **Medical Patients with Restricted Mobility** subsection:

"In medical patients with restricted mobility during acute illness, the recommended dose of FRAGMIN is 5000 IU administered by s.c. injection once daily. In clinical trials, the usual duration of administration was 12 to 14 days."

The Medical Officer should comment on the new section.

D. **Administration** subsection, ***Instructions for using the prefilled single-dose syringes preassembled with passive needle guard devices*** sub-subsection, ***Graduated syringes*** sub-sub-subsection

In the first paragraph, third sentence that begins, " Prepare the syringe by . . ." the sponsor changed the case in the word "Prepare" from capital letter to lower case and added the phrase "With the [redacted] " prior to the word "Prepare" so that the sentence reads " With the [redacted] prepare the syringe by [redacted] the plunger down to the desired dose or volume, discarding the extra solution in an appropriate manner."

The Medical Officer should comment on the proposed revision.

Conclusions

1. **The following revisions to the PI submitted February 7, 2003 (received February 10, 2003) are editorial and acceptable: I., IV.A., V.B., VI., A.1.-3., VII.A.1., VII.A.2.a., VII.B.1.-2.**

2. **The following items should be reviewed by the Medical Officer: II., III., VI.A.4., VI.B., VII.A.2.b., VII.C.-D.**

3. **The following items should be conveyed to the sponsor: IV. B., V.A., V.C.,**

4. **This labeling supplement could be approved pending comments from the Medical Officer and incorporation of the PRECAUTIONS section, Geriatric Use subsection and minor editorial revisions.**

Diane Moore, B.S.
Regulatory Health Project Manager

Julieann DuBeau, MSN, RN
Chief, Project Management Staff

Drafted: dm/November 4, 2003
Revised: J.DuBeau 11.6.03
Initialed: J.DuBeau 11.6.03
Finalized: November 6, 2003
Filename: N20287S32Lblrev.doc

RPM LABELING REVIEW

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/s/

Diane V. Moore
11/6/03 04:35:45 PM
CSO

Julieann DuBeau
11/6/03 04:42:28 PM
CSO

Division of Gastrointestinal and Coagulation Drug Products

REGULATORY PROJECT MANAGEMENT LABELING REVIEW

Application Number: NDA 20-287/SCP-032 Final Printed Labeling (FPL)

Name of Drug: Fragmin® (dalteparin sodium) Injection

Sponsor: Pharmacia & Upjohn Company

Materials Reviewed: Package Insert (PI)

Submission Date: January 9, 2004
Receipt Date: January 12, 2004

Background and Summary

Background:

This FPL is to NDA 20-287/SE1-032 (S-032), submitted February 7, 2003, received February 10, 2004, amended December 10, 2003; received December 10, 2003; approved on draft December 10, 2003. Supplement-032 provided for the use of Fragmin® (dalteparin sodium) injection for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

Review

Package Insert

The Final Printed package insert (PI) proposed for Fragmin® (dalteparin sodium, injection), S-032 submitted January 9, 2004 (received January 12, 2004) identified as version control code "5R7065 376 818 312 111" (Revised December 2003) was compared to the approved labeling from S-032 (submitted February 7, 2003, received February 10, 2003, amended December 10, 2003; received December 10, 2003; approved on draft December 10, 2003) no identifier number. The submitted package insert is identical to the approved package insert submitted December 10, 2003, except for the following:

I. **Black Box Warning** section

In the fourth paragraph, first sentence that begins, "The physician should . . ." the words "WARNINGS," "Hemorrhage," "PRECAUTIONS," and "Drug Interactions" are bolded so that the sentence reads "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**)."

The bolding is editorial and acceptable.

II. **PRECAUTIONS** section, **Nonteratogenic Effects** subsection

In the first paragraph, the sponsor has not revised the second sentence that read "The 9.5 mL multiple-dose vial of FRAGMIN contains 14 mg/mL of benzyl alcohol." The sentence was revised in S-032 to read "The multiple-dose vials of FRAGMIN contain 14 mg/mL of benzyl alcohol."

The omission of the revision is not acceptable.

III. **DOSAGE AND ADMINISTRATION** section, **Administration** subsection, *Subcutaneous injection technique* sub-subsection

A. *Fixed dose syringes* sub-sub-subsection

The following sentence was moved from after the first sentence of the **DOSAGE AND ADMINISTRATION** section, **Administration** subsection, *Subcutaneous Injection technique* sub-subsection that reads, "Patients should be sitting or lying down and FRAGMIN administered by deep s.c. injection." to the first sentence of the **DOSAGE AND ADMINISTRATION** section, **Administration** subsection *Subcutaneous injection technique* sub-subsection *Fixed dose syringes* sub-sub-subsection:

"To ensure delivery of the full dose, do not expel the air bubble from the prefilled syringe before injection."

The deletion of the second sentence from the DOSAGE AND ADMINISTRATION section, Administration subsection, *Subcutaneous Injection technique* sub-subsection and the addition of the same sentence to the DOSAGE AND ADMINISTRATION section, Administration subsection *Subcutaneous Injection technique* sub-subsection *Fixed dose syringes* sub-sub-subsection is the object of review in SLR-034. The revision here is not acceptable.

B. *Graduated syringes* sub-sub-subsection

In the third sentence that reads "With the needle pointing up, prepare the syringe by expelling the air bubble and then continuing to depress the plunger to the desired dose or volume, discarding the extra solution in an appropriate manner." the sponsor has replaced the word "depress" with the word "press" and added the word "down" after the word "plunger" so that the sentence reads "With the needle pointing up, prepare the syringe by expelling the air bubble and then continuing to push the plunger down to the desired dose or volume, discarding the extra solution in an appropriate manner."

The above proposed revision is the object of review in SLR-034. The revision here is not acceptable.

CONCLUSIONS

1. **The FPL for NDA 20-287/S-031 (submitted January 9, 2004, received January 12, 2004 is not acceptable.**

4. **A "not acknowledgement and retain" letter should be sent to the sponsor for the final printed labeling for NDA 20-287/S-032.**

Diane Moore, B.S.
Regulatory Health Project Manager

Drafted: dm/February 4, 2004
Finalized: February 4, 2004
Filename: N20287FAS32rev.doc

RPM LABELING REVIEW

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/s/

Diane V. Moore
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CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-032

MEDICAL REVIEW

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

NDA:	20-287/S-032
SPONSOR:	PHARMACIA & UPJOHN 7000 Portage Road Kalamazoo, MI 49001-0199
Drug name:	**FRAGMIN** (Dalteparin sodium injection)
Subject:	Efficacy Supplement for the indication of the prophylaxis of DVT, which may lead to PE in patients who are at risk of thromboembolic complications due to restricted mobility during acute illness.
Date submitted:	February 7, 2003 electronically on CD-ROM
Date received:	February 12, 2003
Review completed:	November 12, 2003
Reviewer:	Ruyi He, M.D.

Table of Contents

Clinical Review for NDA 20-287/S-032

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Dalteparin sodium is approvable as an additional option to the physician considering thromboprophylaxis of deep vein thrombosis (DVT, see Appendix B for abbreviation), which may lead to pulmonary embolism (PE) in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness. The recommended dose of dalteparin sodium is 5000 IU subcutaneously once daily for 12 to 14 days. For approval for this proposed indication, the sponsor should modify the dalteparin sodium labeling, as recommended in my Medical Officer's Labeling Review (appendix A) and in the FDA Consumer Safety Officer's Labeling Review.

The request for waiver of a requirement for pediatric study should be granted for this indication (prophylaxis of DVT, which may lead to PE in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness). The proposed new indication for dalteparin sodium injection has a rare occurrence in the pediatric population. With the rarity of this condition among the pediatric population, conducting clinical trials would not be possible.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The postmarketing database should be monitored for thrombocytosis to assess the possibility of a direct causal relationship with dalteparin use.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Venous thromboembolism (VTE), defined as DVT and/or PE, is an important cause of morbidity and mortality among hospitalized patients. Established methods of prophylaxis include various mechanical devices, oral anticoagulation, dextran, unfractionated heparin (UFH) in low doses and low molecular weight heparin (LMWH).

Dalteparin sodium is a low molecular weight heparin (LMWH) and was first approved in the US in December 1994. In this submission, the sponsor proposed to expand the indication for prophylaxis of DVT, which may lead to PE in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness.

The efficacy evaluation of the proposed indication is based on a single clinical trial conducted by the sponsor (the PREVENT study). This study was a prospective, randomized, double-blind, parallel group, placebo-controlled, multicenter study. A total of 3706 patients was randomized; 3681 comprised the ITT/safety population (1848 in the dalteparin sodium group and 1833 in the placebo group). The Per Protocol population comprised 2805 patients, 1422 in the dalteparin sodium group and 1383 in the placebo group. Patients were randomized (1:1) to receive either dalteparin sodium 5000 IU or placebo subcutaneously once daily. Study treatment was to be taken for 14 days (not less than 12 days). The study included a 90-day follow-up period.

The safety evaluation included assessment of the data from the PREVENT study, postmarketing safety update and literature reports.

B. Efficacy

Analysis of the primary efficacy endpoint at Day 21+3 demonstrated that, compared with placebo, prophylactic treatment with dalteparin sodium was associated with a clinically relevant 44% decrease in the risk of experiencing a symptomatic DVT (proximal and distal), asymptomatic proximal DVT, non-fatal or fatal PE and/or sudden death. The incidence of the events comprising the primary endpoint at Day 21+3 was 2.77 in the dalteparin sodium treated patients compared with 4.96 in placebo treated patients (difference: -2.19; 95% CI: -3.57 to -0.81; p=0.0015). Although the p-value was higher than the pre-specified limit of 0.001, it does provide statistical evidence of a treatment effect. These results are clinically meaningful, as demonstrated by the 44% reduction in risk with respect to the primary endpoint. The analysis of the cumulative probability of the primary endpoint showed that the greatest difference between the treatment groups occurred from Day 21 to Day 24, the time period for the evaluation of asymptomatic proximal DVT. Therefore, in this study dalteparin mainly prevented asymptomatic proximal DVT. The results of the per protocol (PP) analysis were consistent with those of the intent-to-treat (ITT) analysis.

The results of the secondary efficacy analyses supported the analysis of the primary endpoint. Compared with the placebo group, dalteparin sodium reduced the incidences of VTE (2.45% vs. 4.76%), DVT (2.12% vs. 4.37%), symptomatic VTE (0.57% vs. 0.98%) and proximal DVT (symptomatic and asymptomatic, 1.91% vs. 4.07%). Event rates were too low for conclusions to be drawn about the incidence of symptomatic PE, fatal PE and distal symptomatic DVT by Day 21. Three cases of sudden death were reported by Day 14, all of which occurred in the dalteparin sodium group. By Day 21 there were 5 cases of sudden death in the dalteparin sodium group as compared to 3 cases in the placebo group. The incidence rate for all deaths was similar in each treatment group.

C. Safety

Dalteparin sodium was well tolerated. The proportion of patients reporting at least 1 adverse event (AE) was similar in each treatment group (39.7% and 39.8% in the dalteparin sodium and placebo groups, respectively). The most frequently reported AE in both treatment groups was exacerbation of chronic obstructive airways disease, reported for 29 patients (1.6%) in the dalteparin sodium group and 39 patients (2.1%) in the placebo group. There were no notable differences between the treatment groups in the incidences of AEs. More dalteparin sodium-treated patients than placebo patients had drug-related AEs (52 [2.8%] patients vs 30 [1.6%] patients). The most commonly reported drug-related AE was thrombocytopenia/ thrombocytopenia aggravated, reported by 6 patients in each treatment group.

A higher number of patients in the dalteparin sodium group had major bleeds than in the placebo group at Day 14 (or discontinuation) and at Day 21 (9/1848 vs. 3/1833). Of the 12 major bleeds occurring by Day 21, 3 cases were fatal (2 in the dalteparin sodium group and 1 case in the placebo group).

A similar proportion of patients in each treatment group had at least 1 AE that led to death from Day 1 to Day 90 (105 patients [5.7%] and 101 patients [5.5%] in the dalteparin sodium and placebo groups, respectively). Adverse events leading to death were most commonly associated with the cardiac disorders system organ class (47 patients [2.5%] and 45 [2.5%] patients in the dalteparin sodium and placebo groups, respectively) and the infections and infestations system organ class (24 patients [1.3%] and 19 patients [1.0%], respectively). The most frequently reported reasons for death were pneumonia, myocardial infarction and cardiac failure. Sixteen of the deaths reported during the study were classified as sudden deaths (i.e., occurred within 24 hours of the onset of an acute event). Of these, 7 cases occurred in dalteparin sodium-treated patients and 9 cases occurred in placebo patients. Eight sudden deaths were reported up to Day 21 (5 in the dalteparin sodium group and 3 in the placebo group); 8 other sudden deaths were reported beyond Day 21. None of the events leading to sudden death was considered related to study medication by investigators. The incidence rates for all cause death were similar in the two treatment groups at Day 90, Day 21 and Day 14.

By Day 90, a total of 251 patients (13.6%) in the dalteparin sodium group and 243 patients (13.3%) in the placebo group reported SAEs. The most frequently reported SAE in both treatment groups was exacerbation of chronic obstructive airways disease, reported for 27 patients (1.5%) in the dalteparin sodium group and 34 patients (1.9%) in the placebo group. Very few patients had SAEs reported to be drug-related (7 and 5 patients in the dalteparin sodium and placebo groups, respectively).

D. Dosing

In medical patients with restricted mobility during acute illness, the recommended dose of

FRAGMIN is 5000 IU administered by s.c. injection once daily. In clinical trials, the usual duration of administration was 12 to 14 days.

No dose-response study was done for the new indication. The recommended dose of dalteparin sodium in surgical patients with a high risk of VTE is 5000 IU and this dose of dalteparin sodium is associated with acceptable safety in surgical patients. Thus, a dose of 5000 IU once daily of dalteparin sodium was chosen for this study.

The 14-day treatment period should be sufficient for most patients to become mobile at which point, from a pathophysiological standpoint, the risk of VTE should diminish.

E. Special Populations

Slightly more female patients than male patients were enrolled into the study (52% vs. 48%). The incidence of the primary endpoint was lower in the dalteparin sodium-treated patients than in the placebo-treated patients for both male and female patients. The risk reduction was similar for males and females. Major bleeds were seen in more females (6/964) than males (3/884). More males (13/884) than females (6/964) had minor bleeds. There was no difference between genders for the overall incidence of bleeding.

Most patients in this study were aged 65 or over (66%) and most were white (92%). In patients < 65 years and in patients $\geq$ 65 years, the incidence of the primary endpoint was lower in the dalteparin sodium-treated patients than in the placebo-treated patients. The incidences of the primary endpoint in both treatment groups were also lower in patients <65 years than in patients $\geq$ 65 years. In patients aged $\geq$ 65 years compared to those aged < 65 years, there appeared to be a slightly higher incidence of major (7/1224 vs. 2/624) and minor bleeds (14/1224 vs. 5/624). Since the groups of non-Caucasian patients were small (about 8%), subgroup analysis of race on response rate did not seem meaningful.

The proposed new indication for dalteparin sodium injection is uncommon in the pediatric population. The sponsor requests a full waiver authorization from providing Pediatric Use information. No pediatric studies are recommended at this time.

The safety of dalteparin sodium in pregnant women has not been evaluated. No pregnancies were reported during the study.

No data were provided in this submission regarding dalteparin sodium use in other populations such as renal or hepatic compromised patients.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Dalteparin sodium (injection; Fragmin, PNU-180524E, Kabi 2165) is a low molecular weight heparin (LMWH).

Dalteparin sodium is the sodium salt of depolymerized heparin, derived from porcine intestinal mucosa. It consists of a distribution of sulphated polysaccharides with an average molecular weight of 6000 daltons. It is an antithrombotic agent, which derives its efficacy from the ability to inhibit activated coagulation factors by catalyzing the effect of antithrombin. Dalteparin sodium potentiates both Factor Xa and Factor IIa inhibition, but the potentiality of Factor Xa inhibition is two to three times higher than Factor IIa. It exerts smaller effects on coagulation time, platelet function and lipolysis than heparin, and is less sensitive to neutralizing components in blood, which results in more predictable dose-response and diminished need for monitoring.

Dalteparin sodium was first approved in the US in December 1994 (NDA 20-287), and has been marketed by Pharmacia since 1985. Currently, dalteparin sodium is approved in over 60 countries worldwide for prevention and/or treatment venous thromboembolism.

In the U.S., dalteparin sodium is approved for:

- The prophylaxis of ischemic complications in unstable coronary artery disease (unstable angina and non-Q-wave myocardial infarction).
- The prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing hip replacement surgery; in patients undergoing abdominal surgery who are at risk for thromboembolic complications.

In this submission, the sponsor proposed to expand the indication for dalteparin sodium (5000 IU subcutaneously injection once daily for 14 days) to include the prophylaxis of DVT, which may lead to PE in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness.

B. State of Armamentarium for Indication(s)

Venous thromboembolism (VTE), defined as DVT and/or PE, is an important cause of morbidity and mortality among hospitalized patients.

Although the frequency of VTE has not been precisely established in general medical patients, it has been reported as high as 12% of medical patients with severely restricted mobility during acute illness will develop VTE (Lovenox package insert).

Established methods of prophylaxis include various mechanical devices, oral anticoagulation, dextran, unfractionated heparin (UFH) in low doses and LMWH. Lovenox (enoxaparin sodium, another LMWH) is approved for the indication of prophylaxis of VTE in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

There are no reported trials of mechanical methods of prophylaxis, such as graduated elastic compression stockings or intermittent pneumatic compression (IPC) in medical patients. Heparins are widely used in moderate- and high-risk surgical patients to prevent DVT and PE. The American College of Chest Physicians (ACCP) recommends treatment with low-dose unfractionated heparin (LDUH) (5000 IU 2-3 times daily) or LMWH (dose not specified).

C. Important Milestones in Product Development

Fragmin was approved December 22, 1994, for prophylaxis of DVT, which may lead to PE in patients undergoing abdominal surgery who are at risk for thromboembolic complications. Fragmin is also indicated for prophylaxis of DVT, which may lead to PE in patients undergoing hip replacement surgery who are at risk for thromboembolic complications. On May 25, 1999, Fragmin was approved for prophylaxis of ischemic complications in unstable angina and non-Q-Wave Myocardial Infarction, when concurrently administered with aspirin therapy.

On August 4, 2000, Pharmacia & Upjohn submitted a meeting request to IND 25,924 to discuss a clinical development program for a new indication: thromboprophylaxis in patients who require prolonged hospitalization for acute medical conditions and who are at risk for thromboembolic complications. The Agency denied the meeting request, but provided a written response to the questions posed in the background package for that meeting in a regulatory letter on August 23, 2000. On January 30, 2001, the sponsor submitted an amendment to the December 21, 2000 background package to provide for a revised protocol summary for the proposed double-blind, placebo-controlled study entitled "Fragmin Injection Thromboprophylaxis in General Medical Patients." A Pre-Supplement Submission Meeting (End of Phase 2) was held on February 15, 2001, between the Division and Pharmacia & Upjohn Company to discuss the revised clinical development plan, the scientific rationale for use of compression ultrasound in the evaluation of anti-thrombotic drugs in the prophylaxis of venous thromboembolic disease and the dose selection criteria. The Agency provided recommendations to the sponsor regarding these issues (see March 14, 2001, Memorandum of Meeting Minutes to February 15, 2001, meeting under IND 25,924).

The sponsor has performed the study entitled "Prophylaxis of venous thromboembolism in patients with acute medical conditions requiring prolonged immobilization: a comparison of dalteparin (FRAGMIN) 5000 IU Vs placebo in a double-blind, randomized, multi-center study (PREVENT)" (Study 524-E-CVD-0042-033)." On October 10, 2002, the sponsor requested a

pre-NDA meeting to discuss the results of this study. Pharmacia & Upjohn submitted the background package and revised questions for this meeting on November 4, 2002 (received November 5, 2002). The pre-NDA meeting was held on December 4, 2002 and the Division provided the responses to the questions in the meeting package (meeting minute dated December 4, 2002).

D. Other Relevant Information

Fragmin is currently registered in sixty-one counties worldwide for:

- Treatment of acute deep vein thrombosis and pulmonary embolism
- Thromboprophylaxis in patients undergoing surgery
- Thromboprophylaxis in unstable coronary artery disease (unstable angina and non-Q-wave myocardial infarction)
- Thromboprophylaxis during hemodialysis and hemofiltration in patients with acute renal failure or chronic renal insufficiency

First registration was granted in Germany, on 26 August 1985.

During the period under review there have been no rejections of new license applications for safety reasons, and no drug suspensions or restriction on distribution for Fragmin. No pharmaceutical changes were made to the product anywhere in the world, for safety reasons.

E. Important Issues with Pharmacologically Related Agents

Lovenox, a LMWH, is approved for the indication of prophylaxis of VTE in medical patients who are at risk for thromboembilic complications due to severely restricted mobility during acute illness.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Dalteparin sodium (PNU-180524, CAS 9041-08-1) also referred to as Kabi 2165, is produced through controlled nitrous acid depolymerization of sodium heparin from porcine intestinal mucosa. It is composed of strongly acidic sulphated polysaccaride chains (oligosaccaride, containing 2,5-anhydro-D-mannitol residues as end groups) with an average molecular weight of 6000 daltons and about 90% of the material within the range 2000 to 9000 daltons.

Chemistry and CMC information for dalteparin sodium is well established and is not included in this efficacy supplement.

Please see Fragmin package insert for the information about Pharmacology and Biopharmaceutics. See Statistics review for the information about statistical issues.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Pharmacokinetics studies were reviewed from previous submission. Please see Fragmin package insert for details. No new pharmacokinetic data have been included in this submission.

B. Pharmacodynamics

Pharmacodynamics studies were reviewed from previous submission. Please see Fragmin package insert for details. No new pharmacodynamic data have been included in this submission.

IV. Description of Clinical Data and Sources

A. Overall Data

The source of data evaluated in the review is a single clinical trial conducted by the sponsor (the PREVENT study). This study was a prospective, randomized, double-blind, parallel group, placebo-controlled, multicenter study. The thromboprophylactic efficacy of dalteparin sodium was assessed by measuring prevention of verified symptomatic VTE (DVT and/or PE), sudden death and asymptomatic proximal DVT in immobilized, patients at risk of VTE for whom prolonged hospitalization (4 days) was anticipated. Patients were not to have been immobilized for more than 3 days before inclusion in the study. Patients were randomized (1:1) to receive either dalteparin sodium 5000 IU or placebo subcutaneously once daily. Study treatment was to be taken for 14 days (not less than 12 days).

B. Tables Listing the Clinical Trials

One single clinical trial conducted by the sponsor (the PREVENT study) was provided in this submission. This study was a prospective, randomized, double-blind, parallel group, placebo-controlled, multicenter study. A total of 3706 patients were randomized, 3681 comprised the ITT/safety population (1848 in the dalteparin sodium group and 1833 in the placebo group). The Per Protocol population comprised 2805 patients, 1422 in the dalteparin sodium group and 1383 in the placebo group.

Patients were randomized (1:1) to receive either dalteparin sodium 5000 IU or placebo subcutaneously once daily. Study treatment was to be taken for 14 days (not less than 12 days). The study included a 90-day follow-up period.

C. Postmarketing Experience

Two postmarketing safety update reports are provided in this submission. One covers the period from 1 July 1996 to 19 September 1999, and the other covers the period from 19 September 1999 to 29 November 2001. In addition, line listings are provided covering the periods from 29 November 2001 to 15 August 2002.

The listed adverse events for dalteparin sodium (last updated: 30 October 2000) include: hemorrhage (bleeding), hematoma at the injection site, reversible non-immunologically mediated thrombocytopenia (type I), pain at injection site, allergic reactions and transient elevations of liver transaminases. Other reported events from post-marketing surveillance include: immunologically-mediated thrombocytopenia (type II), skin necrosis, anaphylactic reactions, and spinal or epidural hematoma.

During the reporting period 01 July 1996 through 19 September 1999, the estimated exposure to dalteparin sodium based on sales volume and average units consumption per approved indication was over ——— patients. A total of 369 serious spontaneous cases were obtained for a total of 477 events. In the same period, 279 non-serious spontaneous cases were obtained for a total of 332 events. The spontaneous serious unlisted events reported three times or more are detailed in Table below.

Table 1: Spontaneously Reported Serious Unlisted Events Reported three times or more from 01 July 1996 through 19 September 1999

Serious unlisted event description	Total number
Pulmonary embolism	36
Thrombophlebitis (all types)	14
Anemia	10
Injection and application site reaction/Surgical complication	6
Thrombosis	5
Fever	4
Death/Leucopenia/Myocardial infarction/Sepsis/Vasculitis	3

From the sponsor's Table 2.7.4: 39 and Module 5.3.6

There was no new safety information that altered the benefit-risk assessment of dalteparin sodium in this report for the period of 01 July 1996 through 19 September 1999.

During the reporting period 20 September 1999 though 29 November 2001, the estimated exposure to dalteparin sodium based on sales volume and average units consumption per approved indication was over ——— patients. A total of 363 serious spontaneous cases were obtained for a total of 547 events. In the same period, 284 non-serious spontaneous cases were obtained for a total of 380 events. The spontaneous serious unlisted events

reported three times or more are included PE/Thrombosis, Anemia/Thrombocythemia, Pyrexia/Phlebitis, Myocardial infarction/Acute circulatory failure/Hypotension, Abdominal pain/Nausea/Chest pain/Hepatitis/Dyspnea, and Duodenitis/Vomiting/Death/Pain in limb/Loss of consciousness/Renal impairment.

Review of all the pharmacovigilance data from July 1996 through to the end of 2001, the number of patients exposed to the product exceeded 16.5 million and a total of 1695 serious adverse events and 866 non-serious adverse events were reported. Approximately half of the serious adverse events (n=840) represented known reactions to dalteparin sodium (such as bleeding episodes, coagulation disorders, and thrombocytopenia). In total, 110 fatal cases with bleeding were reported.

The majority of events are expected reactions to the drug. No changes in severity of the suspected adverse drug reactions (serious and non serious) were observed in the reporting period, as compared with the known safety profile of dalteparin sodium. Thus, there was no new safety information to alter the benefit-risk assessment of dalteparin sodium.

D. Literature Review

The sponsor submitted 50 published literatures related to Fragmin in clinical study reports section. The reviewer has also searched the literatures related to Fragmin up to the date and incorporated them into the review.

V. Clinical Review Methods

A. How the Review was Conducted

The efficacy evaluation of proposed indication is based on only one clinical trial conducted by the sponsor (the PREVENT study). This study was a prospective, randomized, double-blind, parallel group, placebo-controlled, multicenter study. A total of 3706 patients was randomized, 3681 comprised the ITT/safety population (1848 in the dalteparin sodium group and 1833 in the placebo group). The Per Protocol population comprised 2805 patients, 1422 in the dalteparin sodium group and 1383 in the placebo group. Patients were randomized (1:1) to receive either dalteparin sodium 5000 IU or placebo subcutaneously once daily. Study treatment was to be taken for 14 days (not less than 12 days). The study included a 90-day follow-up period.

The safety evaluation included assessment of the data from the PREVENT study, postmarketing safety update and literature reports.

B. Overview of Materials Consulted in Review

The sponsor submitted four CD-ROM's (2.2 GB) in common technical document format as an efficacy supplement to NDA 20-287. Contents of these CD-ROMs are as follows: Cover letter, Labeling, Summaries, Non-clinical study reports, and Clinical study report. In this review, I have

examined material in following sections: Cover letter, Labeling, Summaries, and Clinical study report.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The Division of Scientific Investigations has not been consulted for this efficacy supplement submission. A total of 219 centers were involved in this international study (8 in the USA). The final conclusion was not found to be significantly influenced by the result from any single investigation center.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor has submitted informed consent with each clinical trial protocol. According to the sponsor, the protocol and all amendments for this study were reviewed by an Independent Ethics Committee (IEC), and monitoring and audit procedures performed prior to, during, and upon completion of this study have verified that this study was conducted in accordance with the ethical principles with the following exception:

False data had been submitted to the sponsor for 2 patients by Site No. —— Dr. ——, MD, ——————————. The center's involvement in the study was terminated and no data from this center were entered into the study database.

E. Evaluation of Financial Disclosure

The sponsor submitted a FDA Form 3454 certifying that no investigator of any of the covered clinical studies had any financial interests to disclose.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Analysis of the primary efficacy endpoint at Day 21+3 demonstrated that, compared with placebo, prophylactic treatment with dalteparin sodium was associated with a clinically relevant 44% decrease in the risk of experiencing a symptomatic DVT (proximal and distal), asymptomatic proximal DVT and/or non-fatal and fatal PE and sudden death the primary endpoint). The incidence of the primary endpoint at Day 21+3 was 2.77% (42/1518) in the dalteparin sodium treated patients compared with 4.96% (73/1473) in placebo treated patients (difference: -2.19; 95%CI: -3.57 to -0.81; p=0.0015). Although the p-value was higher than the pre-specified limit of 0.001, it does provide statistical evidence of a treatment effect. These results are clinically meaningful, as demonstrated by the 44% reduction in risk with respect to the primary endpoint. The analysis of the cumulative probability of the primary endpoint showed that the greatest difference between the treatment groups occurred from Day 21 to Day 24, the time period for the evaluation of asymptomatic proximal DVT. Therefore, this study indicates

that dalteparin mainly prevents asymptomatic proximal DVT. The results of the PP analysis were consistent with those of the ITT analysis.

The results of the secondary efficacy analyses supported the analysis of the primary endpoint. Compared with the placebo group, dalteparin sodium reduced the incidences of VTE (2.45% vs. 4.76%), DVT (2.12% vs. 4.37%), symptomatic VTE (0.57% vs. 0.98%) and proximal DVT (symptomatic and asymptomatic, 1.91% vs. 4.07%). Event rates were too low for conclusions to be drawn about the incidence of symptomatic PE, fatal PE and distal symptomatic DVT by Day 21. Three cases of sudden death were reported by Day 14, all of which occurred in the dalteparin sodium group. By Day 21 there were 5 cases of sudden death in the dalteparin sodium group as compared to 3 cases in the placebo group. The incidence rate for all deaths was similar in each treatment group.

B. General Approach to Review of the Efficacy of the Drug

This efficacy supplement submission is based on one pivotal study (the PREVENT study). This study was a prospective, randomized, double-blind, parallel group, placebo-controlled, multicenter study. This study was reviewed in detail.

C. Detailed Review of Trials by Indication

1. Study Design

The PREVENT study was a prospective, randomized, double-blind, parallel group, placebo-controlled, multicenter study that was conducted to establish the thromboprophylactic efficacy and safety of dalteparin sodium in comparison with placebo.

The thromboprophylactic efficacy of dalteparin sodium was assessed by measuring prevention of verified symptomatic VTE (DVT and/or PE), sudden death and asymptomatic proximal DVT in immobilized patients at risk of VTE for whom prolonged hospitalization 4 days) was anticipated. Patients were randomized (1:1) to receive either dalteparin sodium 5000 IU or placebo subcutaneously once daily. Study treatment was to be taken for 14 days (not less than 12 days) and the follow-up was up to 90 days.

During the study, signs and symptoms of VTE were evaluated daily, and at Day 21. Symptomatic DVT was verified by compression ultrasonography (CUS) or venography, and PE was verified by diagnositic ventilation-perfusion (V/Q) lung scan, pulmonary angiography, pulmonary computed tomography (CT), magnetic resonance imaging (MRI) or autopsy. Asymptomatic proximal DVT was verified by CUS on Day 21 with venography used for confirmation only if the results of the CUS were inconclusive. Patients had to report any signs and symptoms of DVT or PE after hospital discharge.

The CUS findings were sent to a central reading facility, the [redacted] where they underwent independent blinded central adjudication for asymptomatic proximal DVTs.

2. Efficacy Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint included the occurrence of one or more clinically relevant thromboembolic events as follows: objectively verified symptomatic DVT (proximal and distal), symptomatic fatal or non-fatal PE, or sudden death by Day 21, or asymptomatic proximal DVT by Day 21+3 (Days 21 through 24).

Secondary Efficacy Endpoints

At Day 21, to compare the incidence in the dalteparin sodium versus the placebo groups of objectively verified:

- symptomatic VTE and sudden death
- VTE
- all DVT (proximal and distal symptomatic DVT)
- proximal DVT (symptomatic and asymptomatic)
- distal symptomatic DVT
- symptomatic PE
- symptomatic VTE (DVT and PE)
- fatal PE
- all cause of death
- sudden death.

At Day 14, or on the day of discontinuation of study medication if this was prior to Day 14, to compare the incidences in the dalteparin sodium versus the placebo group of objectively verified:

- symptomatic VTE and sudden death
- symptomatic VTE
- symptomatic DVT
- symptomatic PE
- fatal PE
- all cause death
- sudden death.

At Day 90 to compare the incidence in the dalteparin sodium versus the placebo groups of symptomatic VTE (DVT and PE), and all cause death.

3. Statistical Methods

The intent-to-treat (ITT) population included all randomized patients who received at least one dose of study drug. The cohort of patients included in the analysis of the primary endpoint comprised all dosed patients who had at least: one conclusive (positive or negative according to ——) CUS or venogram; or who had sudden death between Day 1 and 21; or who had a symptomatic DVT (confirmed by the CEC) between Day 1 and 21; or who had a fatal or non-fatal PE (confirmed by the CEC) between Day 1 and 21. Patients without such conditions were treated as missing for the purpose of analyzing the primary endpoint.

The per protocol (PP) population comprised all randomized patients who met all inclusion criteria, who received at least 12 days of treatment, who missed fewer than two consecutive days of treatment, and who had either an evaluable bilateral DVT assessment according to the protocol or had a verified endpoint (symptomatic DVT, PE or sudden death) or death due to any cause, up to Day 21.

The null hypothesis was that dalteparin sodium and placebo incidence rates were equal, and the alternative hypothesis was that the incidence rates were different. The null hypothesis was to be tested at the 0.001 level of significance with a Cochran-Mantel-Haenszel test, stratified by geographic region. The Breslow-Day test was to be used to test the homogeneity of the strata. A very stringent final alpha level of 0.001 was selected, as a conclusive result was desired from the study. The primary efficacy analysis was based on the ITT population; a PP analysis was also performed.

Additionally, the primary endpoint was further described by calculating two-sided 95% confidence intervals (CIs) not only for each treatment group but for the difference in incidence between the two treatment groups as well. The time until occurrence of the primary endpoint was described by Kaplan-Meier curves.

The secondary efficacy endpoints were presented descriptively in frequency tables.

There was one interim assessment of efficacy performed after endpoint data were collected on 1893 recruited patients. This used a composite endpoint based on the incidence of objectively verified symptomatic distal or proximal DVT, symptomatic fatal or non-fatal PE, and sudden death by Day 21. The alpha spent in the interim analysis was as small as 0.000003, therefore, the alpha level for the final analysis was not adjusted.

4. Summary of Results

4.1. Study Population Information

In total, 3706 patients were randomized to receive study treatment: 1856 to the dalteparin sodium group and 1850 to the placebo group. A summary of the numbers of patients in each treatment group and in each patient population as well as the numbers of patients withdrawing from the study is presented in Table 2.

Table 2. Patient disposition for each treatment group

	Dalteparin sodium N=1856	Placebo N=1850
	n (%*)	n (%*)
Total no. of patients randomized	1856 (100)	1850 (100)
Randomized but did not receive any study medication	8 (0.4)	17 (0.9)
ITT/Safety population	1848 (99.6)	1833 (99.1)
PP population	1422 (76.6)	1383 (74.8)
Reason for treatment withdrawal**		
Total	199 (10.7)	202 (10.9)
AE	94 (5.1)	83 (4.5)
Protocol violation	40 (2.2)	44 (2.4)
Consent withdrawn	49 (2.6)	56 (3.0)
Protocol specific withdrawal criteria	11 (0.6)	19 (1.0)
Lost to follow-up	5 (0.3)	0
Number of patients completing at Day 90+6	1660 (89.4)	1632 (88.2)
Reasons for withdrawal by Day 90+6		
Total	188 (10.1)	201 (10.9)
Consent withdrawn	48 (2.6)	63 (3.4)
Lost to follow-up	41 (2.2)	42 (2.3)
Death†	99 (5.3)	96 (5.2)

* *% = n/N, where N is the number of patients in each group*

** *Patients were followed for the duration of the study, even if study drug was discontinued. The "reason for treatment withdrawal" data in this table were obtained from the "Completion of Study Medication" section of the CRF.*

† *A further 16 patients died during the study but are not included in the above table for the following reasons: 7 (4 placebo, 3 dalteparin sodium) were lost to follow-up, 8 (5 placebo, 3 dalteparin sodium) withdrew consent, one (Patient 25042) completed the study but died on Day 130. One of these patients (10163) was untreated and excluded from the ITT population.*

There were 25 patients (8 in the dalteparin sodium group and 17 in the placebo group) who were randomized but did not receive any study medication, as follows:

- 7 patients (2 in the dalteparin sodium group and 5 in the placebo group) withdrew their consent
- 3 patients in the placebo group were observed to be protocol violators
- 2 patients in the placebo group were withdrawn due to protocol specific withdrawal criteria
- 1 patient in the dalteparin sodium group was withdrawn due to an adverse event
- 4 patients (1 in the dalteparin sodium group and 3 in the placebo group) gave their informed consent to participate in the study after the official end of the patient recruitment period.
- For the remaining 8 patients (4 in the dalteparin sodium group and 4 in the placebo group) the reason could not be determined from the database.

The main reason for treatment withdrawal in both groups was AEs. Patients who discontinued treatment due to AEs are further described in safety evaluation: Discontinuations Due to Adverse Events. The numbers of patients completing the study were similar in the dalteparin sodium group in comparison with the placebo group.

4.2 Protocol Violations

Major protocol deviations are summarized in Table 3.

Table 3. Summary of patients with major protocol deviations. All randomized patients

Criteria deviations*	Dalteparin sodium N=1856	Placebo N=1850	Total N=3706
	n (%)	n (%)	n (%)
Failed to meet inclusion criteria	19 (1.0)	19 (1.0)	38 (1.0)
Met exclusion criteria	2 (0.1)	3 (0.2)	5 (0.1)
Incorrectly treated**	173 (9.3)	172 (9.3)	345 (9.3)
Ultrasound screening Day 21+3 not performed	154 (8.3)	179 (9.7)	333 (9.0)
Ultrasound screening evaluation not interpretable	159 (8.6)	175 (9.5)	334 (9.0)
Developed HIT but not withdrawn†	1 (0.1)	3 (0.2)	4 (0.1)
No visit Day 21+3	91 (4.9)	114 (6.2)	205 (5.5)
Anticoagulants used incorrectly‡	72 (3.9)	61 (3.3)	133 (3.6)
Total No of patients with major violation	434 (23.4)	467 (25.2)	901 (24.3)
Total No of major violations	671	726	1397

* *each patient can have >1 deviation/violation*

** *i.e. Patients who received less than 12 injections without reaching a study endpoint or missed more than 2 consecutive days of treatment.*

† *i.e. Patients who had HIT suspected or verified before completing study treatment, but were not withdrawn from study treatment, as per protocol (see Section 6.4.9).*

‡ *i.e. Patients who received anticoagulant therapy contrary to the protocol (see Section 6.4.7).*

% = n/N, where N is the number of patients in each treatment group

A total of 901 patients had major protocol violations (434 [23.4%] in the dalteparin sodium group and 467 [25.2%] in the placebo group). Although there were no significant differences in the numbers of patients with protocol violations in the dalteparin sodium group in comparison with the placebo group for the above listed criteria, more patients in the placebo group did not perform ultrasound at Day 21+3 (9.7% vs. 8.3%), or ultrasound evaluation not interpretable (9.5% vs. 8.6%) and no visit at Day 21+3 (6.2% vs. 4.9%).

The major reasons for protocol deviations (accounting for approximately 70% of deviations recorded) were that patients were incorrectly treated (i.e. they received fewer than 12 injections without reaching a study endpoint or else they missed more than 2 consecutive days of treatment) or the Day 21 ultrasound screening was either not performed or it was unevaluable.

The ITT population was based on all randomized patients who had received at least 1 dose of study medication. A number of patients in the ITT population could not contribute to the analysis of the primary efficacy endpoint because they did not have an evaluable assessment of any of the endpoints included in the primary endpoint. These patients are presented in Table 4.

Table 4. Patients in the ITT population not contributing to the primary efficacy analysis

Reason	Dalteparin sodium N=1848	Placebo N=1833	Total N=3681
	n (%)	n (%)	n (%)
Reason for no screening of DVT			
- Death (other than sudden death or fatal PE)	44 (2.4)	43 (2.3)	87 (2.4)
- Adverse event	15 (0.8)	19 (1.0)	34 (0.9)
- Protocol violation	21 (1.1)	22 (1.2)	43 (1.2)
- Consent withdrawn	45 (2.4)	63 (3.4)	108 (2.9)
- Lost to follow-up	16 (0.9)	12 (0.7)	28 (0.8)
- Protocol specific withdrawal criteria	2 (0.1)	1 (0.1)	3 (0.1)
- Other reasons			
-- Local evaluation performed but no central evaluation	6 (0.3)	7 (0.4)	13 (0.4)
-- CUS/venography non evaluable/non diagnostic	155 (8.4)	172 (9.4)	327 (8.9)
-- Only 1 leg evaluated	2 (0.1)	1 (0.1)	3 (0.1)
-- Symptomatic evaluation therefore no screening	8 (0.4)	11 (0.6)	19 (0.5)
-- Not reporting*	12 (0.6)	9 (0.5)	21 (0.6)
Last known day with no symptoms < 21	4 (0.2)	0	4 (0.1)
Total	330 (17.9)	360 (19.6)	690 (18.7)

% = n/N, where N is the number of patients in the ITT population

* *These 21 patients did not have a Day 21 visit and consequently no CRFs were completed at Day 21.*

4.3 Demographic and Other Baseline Characteristics

Table 5 presents the demographic data and baseline vital signs for the ITT population.

Table 5. Demographics and baseline vital signs, ITT population

		Dalteparin sodium N=1848	Placebo N=1833
Sex	Male, n (%)	884 (47.8)	888 (48.4)
	Female, n (%)	964 (52.2)	945 (51.6)
Age at baseline (years)	Mean (SD)	68.5 (11.1)	68.5 (11.7)
	Median (min-max)	70.0 (40.0 to 97.0)	70.0 (26.0 to 99.0)
	Patients not reporting	0	0
Age group	<65, n (%)	624 (33.8)	618 (33.7)
	≥65, n (%)	1224 (66.2)	1215 (66.3)
Race	White, n (%)	1699 (91.9)	1692 (92.3)
	Black, n (%)	27 (1.5)	25 (1.4)
	Asian or Pacific Islander, n (%)	7 (0.4)	4 (0.2)
	Mixed, n (%)	110 (6.0)	100 (5.5)
	Not listed, n (%)	5 (0.3)	12 (0.7)
Weight (kg)	Mean (SD)	75.1 (17.6)	75.4 (18.0)
	Median (min-max)	74.0 (31.7 to 173.5)	74.5 (31.8 to 235.0)
	Patients not reporting	3	3
Height (cm)	Mean (SD)	165.5 (9.3)	165.4 (9.4)
	Median (min-max)	165.0 (135.0 to 193.0)	165.0 (127.0 to 197.0)
	Patients not reporting	4	2
BMI (kg/m^2)	Mean (SD)	27.4 (5.9)	27.5 (6.0)
	Median (min-max)	26.6 (12.2 to 54.7)	26.7 (11.3 to 61.2)
	Patients not reporting	4	3
BMI (kg/m^2) group	<30, n (%)	1320 (71.4)	1276 (69.6)
	≥30, n (%)	524 (28.4)	554 (30.2)
	Patients not reporting, n (%)	4 (0.2)	3 (0.2)

Abbreviations: BMI = body mass index (weight in Kg / [height in m]^2)

%=n/N, where N is the number of patients reporting a measurement in the ITT population

A slightly higher proportion of female patients than male patients was enrolled into the study. The majority of patients were aged 65 or over and most were white. Mean height, weight and BMI were similar in the dalteparin sodium group in comparison with the placebo group. All demographic characteristics were similar between the treatment groups.

The reason for hospitalization according to the inclusion criteria is presented in Table 6 and the additional risk factors are presented in Table 7.

Table 6. Reason for hospitalization of patients according to the inclusion criteria. ITT population

Reason for Hospitalization*	Dalteparin sodium N=1848	Placebo N=1833
	n (%)	n (%)
Congestive heart failure (NYHA class III or IV)	965 (52.2)	940 (51.3)
Acute respiratory failure not requiring ventilatory support	561 (30.4)	560 (30.6)
Any of the following acute conditions and at least 1 risk factor**	749 (40.5)	781 (42.6)
Acute infection without septic shock	673 (36.4)	687 (37.5)
Episode of inflammatory bowel disease	10 (0.5)	8 (0.4)
Acute rheumatic disorders	49 (2.7)	36 (2.0)
Acute lumbar pain or sciatica or vertebral compression (caused by osteoporosis or tumor)	99 (5.4)	99 (5.4)
Acute arthritis of the legs	60 (3.2)	64 (3.5)
Acute episode of rheumatoid arthritis in the legs	46 (2.5)	45 (2.5)

* *More than 1 reason can be given for each patient*
** *Risk factors are presented in Table 7*
%=n/N. where N is the number of patients reporting in the ITT population

The proportions of patients reporting each of the acute reasons for hospitalization were similar in the dalteparin sodium group in comparison with the placebo group. The most common reason for hospitalization was congestive heart failure. For patients who were included in the study with an acute condition and at least 1 risk factor, the most common condition leading to hospitalization was acute infection without septic shock.

Table 7. Risk factors according to the inclusion criteria. ITT population

Risk factors*	Dalteparin sodium N=1848	Placebo N=1833
	n (%)	n (%)
≥75 years of age	611 (33.1)	615 (33.6)
Cancer	85 (4.6)	105 (5.7)
Previous DVT/PE	62 (3.4)	80 (4.4)
Obesity**	558 (30.2)	560 (30.6)
Varicose veins and/or chronic venous insufficiency	487 (26.4)	530 (28.9)
Hormone therapy (antiandrogen or estrogen)	33 (1.8)	30 (1.6)
Chronic heart failure	925 (50.1)	946 (51.6)
Chronic respiratory failure***	176 (9.5)	183 (10.0)
Myeloproliferative syndrome	5 (0.3)	9 (0.5)

* *More than 1 risk factor can be given for each patient.*
** *BMI ≥30 kg/m^2 for men and ≥28.6 kg/m^2 for women*
*** *Defined as chronic oxygen supplementation or pO_2 <60mmHg or pCO_2 >45mmHg*
%=n/N. where N is the number of patients reporting in the ITT population

Although the proportions of patients in each group with each of the additional risk factors were generally similar, higher proportions of patients were enrolled in the placebo group for 8 of 9 risk factors. The most common risk factors were chronic heart failure, old age, obesity and varicose veins and/or chronic venous insufficiency.

There were no differences between the dalteparin sodium and placebo groups in the mean duration of time spent in hospital (13.3 vs. 13.1 days).

The most commonly received concomitant medications were diuretics, which were taken by more than 60% of patients, and agents acting on the renin-angiotensin system, which were taken by just under 60% of patients. Cardiac therapy, antibacterials for systemic use and antithrombotic agents were each received by approximately 50% of patients. There were no notable differences between the treatment groups in intake of concomitant medications.

The duration of treatment was 14 days (median, from 1 to 16 days).

4.4 Efficacy Results

Primary Efficacy Variable

The primary efficacy variable was the incidence of 1 or more clinically relevant thromboembolic events, defined as VTE (i.e., objectively verified symptomatic DVT [proximal and distal], asymptomatic proximal DVT and/or non-fatal and fatal PE, and sudden death).

Table 8 presents the incidence of the primary endpoint (symptomatic VTE, asymptomatic proximal DVT and/or PE, and sudden death by Day 21+3).

Table 8. Incidence of the Primary Endpoint in ITT Population

Visit		Dalteparin sodium N=1848	Placebo N=1833	Difference in Incidence*	RR
By Day 21+3	n/N'	42/1518	73/1473		
	Incidence	2.77	4.96	-2.19	0.55
	95% CI	(1.94 to 3.59)	(3.85 to 6.06)	(-3.57 to -0.81)	(0.38 to 0.80)
	p-value**			0.0015	

* *Dalteparin sodium minus placebo*

** *Cochran-Mantel-Haenszel test, significance is achieved if p<0.001*

Incidence = n/N', where N' is the number of patients in the ITT population with observed values at the specific visit

There was a clinically relevant reduction in the incidence of the events comprising the primary endpoint in the dalteparin sodium group compared with the placebo group. By Day 21+3 the relative risk of experiencing these events was 44% lower in the dalteparin sodium group than in the placebo group for the ITT population. Although the p-value was higher than the pre-specified limit of 0.001, it does provide statistical evidence of a treatment effect. These results are clinically meaningful, as demonstrated by the 45% reduction in risk with respect to the primary endpoint.

The results of the PP analysis confirmed the results of the ITT analysis, with a reduction of 46% in the relative risk of experiencing these events in the dalteparin sodium group compared with the placebo group (p=0.0018).

Table 9. Incidence of the Primary Endpoint in Per Protocol Population

Visit		Dalteparin N=1422	Placebo N=1383	Difference in incidence	RR
By Day 21+3	N/N	36/1392	65/1354		
	Incidence	2.59	4.80	-2.21	0.54
	95% CI	(1.75 to 3.42)	(3.66 to 5.94)	(-3.63 to –0.80)	(0.36 to 0.80)
	P-value			0.0018	

RR = Risk Ratio

Statistical test used in this table is Cochran-Mantel-Haenszel. Statistical significance is reached if p-value < 0.001. Incidence = n/N′, where N′ is the number of patients in the per protocol (PP) populations with observed values at the specific visit.

The subgroup analyses by geographic region indicate that the incidence of the primary endpoint occurring was lower in Eastern Europe than in Western Europe. In Eastern Europe, incidence rates of 2.12 and 4.19 were seen in the dalteparin sodium and placebo groups, respectively, compared with rates of 4.57 and 7.88, respectively, in Western Europe. However, no single geographic region significantly influences the final results.

Tables 10 summarizes the incidence of the primary endpoint by categorization of patients according to inclusion criteria (i.e., congestive heart failure, acute respiratory failure not requiring ventilatory support or specified acute conditions).

Table 10. Incidence of the Primary Endpoint by Day 21 by Inclusion Criteria, ITT Population

Inclusion			Dalteparin sodium N=1848	Placebo N=1833	Difference in Incidence	RR
Congestive heart failure (NYHA class III or IV)	Yes	n/N'	25/814	33/781		
		Incidence	3.07	4.23	-1.15	0.73
		95% CI	(1.89 to 4.26)	(2.81 to 5.64)	(-3.00 to 0.69)	(0.44 to 1.21)
	No	n/N'	17/704	40/692		
		Incidence	2.41	5.78	-3.37	0.42
		95% CI	(1.28 to 3.55)	(4.04 to 7.52)	(-5.44 to -1.29)	(0.24 to 0.73)
Acute respiratory failure not requiring ventilatory support	Yes	n/N'	16/442	22/435		
		Incidence	3.62	5.06	-1.44	0.72
		95% CI	(1.88 to 5.36)	(3.00 to 7.12)	(-4.13 to 1.26)	(0.38 to 1.34)
	No	n/N'	26/1076	51/1038		
		Incidence	2.42	4.91	-2.50	0.49
		95% CI	(1.50 to 3.33)	(3.60 to 6.23)	(-4.10 to -0.89)	(0.31 to 0.78)

(Continued)

Inclusion			Dalteparin sodium N=1848	Placebo N=1833	Difference in Incioence	RR
Specified acute conditions	Yes	n/N'	18/605	35/617		
		Incidence	2.98	5.67	-2.70	0.52
		95% CI	(1.62 to 4.33)	(3.85 to 7.50)	(-4.97 to -0.42)	(0.30 to 0.92)
	No	n/N'	24/913	38/856		
		Incidence	2.63	4.44	-1.81	0.59
		95% CI	(1.59 to 3.67)	(3.06 to 5.82)	(-3.54 to -0.08)	(0.36 to 0.98)

The cumulative probability of the primary endpoint occurring vs the days after treatment up to Day 24 is presented in Figure 1.

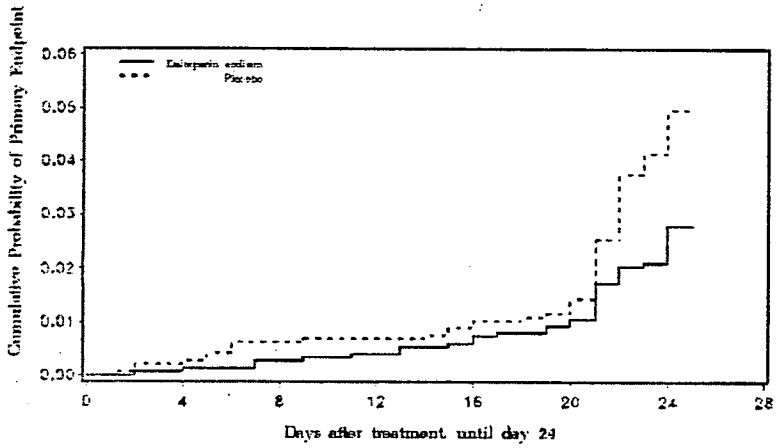


Figure 1. The cumulative probability of the primary endpoint by time.

These results indicate that large change in the cumulative probability of the primary endpoint occurring from Day 21 to Day 24, because the evaluation of asymptomatic proximal DVT was only performed at this time. In another word, this study indicates that dalteparin mainly prevents asymptomatic proximal DVT, in comparison with symptomatic VTE and/or PE, and sudden death by Day 21+3.

Secondary Efficacy Variable

The incidence of symptomatic VTE (DVT and/or PE) by Day 14, 21 and 90 are presented in Table 11.

Table 11. Incidence of symptomatic VTE by Day 14, 21 and 90. ITT population

Visit		Dalteparin sodium N=1848	Placebo N=1833	Difference in Incidence**	RR
Day 14 (or discontinuation)	n/N'	3/1835	6/1818		
	Incidence	0.16	0.33	-0.17	0.50
	95% CI	---	(0.07 to 0.59)	---	---
Day 21	n/N'	10/1759	17/1740		
	Incidence	0.57	0.98	-0.41	0.58
	95% CI	(0.22 to 0.92)	(0.51 to 1.44)	(-0.99 to 0.17)	(0.27 to 1.27)
Day 90	n/N'	15/1615	21/1583		
	Incidence	0.93	1.33	-0.40	0.70
	95% CI	(0.46 to 1.40)	(0.76 to 1.89)	(-1.13 to 0.33)	(0.36 to 1.35)

* *This table includes Patients 31078 and 34020. For these patients, cause of death was evaluated by the CEC as VTE related; but they died before the confirmatory PE evaluations could be performed. In accordance with the data decisions agreed before database close, these patients were included as symptomatic PEs.*

** *Dalteparin sodium minus placebo*

Incidence = n/N', where N' is the number of patients in the ITT population with an observed value at the specific visit

95% CI are not presented if fewer than 5 patients in either treatment group experienced an event

The incidence of symptomatic VTE (DVT and/or PE) was lower in the dalteparin sodium group in comparison with the placebo group at Days 14 (or discontinuation), 21 and 90. Compared with placebo, reductions of 50%, 42% and 30% were seen in the relative risk of experiencing a symptomatic VTE in the dalteparin sodium group by Day 14, 21 and 90, respectively.

Incidence of VTE (primary endpoint excluding sudden death)

The incidence of VTE at Day 21 (defined as patients having a symptomatic [proximal and/or distal] DVT by Day 21 and/or a symptomatic PE by Day 21 and/or a fatal PE by Day 21 or an asymptomatic proximal DVT at Day 21+3) is presented in Table 12.

Table 12. Incidence of VTE by Day 21. ITT population with observed values

Visit		Dalteparin sodium N=1848	Placebo N=1833	Difference in Incidence*	RR
Day 21	n/N'	37/1513	70/1470		
	Incidence	2.45	4.76	-2.32	0.51
	95% CI	(1.67 to 3.22)	(3.67 to 5.85)	(-3.65 to -0.98)	(0.35 to 0.76)

* *Dalteparin sodium minus placebo*

Incidence = n/N', where N' is the number of patients in the ITT population with an observed value at the specific visit

The incidence of VTE was lower in the dalteparin sodium group in comparison with the placebo group at Day 21. There was a 49% reduction in the relative risk of experiencing a

VTE in the dalteparin sodium group compared with the placebo group.

Incidence of proximal DVT (symptomatic and/or asymptomatic)

The incidence of proximal DVT (symptomatic and/or asymptomatic) by Day 21 is presented in Table 13.

Table 13. Incidence of proximal DVT (symptomatic and/or asymptomatic) by Day 21. ITT population with observed values

Visit		Dalteparin sodium N=1848	Placebo N=1833	Difference in Incidence*	RR
Day 21	n/N'	29/1518	60/1474		
	Incidence	1.91	4.07	-2.16	0.47
	95% CI	(1.22 to 2.60)	(3.06 to 5.08)	(-3.38 to -0.94)	(0.30 to 0.73)

* *Dalteparin sodium minus placebo*

Incidence = n/N', where N' is the number of patients in the ITT population with an observed value at the specific visit

The incidence of proximal DVT (symptomatic and/or asymptomatic) was lower in the dalteparin sodium group in comparison with the placebo group at Day 21. There was a 53% reduction in the relative risk of experiencing a proximal DVT in the dalteparin sodium group compared with the placebo group.

Incidence of symptomatic PE and fatal PE

The incidence of symptomatic PE at Day 14 (or discontinuation) and Day 21 is presented in Table 14. As expected, the overall incidence of symptomatic PE was very low, with a total of 11 events observed in 3499 patients by Day 21.

Table 14. Incidence of symptomatic PE at Day 14 and Day 21* (ITT population)

Visit		Dalteparin sodium N=1848	Placebo N=1833	Difference in Incidence**	RR
Day 14 (or discontinuation)	n/N'	2/1835	4/1819		
	Incidence	0.11	0.22	-0.11	0.50
	95% CI	---	---	---	---
Day 21	n/N'	5/1759	6/1740		
	Incidence	0.28	0.34	-0.06	0.82
	95% CI	(0.04 to 0.53)	(0.07 to 0.62)	(-0.43 to 0.31)	(0.25 to 2.70)

* *This table includes Patients 31078 and 34020. For these patients, cause of death was evaluated by the CEC as VTE related; but they died before the confirmatory PE evaluations could be performed. In accordance with the data decisions agreed before database close, these patients were included as symptomatic PEs.*

** *Dalteparin sodium minus placebo*

Incidence = n/N', where N' is the number of patients in the ITT population with an observed value at the specific visit

95% CI were not produced if fewer than 5 patients in either treatment group experienced an event

The incidence of symptomatic PE was lower in the dalteparin sodium group than in the placebo group at Day 14 (or day of discontinuation) and similar in both groups at Day 21. There were no occurrences of fatal PE in either treatment group by Day 14 (or study discontinuation), however, by Day 21, 2 patients in the placebo group had experienced fatal PEs. Both of these patients had symptomatic PEs and are included in Table 14.

Incidence of Death (all causes)

The incidence of death (all causes) by Day 14 (or discontinuation), Day 21 and Day 90 is presented in Table 15.

Table 15. Incidence of death (all causes) by Day 14, 21 and 90

Visit		Dalteparin sodium N=1848	Placebo N=1833	Difference in Incidence*	RR
Day 14 (or discontinuation)	n/N	8/1845	7/1831		
	Incidence	0.43	0.38	0.05	1.13
	95% CI	(0.13 to 0.73)	(0.10 to 0.66)	(-0.35 to 0.46)	(0.41 to 3.12)
Day 21	n/N	43/1829	42/1807		
	Incidence	2.35	2.32	0.03	1.01
	95% CI	(1.66 to 3.05)	(1.63 to 3.02)	(-0.96 to 1.01)	(0.66 to 1.54)
Day 90**	n/N	107/1747	103/1715		
	Incidence	6.12	6.01	0.12	1.02
	95% CI	(5.00 to 7.25)	(4.88 to 7.13)	(-1.47 to 1.71)	(0.78 to 1.33)

Incidence = n/N, where N is the number of patients in the ITT population with an observed value at the specific visit

* *Dalteparin sodium minus placebo*

** *Patient 25042 (dalteparin sodium) died on Day 130 but is also included.*

The incidence of death was similar in both treatment groups.

Sudden death was defined as unexpected death occurring within 24 hours from the start of an acute event. All cases of sudden death were adjudicated by the CEC.

Three cases of sudden death were reported by Day 14, all of which occurred in the dalteparin sodium group. The incidence of sudden death was higher in the dalteparin sodium group in comparison with the placebo group at Day 21 (5 vs 3 cases).

D. Efficacy Conclusions

Although the proportions of patients in each group with each of the additional risk factors were generally similar, higher proportions of patients were enrolled in the placebo group for 8 of 9 risk factors. The most common risk factors were chronic heart failure, old age, obesity and varicose veins and/or chronic venous insufficiency.

Analysis of the primary efficacy endpoint at Day 21+3 demonstrated that, compared with placebo, prophylactic treatment with dalteparin sodium was associated with a clinically relevant 44% decrease in the risk of experiencing the composite primary endpoint of symptomatic DVT (proximal and distal), asymptomatic proximal DVT, non-fatal or fatal PE

and/or sudden death. The incidence of the primary endpoint at Day 21+3 was 2.77% (42/1518) in the dalteparin sodium treated patients compared with 4.96% (73/1473) in placebo treated patients (difference: -2.19; 95%CI: -3.57 to -0.81; p=0.0015). Although the p-value was higher than the pre-specified limit of 0.001, it does provide statistical evidence of a treatment effect. These results are clinically meaningful, as demonstrated by the 44% reduction in risk with respect to the primary endpoint, although this study indicates that delteparin mainly prevents asymptomatic proximal DVT, in comparison with symptomatic VTE and/or PE, and sudden death by Day 21+3. The results of the PP analysis were consistent with those of the ITT analysis.

The results of the secondary efficacy analyses supported the analysis of the primary endpoint. Compared with the placebo group, dalteparin sodium reduced the incidences of VTE (2.45% vs. 4.76%), DVT (2.12% vs. 4.37%), symptomatic VTE (0.57% vs. 0.98%) and proximal DVT (symptomatic and asymptomatic, 1.91% vs. 4.07%). Event rates were too low for conclusions to be drawn about the incidence of symptomatic PE, fatal PE and distal symptomatic DVT by Day 21. Three cases of sudden death were reported by Day 14, all of which occurred in the dalteparin sodium group. By Day 21 there were 5 cases of sudden death in the dalteparin sodium group as compared to 3 cases in the placebo group. The incidence rate for all deaths was similar in each treatment group.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Dalteparin sodium was well tolerated. The proportion of patients reporting at least 1 AE was similar in each treatment group (39.7% and 39.8% in the dalteparin sodium and placebo groups, respectively). The most frequently reported AE in both treatment groups was exacerbation of chronic obstructive airways disease, reported for 29 patients (1.6%) in the dalteparin sodium group and 39 patients (2.1%) in the placebo group. There were no notable differences between the treatment groups in the incidences of AEs. More dalteparin sodium-treated patients than placebo patients had drug-related AEs (52 [2.8%] patients vs 30 [1.6%] patients). The most commonly reported drug-related AE was thrombocytopenia/thrombocytopenia aggravated, reported by 6 patients in each treatment group.

A higher number of patients in the dalteparin sodium group had major bleeds than in the placebo group at Day 14 (or discontinuation) and at Day 21 (9/1848 vs. 3/1833). Of the 12 major bleeds occurring by Day 21, 3 cases were fatal (2 in the dalteparin sodium group and 1 case in the placebo group).

A similar proportion of patients in each treatment group had at least 1 AE that led to death from Day 1 to Day 90 (105 patients [5.7%] and 101 patients [5.5%] in the dalteparin sodium and placebo groups, respectively). Adverse events leading to death were most commonly associated with the cardiac disorders system organ class (47 patients [2.5%] and 45 [2.5%] patients in the dalteparin sodium and placebo groups, respectively) and the infections and infestations system organ class (24 patients [1.3%] and 19 patients [1.0%], respectively).

Sixteen of the deaths reported during the study were classified as sudden deaths (i.e., occurred within 24 hours of the onset of an acute event). Of these, 7 cases occurred in dalteparin sodium-treated patients and 9 cases occurred in placebo patients. Eight sudden deaths were reported up to Day 21 (5 in the dalteparin sodium group and 3 in the placebo group). None of the events leading to sudden death was considered related to study medication by investigators. The incidence rate for all cause death was similar in each treatment group at Day 90, Day 21 and Day 14. The overall incidence of death due to all causes was lower than expected for this patient population.

By Day 90, a total of 251 patients (13.6%) in the dalteparin sodium group and 243 patients (13.3%) in the placebo group reported SAEs. The most frequently reported SAE in both treatment groups was exacerbation of chronic obstructive airways disease, reported for 27 patients (1.5%) in the dalteparin sodium group and 34 patients (1.9%) in the placebo group. Very few patients reported drug-related SAEs (7 and 5 patients in the dalteparin sodium and placebo groups, respectively).

B. Description of Patient Exposure

In total, 3706 patients were randomized to receive study treatment: 1856 to the dalteparin sodium group and 1850 to the placebo group. Eight patients who were randomized to dalteparin sodium did not receive any study medication.

The duration of treatment for the ITT/Safety and PP populations is shown in Table 16.

Table 16. Duration of treatment (days)

Duration of treatment		Dalteparin sodium	Placebo
ITT/Safety population	Mean (SD)	12.6 (3.0)	12.6 (2.9)
	Median (min-max*)	14 (1 to 16)	14 (1 to 17)
	Patients reporting	1848	1833
PP population	Mean (SD)	13.4 (1.4)	13.3 (1.5)
	Median (min-max)	14 (1 to 16)	14 (1 to 15)
	Patients reporting	1422	1383

One placebo patient had an incorrect date entered which has affected the maximum duration of treatment reported in Table T24. The above table shows the correct data.

It should be noted that patients were immediately withdrawn from study treatment if DVT or PE was objectively verified.

Treatment compliance was assured during the in-hospital period because study drug was administered by study personnel. During the period at home, the patients recorded details of administration in their diary card. In the ITT population, the mean number of injections was 12.6 in both treatment groups.

C. Methods and Specific Findings of Safety Review

1 All Treatment-Emergent Adverse Events

A summary of AEs reported by ≥1% of patients in any treatment group is presented in Table 17, by system organ class and preferred term.

Table 17. AEs reported in ≥1% of patients in any treatment group by system organ class and preferred term (Day 1 to Day 90). Safety population

System organ class preferred term (MedDRA)	Dalteparin sodium N=1848	Placebo N=1833
	n (%)	n (%)
Cardiac disorders		
– Atrial fibrillation	16 (0.9)	20 (1.1)
Gastrointestinal disorders		
– Diarrhea NOS	23 (1.2)	26 (1.4)
– Nausea	15 (0.8)	23 (1.3)
– Vomiting NOS	20 (1.1)	12 (0.7)
General disorders and administration site conditions		
– Chest pain NEC	18 (1.0)	21 (1.1)
Infections and infestations		
– Pneumonia NOS	28 (1.5)	22 (1.2)
– Urinary tract infection NOS	17 (0.9)	21 (1.1)
Musculoskeletal, connective tissue and bone disorders		
– Back pain	11(0.6)	18(1.0)
Nervous system disorders		
– Headache NOS	20 (1.1)	24 (1.3)
– Insomnia NEC	18 (1.0)	21 (1.1)
Respiratory, thoracic and mediastinal disorders		
– Chronic obstructive airways disease exacerbated	29 (1.6)	39 (2.1)

% = n/N, where N is the number of patients in the Safety population

The most frequently reported AE in both treatment groups was exacerbation of chronic obstructive airways disease and followed by pneumonia, diarrhea and headache. There were no notable differences between the dalteparin sodium and placebo groups in the incidences of AEs.

2 Drug-Related Treatment-Emergent Adverse Events

There was a low incidence of drug-related AEs. Drug-related AEs were most commonly associated with the gastrointestinal disorders system organ class in the dalteparin sodium group (9, 0.5%). These were mainly bleeding events. In the placebo group, drug-related events were most commonly associated with the blood and lymphatic system and the skin and subcutaneous tissues (7, 0.4% in each system). The most frequently reported drug-related AE (by preferred term) in both treatment groups was thrombocytopenia/thrombocytopenia aggravated, which was reported for 6 patients in each group. There were differences between the treatment groups in the incidence of subcutaneous hematoma (reported by 5 patients in the dalteparin sodium group compared with no reports in the placebo group), and epistaxis (reported by 6 patients in dalteparin sodium group compared with 3 patients in the placebo group).

The majority of events were of mild or moderate intensity. Gastrointestinal hemorrhage NOS (reported for 2 dalteparin sodium-treated patients) was the only drug-related severe AE to be reported by more than 1 patient in either treatment group.

3 Deaths

Table 18 provides an overview of deaths (Day 1 to Day 90) by system organ class.

Table 18. Patients who had AEs leading to death by system organ class. Safety population

System organ class preferred term (MedDRA)	Dalteparin sodium N=1848	Placebo N=1833
	n (%)	n (%)
Blood and lymphatic system disorders	7 (0.4)	7 (0.4)
Eye disorders	0	1 (0.1)
Gastrointestinal disorders	9 (0.5)	5 (0.3)
General disorders and administration site conditions	8 (0.4)	1 (0.1)
Injury and poisoning	6 (0.3)	0
Investigations*	4 (0.2)	3 (0.2)
Metabolism and nutrition disorders	1 (0.1)	0
Musculoskeletal, connective tissue and bone disorders	2 (0.1)	0
Psychiatric disorders	1 (0.1)	0
Renal and urinary disorders	1 (0.1)	0
Reproductive system and breast disorders	1 (0.1)	3 (0.2)
Respiratory, thoracic and mediastinal disorders	7 (0.4)	4 (0.2)
Skin & subcutaneous tissue disorders	6 (0.3)	7 (0.4)
Vascular disorders	2 (0.1)	1 (0.1)

% = n/N, where N is the number of patients in the Safety population

* *e.g. abnormal findings from diagnostic tests, e.g. laboratory tests*

Deaths occurring during the study were most commonly due to cardiac disorders and infections and infestations. In the dalteparin sodium group, the most frequently reported reason for death (by preferred term) was pneumonia NOS (10 patients), followed by myocardial infarction (9 patients) and cardiac failure NOS (8 patients). Cardiac failure NOS was the most frequently reported reason for death in the placebo group (9 patients), followed by pneumonia NOS (7 patients) and exacerbation of chronic obstructive airways disease (7 patients). There were no notable differences between the dalteparin sodium and placebo groups in any of the system organ classes in the proportions of patients who died during the study.

Sixteen patients died suddenly during the study (i.e., within 24 hours from the start of an acute event). Seven of these cases occurred in the dalteparin sodium group and 9 occurred in the placebo group. Eight of the 16 sudden deaths occurred by Day 21 (5 in the dalteparin sodium group and 3 in the placebo group) and the remainder cases occurred beyond the treatment period (Day 21). None of the cases of sudden death were considered drug-related by investigators.

Brief summaries of the events leading to sudden death in the dalteparin sodium group by Day 21 are provided below:

- Patient 15061 was a 72-year-old female in the dalteparin sodium group. On Day 5 of the study she died due to chronic pulmonary and aggravation of heart disease.

- Patient 24127 was a 67-year old female in the dalteparin sodium group with a history of diabetes and heart failure. On Day 2 of the study she died of cardiac arrest and renal failure.

- Patient 31010 was a 44-year-old male in the dalteparin sodium group with a history of heart failure, pneumonectomy and respiratory disease. On Day 17 of the study, the patient experienced an aggravation of his heart failure, respiratory failure and a minor gastrointestinal hemorrhage and he died the same day. The cause of death was heart failure.

- Patient 32136 was a 69-year old male in the dalteparin sodium group with a history of congestive heart failure and arrhythmia. The patient completed the course of study medication on Day 11. On the same day, the patient suddenly stopped breathing and became cyanotic. Cardiopulmonary resuscitation was unsuccessful and he died the same day. The cause of death reported on the SAE form by the investigator was PE and exacerbation of cardiac and respiratory failure. However, no specific symptoms of PE were reported on the clinical database and no diagnostic tests for PE were performed. The CEC therefore adjudicated this case as a sudden death.

- Patient 33061 was a 69-year-old male in the dalteparin sodium group with a history of ischemic heart disease, myocardial infarction and nephrosclerosis. The patient received his last dose of medication on Day 9 of the study at 1400 and at 2300 he died suddenly at home. An autopsy was not performed.

Of the 8 cases of sudden death reported after Day 21, 2 were in the dalteparin sodium group and 6 were in the placebo group. Brief narratives for 2 patients in the dalteparin sodium group are provided below:

- Patient 13050, was an 80-year old male in the dalteparin sodium group with a history of epilepsy and heart failure. Approximately 2 weeks after receiving his last dose of study drug, the patient died suddenly during his sleep. An autopsy was not performed. The cause of death as reported on the SAE form was probable arrhythmia, and a possible PE.

- Patient 32421 was a 51-year-old male in the dalteparin sodium group with a history of ischemic dilated cardiomyopathy, congestive heart failure, chronic cor pulmonale and aneurysm. Five weeks after receiving his last dose of study drug, the patient died at home. An autopsy was not performed. The cause of death as reported on the SAE form was acute heart failure.

4 Serious Adverse Events

Table 19 summarizes SAEs reported by ≥1% of patients in either treatment group, by system organ class and preferred term.

Table 19. SAEs (in ≥1% patients in either treatment group) by system organ class and preferred term (Day 1 to Day 90*). Safety population

System organ class Preferred term (MedDRA)	Dalteparin sodium N=1848	Placebo N=1833
	n (%)	n (%)
Infections and infestations		
– Pneumonia NOS	19 (1.0)	15 (0.8)
Respiratory, thoracic and mediastinal disorders		
– Chronic obstructive airways disease exacerbated	27 (1.5)	34 (1.9)

* *Only SAEs leading to death included from Day 44 to Day 90*
% = n/N, where N is the number of patients in the Safety population

The most frequently reported SAE in both treatment groups was exacerbation of chronic obstructive airways disease, which was reported by slightly more patients in the placebo group than in the dalteparin sodium group. The next most frequently reported SAE was pneumonia NOS, which was reported by a similar number of patients in each treatment group. All other SAEs were reported by less than 1% of patients in either treatment group. Patients with drug-related SAEs during the study (Day 1 to Day 90) are summarized by system organ class and preferred term in Table 20.

Table 20. Patients with drug-related SAEs by system organ class and preferred term (Day 1 to Day 90*). Safety population

System organ class Preferred term (MedDRA)	Dalteparin sodium N=1848	Placebo N=1833
	n (%)	n (%)
Patients with at least 1 drug-related SAE	7 (0.4)	5 (0.3)
Blood and lymphatic system disorders		
– Thrombocytopenia	1 (0.1)	1 (0.1)
Gastrointestinal disorders		
– Gastric hemorrhage	0	1 (0.1)
– Gastric ulcer hemorrhage	0	1 (0.1)
– Gastrointestinal hemorrhage NOS	2 (0.1)	0
– Oesophagitis hemorrhagic	0	1 (0.1)
– Peritoneal hemorrhage	1 (0.1)	0
Injury and poisoning		
– Subdural hematoma	1 (0.1)	0
Investigations		
– Hematuria present	1 (0.1)	0
Musculoskeletal, connective tissue and bone disorders		
– Muscle hemorrhage	1 (0.1)	0
Renal and urinary disorders		
– Renal impairment NOS	1 (0.1)	0
Respiratory, thoracic and mediastinal disorders		
– Epistaxis	0	1 (0.1)

* *Only drug-related SAEs leading to death from Day 44 to Day 90*
% = n/N, where N is the number of patients in the Safety population

The most frequently reported drug-related SAEs were associated with the gastrointestinal disorders system organ class in both the dalteparin sodium group and in the placebo group. No individual drug-related SAE was reported by more than 2 patients in either treatment

group. There was a similar proportion of drug-related SAEs in the dalteparin sodium group in comparison with the placebo group. The majority of the drug-related SAEs in both treatment groups were bleeding events.

5 Major Bleeding Events

The incidence of patients with centrally adjudicated major bleeding events by Day 14 (or discontinuation) and by Day 21 is summarized in Table 21.

Table 21. Incidence of major bleeding events (centrally adjudicated) by Day 14 (or day of discontinuation from study medication) and by Day 21. Safety population

Visit		Dalteparin sodium N=1848	Placebo N=1833	Difference in Incidence*	RR
Day 14 (or discontinuation)	n/N	8/1848	0/1833		
	Incidence	0.43	0.00	0.43	—
	95% CI	(0.13 to 0.73)	—	—	—
Day 21	n/N	9/1848	3/1833		
	Incidence	0.49	0.16	0.32	2.98
	95% CI	(0.17 to 0.80)	—	—	—

* *Dalteparin sodium minus placebo*
Incidence = n/N, where N is the number of patients in the Safety population
95% CI were not produced if fewer than 5 patients in either treatment group experienced an event

A higher number of patients in the dalteparin sodium group had major bleeds than in the placebo group at Day 14 (or discontinuation) and at Day 21.

Of the 12 major bleeds occurring by Day 21, 3 cases were fatal (2 in the dalteparin sodium group and 1 case in the placebo group). Brief summaries of these cases are provided below:

- Patient 27292 was an 86-year-old male in the dalteparin sodium group. On Day 4 of the study the patient had a severe gastrointestinal bleed, that was rated as serious. Dalteparin sodium was permanently withdrawn on Day 5. The event was associated with a decrease in Hb of ≥20 g/L and a blood transfusion of >2 units was required. The patient received an intravenous infusion of heparin for a thrombosed superficial femoral artery on Days 16 and 17. The event increased in severity on Day 18 and the patient died as a result of cardiogenic shock on Day 19. It was the investigator™s opinion that the event was related to the study medication.

- Patient 32018 was an 87-year-old female in the dalteparin sodium group. On Day 4 of the study she experienced gastrointestinal bleeding and study medication was permanently discontinued. The event was associated with a decrease in Hb of ≥20 g/L, however, a blood transfusion of >2 units was not given. The patient subsequently developed heart failure and pulmonary edema and died on Day 6. It was the investigator™s opinion that the event was related to the study medication.

- Patient 32437 was a 72-year-old male in the placebo group. On Day 16 of the study he

experienced severe hematemesis that was rated as serious. The event was associated with a decrease in Hb of ≥20 g/L, and a blood transfusion of >2 units was given. The patient's existing cardiac failure subsequently worsened and the patient died on Day 20 of the study.

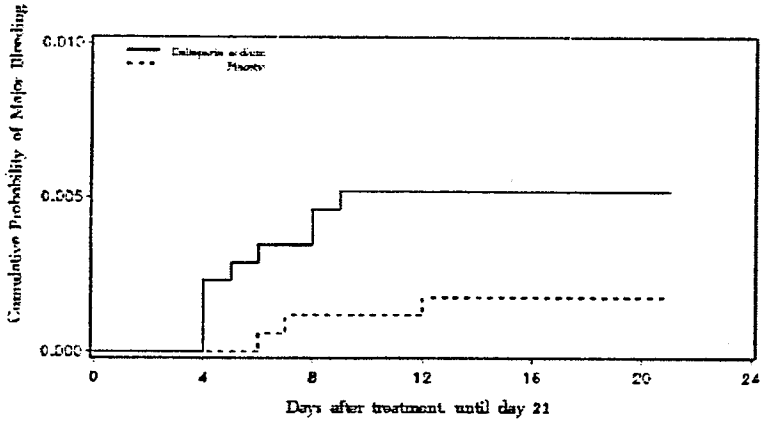
Of the 9 non-fatal major bleeds reported by Day 21, 4 were gastrointestinal bleeds (2 in the dalteparin sodium group and 2 in the placebo group). The remaining 5 bleeds comprised a nasal bleed, a peritoneal bleed, a bleed from the rectus abdominalis muscle, a hemothorax and a hematoma of the right arm. Five of the 9 non-fatal major bleeds reported were considered related to study medication by investigators (3 in the dalteparin sodium group and 2 in the placebo group).

Four patients, all of whom were in the dalteparin sodium group, had non-fatal major bleeds. Patient 27022 had a Mallory-Weiss tear (a mucosal tear in the esophagus leading to eosphageal bleeding); Patient 29028 had a hematoma of the arm; Patient 30079 had a mild rectal bleed and Patient 32061 developed hemothorax as a result of a pleural puncture.

Subgroup analyses indicated that there was a higher incidence of major bleeds in elderly patients. Ten of the 12 major bleeds reported by Day 21 occurred for patients who were aged 65 or over. Seven of the 12 major bleeds occurred in female patients.

The cumulative probability of a major bleeding event occurring over time, up until Day 21, is presented in Figure 2.

Figure 2. Cumulative probability of a major bleeding event vs days after treatment until Day 21. Safety population



The results show that there was a higher probability of a major bleeding event in the dalteparin sodium group in comparison with the placebo group.

6 Minor bleeding events (centrally adjudicated)

The incidence of patients with minor bleeding events by Day 14 (or discontinuation) and by Day 21 is summarized in Table 22.

Table 22. Incidence of minor bleeding events (centrally adjudicated) by Day 14 (or day of discontinuation from study medication) and by Day 21. Safety population

Visit		Dalteparin sodium N=1648	Placebo N=1833	Difference in Incidence*	RR
Day 14 (or discontinuation)	n/N	16/1846	5/1833		
	Incidence	0.87	0.27	0.59	3.17
	95% CI	(0.44 to 1.29)	(0.03 to 0.51)	(0.11 to 1.08)	(1.17 to 8.65)
Day 21	n/N	19/1846	10/1833		
	Incidence	1.03	0.55	0.48	1.88
	95% CI	(0.57 to 1.49)	(0.21 to 0.88)	(-0.09 to 1.05)	(0.88 to 4.04)

* *Dalteparin sodium minus placebo*

Incidence = n/N, where N is the number of patients in the Safety population

The incidence of minor bleeding events was higher in the dalteparin sodium group than in the placebo group at Day 14 (or discontinuation) and at Day 21.

Subgroup analyses of centrally adjudicated minor bleeding events indicated that minor bleeds were more commonly reported by elderly patients (65 years). Slightly more male patients reported minor bleeds than female patients by Day 21.

7 Thrombocytopenia

A summary of the incidence of thrombocytopenia by Day 14 (or day of discontinuation from study medication) and by Day 21 are presented in Table 23.

Table 23. Incidence of thrombocytopenia by Day 14 (or day of discontinuation from study medication) and by Day 21. Safety population

Visit		Dalteparin sodium N=1648	Placebo N=1833	Difference in Incidence*	RR
Day 14 (or discontinuation)	n/N	10/1848	6/1833		
	Incidence	0.54	0.33	0.21	1.65
	95% CI	(0.21 to 0.88)	(0.07 to 0.59)	(-0.21 to 0.64)	(0.60 to 4.54)
Day 21	n/N	10/1848	8/1833		
	Incidence	0.54	0.44	0.10	1.24
	95% CI	(0.21 to 0.88)	(0.13 to 0.74)	(-0.35 to 0.56)	(0.49 to 3.13)

* *Dalteparin sodium minus placebo*

Incidence = n/N, where N is the number of patients in the Safety population

The incidence of thrombocytopenia was slightly higher in the dalteparin sodium group than in the placebo group at Day 14 (or discontinuation) and at Day 21.

None of the 18 patients with thrombocytopenia by Day 21 reported any major or minor bleeding. Adverse event pages were completed by investigators for 17 of these cases. In 15 cases the outcome was recovered, in one case (Patient 15111, dalteparin sodium) the outcome was not recovered and in one case (Patient 34220, placebo) the adverse event had a duration of 4 days but the outcome was stated as "unknown". For Patient 34151 in the dalteparin sodium group, the investigator did not consider the event to meet the protocol definitions of an adverse event.

Subgroup analyses indicated that there was a higher incidence of thrombocytopenia in male patients than in female patients by Day 21 (13 vs 5 cases). The incidence was also higher in elderly patients compared with younger patients (13 vs 5 cases) and in patients with a BMI of <30 kg/m 2 (14 vs 4 cases). There were no obvious geographic variations in the incidence of thrombocytopenia.

8 Discontinuations Due to Adverse Events

A summary of AEs that led to withdrawal of the study drug is presented by system organ class in Table 24.

Table 24. AEs that led to discontinuation of the study drug by system organ class. Treatment Period (until last day of study medication) Safety population

System organ class	Dalteparin sodium N=1848	Placebo N=1833	P-value*
	n (%)	n (%)	
Patients with at least 1 AE leading to treatment withdrawal**	84 (4.5)	78 (4.3)	0.689
Blood and lymphatic system disorders	3 (0.2)	3 (0.2)	1.000
Cardiac disorders	20 (1.1)	19 (1.0)	1.000
Eye disorders	0	1 (0.1)	0.498
Gastrointestinal disorders	11 (0.6)	7 (0.4)	0.480
General disorders and administration site conditions	5 (0.3)	4 (0.2)	1.000
Infections and infestations	10 (0.5)	8 (0.4)	0.814
Injury and poisoning	5 (0.3)	3 (0.2)	0.726
Investigations	6 (0.3)	4 (0.2)	0.754
Metabolism and nutrition disorders	1 (0.1)	1 (0.1)	1.000
Musculoskeletal, connective tissue and bone disorders	1 (0.1)	0	1.000
Neoplasms benign and malignant (including cysts and polyps)	2 (0.1)	2 (0.1)	1.000
Nervous system disorders	4 (0.2)	4 (0.2)	1.000
Psychiatric disorders	3 (0.2)	3 (0.2)	1.000
Renal and urinary disorders	4 (0.2)	5 (0.3)	0.753
Respiratory, thoracic and mediastinal disorders	5 (0.3)	9 (0.5)	0.299
Skin & subcutaneous tissue disorders	5 (0.3)	4 (0.2)	1.000
Vascular disorders	9 (0.5)	6 (0.3)	0.607

* *Fisher's exact test*

** *The data in this table are derived from the AE section of the CRF.*

Patients could have more than 1 AE leading to withdrawal and could therefore be counted under more than 1 system organ class.

% = n/N, where N is the number of patients in the Safety population

The most frequently reported AEs that led to withdrawal in both treatment groups were

cardiac disorders (such as heart failure), which were reported by approximately 1% of patients in each group. The incidence of AEs that led to withdrawal was similar in the dalteparin sodium group in comparison with the placebo group for the majority of AEs. No statistically significant differences were seen between the treatment groups.

9 Drug-related Allergic Reactions

Only 2 drug-related allergic reactions were reported, 1 in the dalteparin sodium group and 1 in the placebo group. Both occurred by Day 14 (or study discontinuation).

In the dalteparin sodium group, Patient 32281 experienced severe pruritus at the injection site on Day 4 and was withdrawn from the study. The patient recovered from the event. In the placebo group, Patient 14169 experienced moderate urticaria on Day 12 and was withdrawn from the study. The patient had not recovered from the event at the time of reporting.

10 Clinical Laboratory Evaluation

The statistical analysis showed that there were no differences between the treatment groups for Hb, HCT and platelet count.

Mean and median hemoglobin and hematocrit values were comparable between the treatment groups at the timepoints of both pretreatment and the last day of treatment. Mean and median values were similar at both timepoints. As would be expected, the dalteparin sodium-treated patients who had a major bleed had low mean and median hemoglobin and hematocrit values at the time of the event.

Mean and median platelet counts were comparable between the treatment groups at pretreatment, at discharge and on the last day of treatment. Values were slightly lower at pretreatment than at discharge and on the last day of treatment.

There were no differences between the dalteparin sodium group and the placebo group in the change from baseline in potassium levels.

D. Update of Safety

The updated summary of safety report incorporates new safety data that have become available from February 1, 2002 to May 1, 2003, which were not included in the sNDA submitted on February 7, 2003. The only additional safety data available are from the 489 reports of suspect Adverse Drug Reactions received by Pharmacia Drug Safety Surveillance from health care professionals, agencies and literature review during this period.

There have been no new studies conducted in this indication and there is no new data from trial 524-E-CVD-0042-033 (PREVENT). The only additional data are from spontaneous reports.

During the period January 2003 to May 1, 2003, one trial was ongoing in an indication other than that claimed in the medical thromboprophylaxis indication. Study 524-CVD-0042-029 is examining the thromboprophylactic effect of FRAGMIN in orthopedic patients undergoing primary total knee replacement surgery. A clean safety database from this study is not yet available but during the course of the study no safety issues were identified.

Overall, 489 reports of suspect Adverse Drug Reactions to dalteparin were received by Pharmacia Drug Safety Surveillance from health care professionals, agencies and literature review from February 1, 2002 to May 1, 2003. Two hundred and seventy-one described serious adverse events and 218 reports described non-serious adverse events.

1. Serious reports with all events considered listed in the Product Safety Information

Of the 218 reports describing serious adverse events, 121 included only events either already specifically described (listed) as undesirable effects in the product safety information in the package insert or considered secondary to such undesirable effects. Table 25 illustrates the distribution of events according to body system. Non-serious events are secondary to a primary serious event. Within this category there were 16 fatal outcomes, 15 of which occurred in patients suffering from a bleeding event. Bleeding events represent the most frequent serious adverse reaction to Fragmin therapy.

Table 25: Serious Events

Body system disorder	Listed Non serious	Unlisted Non serious	Listed Serious	Unlisted Serious	L + U Non serious	L + U Serious	L + U Total
Blood and lymphatic		1	43	26	1	69	70
Cardiac				11		11	11
Eye				2		2	2
Gastrointestinal	1		29	6	1	35	36
General disorders and administration site conditions	1	1	11	13	2	24	26
Hepato-biliary		1	1	4	1	5	6
Immune system			7			7	7
Infections and infestations				9		9	9
Injury, poisoning and procedural complications		1	6	13	1	19	20
Investigations			7	11		18	18
Metabolism and nutrition				8		8	8
Musculoskeletal and connective tissue				11		11	11
Nervous system		2	22	8	2	30	32
Pregnancy, puerperium and perinatal conditions			2	9		11	11
Psychiatric				3		3	3
Renal and urinary			4	10		14	14
Reproductive system and breast			6			6	6
Respiratory, thoracic and mediastinal			3	30		33	33
Skin & subcutaneous tissue disorders			12	5		17	17
Vascular			33	51		84	84
Total	**2**	**6**	**186**	**230**	**8**	**416**	**424**

There were 107 serious bleeding events, distributed in several body systems. They account for 57.5% of all serious listed events (n = 186). The second most frequent primary serious event reported is thrombocytopenia (n = 43). Added to three events of low platelet count, the total

number of events is 46 (24.7%). Two cases of thrombocytopenia had a fatal outcome (one was associated with a bleeding event).

2. Non-Serious reports with all events considered listed in the Product Safety Information

Of the 218 reports including only non-serious adverse events, 72 contain only events either specifically listed in the Product Safety Information or considered secondary to such an event. Among the listed reports, 22 cases refer to bleeding events (30.5%), 25 to some form of allergic reaction to the drug, 11 to the painful reaction to administration, 6 to liver enzyme alterations, 5 to lack of efficacy and 2 to thrombocytopenia. The majority (n=32) of the non-serious listed events belong to the body system "General disorders and administration site condition" (35.9%) and to "Skin and subcutaneous tissue disorders" (n=25, 28.1%). The single most frequent listed event was "injection site pain" (n=10), while all the other events remained within the single digit range.

3. Serious reports with at least one event not listed in the Product Safety Information (150 cases)

Of the 271 reports describing serious adverse events, 150 included at least one event **neither** specifically described (listed) as undesirable effects in the Product Safety Information **nor** considered secondary to such undesirable effects. Table 23 outlines the distribution of unlisted serious events according to body system. Non-serious events are secondary to a primary serious event. Within this category there were 22 fatal outcomes, 9 of which occurred in patients suffering from one unlisted event accompanied by bleeding or thrombocytopenia. Nine fatal outcomes seem to have occurred because of lack of efficacy of the drug and, finally, 4 fatal outcomes were the consequence of other concomitant medical conditions.

There were 23 reports of thrombocytosis (11 serious and 12 non-serious) in the category of unlisted events. The event was reactive in origin in 21 out of 23 patients, rather than caused by Fragmin therapy. Of 21 patients, 20 underwent orthopedic surgery and thrombocytosis occurred in the early postoperative period. In 1 further case, reactive thrombocytosis occurred after the patient developed HIT (case 2000011934). In the remaining 2 cases, the information provided is insufficient to allow a sound causality assessment.

4. Non-Serious reports with at least one event not listed in the Product Safety Information (146 cases)

Of the 218 reports describing non-serious adverse events, 146 included at least one event neither specifically described (listed) as undesirable effects in the product safety information nor considered secondary to such undesirable effects. A number of reports that form this group (n = 97) are registry cases. The most frequent non-serious unlisted events regarded the body system "Injury and poisoning" with 96 adverse reactions, 86 of which refer to registry cases of "exposure in utero" (53 of these reports are accompanied by "normal newborn or full term birth or premature baby", as secondary events). Eight cases refer to administration errors and two spontaneous cases refer to "scalp injury" and to "broken needle". In addition, the second

most frequent non-serious and not listed adverse events fall into the body system "Pregnancy, puerperium and perinatal conditions" (61 cases) and refer mainly to the event "normal newborn". In the body system "General disorders and administration site conditions" there are 18 unlisted events and finally, 10 events appear under the body system "Skin & subcutaneous tissue disorders". All other events remain in the single digit range.

5. Registry cases (97 cases)

Registry cases are typically not associated with adverse events, but may increase the risk of the patient to incur one. Within the time frame of this analysis registry cases were found in the body systems "Injury, poisoning and procedural complications" and "Pregnancy, puerperium and perinatal conditions". Within the body system "Injury, poisoning and procedural complications" 93 cases were identified. Most of the cases (n=84) refer to pregnancy related events: Thirty-one cases refer to drug exposure during pregnancy, 53 refer to drug exposure during pregnancy and normal or premature baby delivery. The remaining cases refer to accidental overdose without adverse event, maladministration or medication error. Within the body system "Pregnancy, puerperium and perinatal conditions" there were 4 registry cases, all complications of maternal exposure to therapeutic drugs.

6. Conclusion

The analysis of the suspect Adverse Drug Reactions to dalteparin from February 1, 2002 to May 1, 2003 provides a picture that is overall in line with the known safety profile for dalteparin sodium solution for injection. Through the examination of all serious unlisted events, thrombocytosis may be kept under surveillance. Excluding events that may have a relationship with the lack of drug efficacy (i.e. thromboembolic events), thrombocytosis is the most represented serious event (11 cases), which seems to occur as reactive in origin. Most of cases occurred in the early postoperative period in patients underwent orthopedic surgery. The postmarketing database should be monitored for thrombocytosis to assess the possibility of a direct causal relationship with dalteparin use.

E. Summary of Critical Safety Findings and Limitations of Data

Dalteparin sodium was well tolerated, based on this study report. The proportion of patients reporting at least 1 AE was similar in each treatment group (39.7% and 39.8% in the dalteparin sodium and placebo groups, respectively). The most frequently reported AE in both treatment groups was exacerbation of chronic obstructive airways disease, reported for 29 patients (1.6%) in the dalteparin sodium group and 39 patients (2.1%) in the placebo group.

More dalteparin sodium-treated patients than placebo patients had drug-related AEs (52 [2.8%] patients vs 30 [1.6%] patients). The most commonly reported drug-related AE was thrombocytopenia/thrombocytopenia aggravated, reported by 6 patients in each treatment group. A similar proportion of patients in each treatment group had at least 1 AE that led to death from Day 1 to Day 90 (105 patients [5.7%] and 101 patients [5.5%] in the dalteparin sodium

and placebo groups, respectively). Adverse events leading to death were most commonly associated with the cardiac disorders system organ class (47 patients [2.5%] and 45 [2.5%] patients in the dalteparin sodium and placebo groups, respectively) and the infections and infestations system organ class (24 patients [1.3%] and 19 patients [1.0%], respectively). Eight sudden deaths were reported up to Day 21 (5 in the dalteparin sodium group and 3 in the placebo group). None of the events leading to sudden death was considered related to study medication by investigators. The incidence rate for all cause death was similar in each treatment group at Day 90, Day 21 and Day 14. The overall incidence of death due to all causes was lower than expected for this patient population.

By Day 90, a total of 251 patients (13.6%) in the dalteparin sodium group and 243 patients (13.3%) in the placebo group reported SAEs. The most frequently reported SAE in both treatment groups was exacerbation of chronic obstructive airways disease, reported for 27 patients (1.5%) in the dalteparin sodium group and 34 patients (1.9%) in the placebo group. Very few patients reported drug-related SAEs (7 and 5 patients in the dalteparin sodium and placebo groups, respectively).

A higher number of patients in the dalteparin sodium group had centrally-adjudicated major bleeds by Day 21 than in the placebo group (9 patients vs 3 patients). Three major bleeds were fatal; 2 gastrointestinal bleeds, both considered related to treatment, occurred in the dalteparin sodium group, and 1 gastrointestinal bleed, which was not considered related to treatment, occurred in the placebo group. Four of the 9 non-fatal major bleeds were gastrointestinal, the remaining 5 bleeds comprised a nasal bleed, a hemothorax, a peritoneal bleed, a hematoma of the arm and a bleed from the rectus abdominalis muscle. Five of the 9 non-fatal major bleeds were considered to be drug-related by investigators (3 and 2 cases in the dalteparin sodium and placebo groups, respectively). Ten of the 12 major bleeds occurred in patients aged 65 years or older.

By Day 21, minor bleeds were reported for 19 dalteparin sodium-treated patients and 10 placebo patients. As for major bleeds, minor bleeds were more commonly reported in patients aged 65 years or older.

The incidence of drug-related allergic reactions up to Day 21 was extremely low (1 case of injection-site pruritus in a dalteparin sodium-treated patient and 1 case of urticaria in a placebo patient). The incidence of thrombocytopenia up to Day 21 was similar in each treatment group (10 and 8 cases in the dalteparin sodium and placebo groups, respectively). There were no notable differences between the treatment groups in mean changes from baseline for laboratory values. Similar proportions of patients reported laboratory abnormalities in each treatment group. None were considered to be a cause of clinical concern.

VIII. Dosing, Regimen, and Administration Issues

In medical patients with restricted mobility during acute illness, the recommended dose of

FRAGMIN is 5000 IU administered by s.c. injection once daily. In clinical trials, the usual duration of administration was 12 to 14 days.

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

No dose-response study was done for this new indication. Patients were given a once daily dose of 5000 IU dalteparin sodium for 14 days. The study enrolled general medical patients at moderate to high risk of VTE. The recommended dose of dalteparin sodium in surgical patients with a high risk of VTE is 5000 IU and this dose of dalteparin sodium is associated with acceptable safety in surgical patients. Thus, a dose of 5000 IU once daily of dalteparin sodium was chosen for this study. The 14-day treatment period should be sufficient for most patients to become mobile at
which point, from a pathophysiological standpoint, the risk of VTE should diminish.

The injections were given at an angle of 45-90 into the abdominal subcutaneous fat in a lifted skin-fold at different sites below the umbilicus. The injections were given as near as possible to the same time each day and within 20 to 28 hours after the previous injection, preferably in the morning.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

A slightly higher proportion of female patients (52%) than male patients was enrolled into the study (see section 4.2).

The incidence of the primary endpoint by gender is presented in Table 26.

Table 26: Gender-specific Incidence Rates of the Primary Endpoint -Symptomatic VTE, Fatal PE, Sudden Death by Day 21, and/or Asymptomatic Proximal DVT by Day 21+3. (ITT With Observed Values)

			Dalteparin sodium N=1848	Placebo N=1833	Difference in incidence*	RR
Visit	Gender					
By Day 21+3	Male	n/N'	22/730	36/711		
		Incidence	3.01	5.06	-2.05	0.60
		95% CI	(1.77, 4.25)	(3.45, 6.67)	(-4.08, -0.02)	(0.35, 1.00)
	Female	n/N'	20/788	37/762		
		Incidence	2.54	4.86	-2.32	0.52
		95% CI	(1.44, 3.64)	(3.33, 6.38)	(-4.20, -0.44)	(0.31, 0.89)

** Dalteparin sodium minus placebo*
Incidence = n/N', where N' is the number of patients in the ITT population with observed values at the specific visit
RR = Risk ratio

The incidence of the primary endpoint was lower in the dalteparin sodium-treated patients than in the placebo-treated patients. The reduction in the risk ratio was similar for males and females. The results of the PP analysis were consistent with those of the ITT analysis.

There was a higher incidence of major bleeds in females (6/964) than male (3/884). There was a higher incidence of minor bleeds in males (13/884) than females (6/964). Consideration of major and minor bleeds together indicates that there was no difference between the genders for the incidence of major and minor bleeds.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The majority of patients in this study were aged 65 or over (66%) and most were white (92%) (see section 4.2 for details).

The incidence of the primary endpoint by age is presented in Table 27.

Table 27: Age-specific Incidence Rates of the Primary Endpoint -Symptomatic VTE, Fatal PE, Sudden Death by Day 21, and/or Asymptomatic Proximal DVT by Day 21+3. (ITT With Observed Values)

			Dalteparin sodium N=1848	Placebo N=1833	Difference in incidence	RR
Visit	Age group					
By Day 21+3	<65 years	n/N'	8/542	17/512		
		Incidence	1.48	3.32	-1.84	0.44
		95% CI	(0.46, 2.49)	(1.77, 4.87)	(-3.70, 0.01)	(0.19, 1.02)
	≥65 years	n/N'	34/976	56/951		
		Incidence	3.48	5.83	-2.34	0.60
		95% CI	(2.33, 4.63)	(4.35, 7.31)	(-4.22, -0.47)	(0.39, 0.91)

Dalteparin sodium minus placebo
Incidence = n/N', where N' is the number of patients in the ITT population with observed values at the specific visit
RR = Risk ratio

In both subgroups of patients, the incidence of the primary endpoint was lower in the dalteparin sodium-treated patients than in the placebo-treated patients. The incidence of the primary endpoint was also lower in patients <65 years than in patients ≥ 65 years. The results of the PP analysis were consistent with those of the ITT analysis.

There appeared to be a slightly higher incidence of major (7/1224 vs. 2/624) and minor bleeds (14/1224 vs. 5/624) in patients aged > 65 years than in those aged < 65 years.

Since the groups of non-Caucasian patients were small (about 8%), subgroup analysis of race on response rate did not seem meaningful.

C. Evaluation of Pediatric Program

The proposed new indication for dalteparin sodium injection has a rare occurrence in the pediatric population. Two nationwide registries (Canada and The Netherlands) have indicated that the annual incidence rate of VTE in pediatric patients is between 0.00007% and 0.000014%. In Canada, the annual incidence rate among hospitalized pediatric patients was 5.3 per 10,000 hospitalized patients. Furthermore, the Dutch registry identified only 115 cases for the entire nation over 2 years, whereas the Canadian registry identified only 137 cases for the entire nation over 30 months. These data indicate clearly that this is not a major public health problem, and with the rarity of this condition among the pediatric population, conducting clinical trials would not be possible. The sponsor requests a full waiver authorization from providing Pediatric Use information.

I recommend that the request of waiver for the pediatric study be granted for the indication of prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness. (note: Currently the Pediatric Rule is not being enforced).

D. Comments on Data Available or Needed in Other Populations

The safety of Fragmin in pregnant women has not been evaluated. No pregnancies were reported during the study.

No data were provided in this submission regarding Fragmin use in other populations such as renal or hepatic compromised patients.

In the current package insert for Fragmin, it is stated that 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 hours, i.e. considerably longer than values observed in healthy volunteers, therefore, greater accumulation can be expected in these patients. Under the section of **PRECAUTIONS, subsection of General,** it is stated that FRAGMIN Injection 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.

X. Conclusions and Recommendations

A. Conclusions

Venous thromboembolism is an important cause of morbidity and mortality among hospitalized patients. The prevention of VTE in general medical patients is a challenging healthcare problem. Methods of prophylaxis include various mechanical devices, oral anticoagulation, UFH in low doses and LMWH. However, available guidelines are based on limited data in medical patients, resulting in variable use across and within countries.

Dalteparin sodium is a well established LMWH already used in over 60 countries. This study confirmed the benefit of thromboprophylaxis with 5000 IU/day dalteparin sodium, administered subcutaneously for 14 days, on clinically relevant endpoints in a population of general medical patients at moderate risk for VTE.

The dalteparin sodium group showed a 44% greater reduction (42/1518 vs. 73/1473) in clinically relevant VTEs than the placebo group at Day 21, and the beneficial risk ratio was maintained at Day 90. The magnitude of the effect in the PREVENT study was consistent with other studies in both medical and surgical patients.

The safety of dalteparin sodium was good in this population. The safety profile was generally comparable with that of placebo, suggesting that many events recorded were a reflection of the patient's underlying conditions.

There was a low incidence of bleeding complications and of thrombocytopenia in the PREVENT study. Although the incidence of major bleeds appeared to increase with age in the dalteparin sodium group, the incidence was low (0.49%). Over half of the patients in the PREVENT study were aged 70 years and over.

The risk of death from all causes was 5.8 (107/1848) in the dalteparin griup and 5.6% (103/1833) in the place group at Day 90. However, for majority of patients with adverse events leading to death, these events were not considered drug-related by the investigator. Most commonly deaths were due to cardiac disorders, and infections and infestations.

The incidence of sudden death was slightly higher in the dalteparin sodium group (5 cases) than in the placebo group (3 cases) at Day 21, but by Day 90, there were fewer cases of sudden death in the dalteparin group (7 cases) than in the placebo group (9 cases). None of the cases of sudden death was considered to be drug-related by investigators.

The risk/benefit profile may be examined in terms of the ratio major bleeds/clinically relevant endpoints. In the PREVENT study, the ratio of major bleeds/clinically relevant VTE was 0.21 (9/42). The ratio of major bleeds/proximal DVT was also more favorable for the PREVENT study (0.31, 9/29).

The rate of clinically relevant VTEs in the PREVENT study was lower than expected but the clinical benefit of prophylactic treatment was clear and associated with a very low risk of bleeding. Thus dalteparin sodium may be considered an effective thromboprophylactic strategy in general medical patients, with an good safety profile.

As compared with the known safety profile of dalteparin sodium, no changes in severity of the suspected adverse drug reactions were observed from review of post-marketing data over a 6-year period. There was no new safety information to alter the risk benefit assessment for dalteparin sodium. A total of 11 cases of thrombocytosis were reported from post market safety update. Thrombocytosis should be monitored to assess the possibility of a direct causal relationship with dalteparin use.

In conclusion, 5000 IU of dalteparin sodium administered subcutaneously once daily for 12 to 14 days is an effective prophylaxis for clinically relevant VTE in general medical patients at risk of VTE for whom prolonged hospitalization is anticipated. The treatment was well tolerated in this patient population, with only events already known and expected from the pharmacology of the drug reported notably more frequently in the dalteparin sodium group than in the placebo group, and the incidence of such events was well within the accepted margins.

The study showed the treatment effects to be consistent across a range of subgroups (age, gender, inclusion criteria). The study was well conducted.

B. Recommendations

Dalteparin sodium is approvable as an additional option to the physician considering thromboprophylaxis of DVT, which may lead to PE in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness. The recommended dose of dalteparin sodium is 5000 IU subcutaneously once daily for 12 to 14 days. To get dalteparin sodium approved for this proposed indication, the sponsor has to do all of the necessary changes in the dalteparin sodium labeling, as recommended in my Medical Officer's Labeling Review (appendix A) and FDA Consumer Safety Officer's Labeling Review.

The request of waiver for the pediatric study should be granted for this indication (prophylaxis of DVT, which may lead to PE in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness). The proposed new indication for dalteparin sodium injection has a rare occurrence in the pediatric population and this is not a major public health problem. With the rarity of this condition among the pediatric population, conducting clinical trials would not be possible. Currently the Pediatric Rule is not being enforced.

The postmarketing database should be monitored for thrombocytosis to assess the possibility of a direct causal relationship with dalteparin use.

XI. APPENDIX

A LABELING REVIEW

In this submission, the sponsor proposed the following changes for the package insert.

1. Under the section of **CLINICAL TRIALS** the following section is added:

Prophylaxis of Deep Vein Thrombosis in Medical Patients at Risk for Thromboembolic Complications due to Restricted Mobility During Acute Illness:
In a double-blind, multi-center, randomized, placebo-controlled clinical trial, general medical patients with restricted mobility who were at risk of venous thromboembolism were randomized to receive either FRAGMIN 5000 IU or placebo s.c. once daily during Days 1 to 14 of the study. The primary endpoint was evaluated at Day 21, and the follow-up period was up to Day 90. These patients had an acute medical condition requiring a projected hospital stay of at least 4 days, and were confined to bed during waking hours. The study included patients with congestive heart failure (NYHA Class III or IV), acute respiratory failure not requiring ventilatory support,

[redacted]

The prophylactic effect was sustained through Day 90.

Table 6
Efficacy of FRAGMIN in the Prophylaxis of Deep Vein Thrombosis, [redacted] in Medical Patients with Restricted Mobility during Acute Illness

Indication	Dosing Regimen	
	FRAGMIN 5000 IU [redacted] s.c.	Placebo [redacted] s.c.
All Treated Medical Patients During Acute Illness	1848	1833

[redacted]

Reviewer's comments and recommendations

- The information for the patients included in this study is not accurate and should be modified as following:

The study included patients with congestive heart failure (NYHA Class III or IV), acute respiratory failure not requiring ventilatory support, and the following acute conditions [redacted]. Risk factors include > 75 years of age, cancer, previous DVT/PE, obesity and chronic venous insufficiency.

- The 1st sentence in the following paragraph can be deleted and 2nd sentence should be modified as following to be consistent with other labeling.

[redacted] DVT by Day 21 (see Table 6). The prophylactic effect was sustained through Day 90.

- Data regarding symptomatic VTE and risk reduction should be added to Table 6. The table should be modified as follows:

Table 6
Efficacy of FRAGMIN in the Prophylaxis of Deep Vein Thrombosis [redacted] in Medical Patients with Restricted Mobility during Acute Illness

Indication	Dosing Regimen	
	FRAGMIN 5000 IU [redacted] qd, s.c.	Placebo [redacted] qd, s.c.
All Treated Medical Patients During Acute Illness	1848	1833
DVT, PE [redacted] or sudden death in evaluable patients (Day 21)	42/1518 (2.77%)[1]	73/1473 (4.96%)
Total thromboembolic events (Day 21)	37/1513 (2.45%)	70/1470 (4.76%)
Total DVT	32/1508 (2.12%)	64/1464 (4.37%)
Proximal DVT	29/1518 (1.91%)	60/1474 (4.07%)
Symptomatic VTE	10/1759 (0.57%)	17/1740 (0.98%)
PE	5/1759	6/1740
Sudden Death	5/1829 (0.27%)	3/1807 (0.17%)

[1] p-value = 0.0015

2. Under the section of **INDICATIONS AND USAGE,** a new indication is added as following:

In medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness.

Reviewer's comment and recommendation:

The change is acceptable.

3. Under the section of **ADVERSE REACTIONS** subsection of **Hemorrhage,** a new subsubsection for medical patients with restricted mobility is added:

Medical Patients with Restricted Mobility:
Table 10 summarizes major bleeding events that occurred in a clinical trial of medical patients with restricted mobility during acute illness.

Table 10
Bleeding Events in Medical Patients with Restricted Mobility

Indication	Dosing Regimen	
Medical Patients with Restricted Mobility	FRAGMIN 5000 IU ——— s.c.	Placebo ——— s.c.
Major Bleeding Events[1] at Day 14	8/1848 (0.43%)	0/1833 (0%)
Major Bleeding Events[1] at Day 21	9/1848 (0.49%)	3/1833 (0.16%)

[1] A bleeding event was considered major if: 1) was accompanied by a decrease in hemoglobin of ≥ 2 g/dL in connection with clinical symptoms; 2) intraocular, spinal/epidural, intracranial, or retroperitoneal bleeding; 3) required transfusion of ≥ 2 units of blood products; 4) required significant medical or surgical intervention; or 5) led to death.

Three of the major bleeding events that occurred by Day 21 were fatal, all due to gastrointestinal hemorrhage (two patients in the group treated with FRAGMIN and one in the group receiving placebo). Two deaths occurred after Day 21: one patient in the placebo group died from a subarachnoid hemorrhage that started on Day 55, and one patient died on day 71 (two months after receiving the last dose of FRAGMIN) from a subdural hematoma.

Reviewer's comment and recommendation:

The change is acceptable.

4. Under the section of **ADVERSE REACTIONS** subsection of ***Ongoing Safety Surveillance,*** following changes are made:

Since first international market introduction in 1985, there have been ~~six~~ nine reports of epidural or spinal hematoma formation with concurrent use of dalteparin sodium and spinal/epidural anesthesia or spinal puncture. Five of the ~~six~~ nine patients had post-operative indwelling

epidural catheters placed for analgesia or received additional drugs affecting hemostasis. The hematomas caused long-term or permanent paralysis (partial or complete) in ~~four~~ seven of these cases. ~~The sixth~~ One patient experienced temporary paraplegia but made a full recovery, and one patient had no neurological deficit. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Reviewer's comment and recommendation:

The changes are acceptable based on updated information on postmarking spontaneous reports of spinal hematomas.

5. Under the section of **DOSAGE AND ADMINISTRATION**, a new subsection is added for **Medical Patients with Restricted Mobility** as following:

In medical patients with restricted mobility during acute illness, the recommended dose of FRAGMIN is 5000 IU administered by s.c. injection once daily. In clinical trials, the usual duration of administration was 12 to 14 days.

Reviewer's comment and recommendation:

The changes are acceptable.

6. Under the section of **DOSAGE AND ADMINISTRATION**, in Table 9 entitled "Volume of FRAGMIN to be Administered by Patient Weight," the sponsor deleted the footnote that reads "calculated volume based on the 9.5 mL multiple-dose vial (10,000 anti-Factor Xa IU/mL)" and moved to the text above the table.

Reviewer's comment and recommendation:

The changes are acceptable.

7. **Administration** subsection, ***Instructions for using the prefilled single-dose syringes preassembled with passive needle guard devices*** sub-subsection, ***Graduated syringes*** sub-sub-subsection
In the first paragraph, third sentence that begins, " Prepare the syringe by . . ." the sponsor changed the case in the word "Prepare" from capital letter to lower case and added the phrase "With the [redacted]' prior to the word "Prepare" so that the sentence reads " With the [redacted], prepare the syringe by [redacted] the plunger down to the desired dose or volume, discarding the extra solution in an appropriate manner."

Reviewer's comment and recommendation:

The changes are unacceptable. It should be "With the syringe in the needle up (not down) position,". The sponsor realized that it is a mistake and proposed change in SLR 034 submission.

The sentence should be modified as following: "With the needle pointing up, prepare the syringe by expelling the air bubble and then continuing to depress the plunger to the desired dose or volume, discarding the extra solution in an appropriate manner".

8. Please see FDA regulatory project manager's labeling review for more comments and recommendations.

APPENDIX B: ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CI	Confidence interval
CRF	Case report form
CT	Computed tomography
CUS	Compression ultrasonography
DVT	Deep vein thrombosis
FXa	Factor Xa
Hb	Hemoglobin
HCT	Hematocrit
HIT	Heparin induced thrombocytopenia
ICH	International Conference on Harmonization
INR	International normalized ratio
ITT	Intent-to-treat
IU	International units
LMWH	Low molecular weight heparin
MRI	Magnetic resonance imaging
NYHA	New York Heart Association
PE	Pulmonary embolism
PP	Per-protocol
RR	Risk ratio
SAE	Serious adverse event
SD	Standard deviation
ULN	Upper limit of the normal range
VTE	Venous thromboembolism
V/Q	Ventilation-perfusion

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/s/

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MEDICAL OFFICER

Kathy Robie-Suh
11/13/03 12:03:28 PM
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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: November 24, 2003

From: Kathy M. Robie-Suh, M.D., Ph.D.
Medical Team Leader, Hematology
Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Subject: NDA 20-287/SE1-032; submitted 2/7/03
Fragmin (dalteparin sodium) Injection

Efficacy supplement to add a new indication for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness

To: NDA 20-287

Fragmin is approved for prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction (MI), when concurrently administered with aspirin. The recommended dose is 120 IU/kg (but not more than 10,000 IU) subcutaneously (s.c.) every 12 hours. The usual duration of treatment is 5 to 8 days.

Fragmin is also approved for prophylaxis of deep venous thrombosis (DVT), which may lead to pulmonary embolus (PE) as shown below:

Indication	Dosing	Duration
Hip replacement surgery patients	• 2500 IU s.c. 4 to 8 hrs after surgery followed by 500 IU s.c. daily; • 2500 IU s.c. within 2 hrs before surgery, followed by 2500 IU s.c. 4 to 8 hours after surgery, followed by 5000 IU s.c. daily, or ; • 5000 IU s.c. 10 to 14 hrs before surgery, followed by 5000 IU s.c. 4 to 8 hours after surgery, followed by 5000 IU s.c. daily	up to 14 days (usual duration 5 to 10 days)
Abdominal surgery patients who are at risk for thromboembolic complications	• 2500 IU s.c. starting 1 to 2 hrs prior to surgery and once daily • [patients with particularly high risk of thrombosis, such as presence of malignancy] 5000 IU s.c. the evening before surgery then once daily postoperatively or 2500 IU s.c. 1 to 2 hrs before surgery followed by 2500 IU s.c. 12 hrs later and then 5000 IU s.c. once daily postoperatively	5 to 10 days

On February 7, 2003 Pharmacia & Upjohn submitted a supplemental New Drug application to support the following indication:

> "FRAGMIN is also indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE): ... In medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness."

The proposed dose is 5000 IU s.c. once daily, with a usual duration of administration of 6 to 14 days.

Lovenox (enoxaparin sodium) is also approved for this indication and heparin is generally approved for thromboprophylaxis.

The sponsor has submitted results of a single pivotal multinational clinical trial (Study 524-E-CVD-0042-033; PREVENT) to support the indication. (See Medical Officer's Review dated 11/13/03). The study is described briefly and major findings presented below.

PREVENT Trial:

PREVENT was a randomized (1:1), double-blind, parallel groups, placebo-controlled, multinational, multicenter clinical trial evaluating safety and effectiveness of dalteparin for thromboprophylaxis in medical patients with restricted mobility. Most sites (and most patients) were in Eastern Europe. The study enrolled patients age 40 years and older having recent (≤3 days) restricted mobilization defined as patients mainly confined to bed during waking hours and hospitalized for: NYHA Class III or IV heart failure; acute respiratory failure not requiring ventilatory support; or acute medical conditions [i.e., acute infection without shock, episode of inflammatory bowel disease, acute rheumatic disorders, acute lumbar pain or sciatica or vertebral compression (caused by osteoporosis or tumor), acute arthritis of the legs, or acute episode of rheumatoid arthritis in the legs)] and having one or more predefined risk factors for venous thromboembolism (VTE). Patients were randomized to receive either: dalteparin 5000 IU s.c. once daily or placebo (normal saline) s.c. once daily for 14 days. Patients were followed for VTE events to day 21. If signs/symptoms of VTE occurred, patients underwent evaluation first with compression ultrasound (CUS). If this test was conclusive positive or negative, no further diagnostic measures were undertaken. In asymptomatic patients end-of-study efficacy assessment was done at day 21+3 (i.e., Day 21-24) using bilateral compression ultrasound (CUS) or bilateral venography. The primary efficacy endpoint was occurrence of any of the following objectively verified symptomatic proximal DVT, symptomatic fatal or non-fatal PE, non-symptomatic DVT verified by CUS or venography [Day 21+3], or sudden death occurring up to Day 21. The primary efficacy analysis compared the incidence of the primary efficacy endpoint in the intent-to-treat population, defined as all randomized patients who received at least one dose of study

drug. A per protocol population was identified as well defined as all patients age ≥18 years who met other inclusion criteria and who received at least 12 days of study treatment missing fewer than two consecutive days of treatment and who have an evaluable bilateral DVT assessment at end of study or a verified VTE event at end-of-study efficacy assessment (Day 21+3).

A total of 3706 patients were randomized in this study (1856 dalteparin, 1850 placebo). Of these, 1848 dalteparin patients and 1833 placebo patients received study drug. Only about 1% of patients were from U.S. sites. Baseline characteristics of the ITT population were mean age 69 years (range 26 to 99 years), 48% males/52% females, 92% white, 6% mixed race. Major reasons for hospitalization included NYHA Class III or IV heart failure (52% of patients), acute respiratory failure (30%), acute infectious disease (37%) and acute lumbar pain or sciatica or vertebral compression (5%). Treatment groups were similar with regard to these characteristics. The most common risk factors for VTE were chronic heart failure (51% of patients), age ≥75 years (33%), chronic heart failure (32%), and obesity (30%). Distribution of risk factors was similar in the two treatment groups.

About 24% of enrolled patients had one or more major protocol violations. The most frequent violations were: incorrectly treated (received less than 12 injections without reaching a study endpoint or missed more than 2 consecutive days of treatment)(9.3% of patients), end-of-study CUS not performed (9.0%), or end-of-study CUS not interpretable (9.0%). Generally, these occurred with similar frequency in the two treatment groups. The rates of uninterpretable CUS and CUS not done were slightly higher in the placebo group (9.5% and 8.6%, respectively, uninterpretable and 9.7% and 8.3%, respectively, not done). Major reasons for premature discontinuation of treatment included adverse events (5% of patients), consent withdrawn (3%), and protocol violations (27% of patients). Frequencies of these were similar in the two treatment groups.

Reasons for exclusion of patients from the primary efficacy analysis are summarized in the sponsor's table below.

Table 4. Patients in the ITT population not contributing to the primary efficacy analysis

Reason	Dalteparin sodium N=1848	Placebo N=1833	Total N=3681
	n (%)	n (%)	n (%)
Reason for no screening of DVT			
- Death (other than sudden death or fatal PE)	44 (2.4)	43 (2.3)	87 (2.4)
- Adverse event	15 (0.8)	19 (1.0)	34 (0.9)
- Protocol violation	21 (1.1)	22 (1.2)	43 (1.2)
- Consent withdrawn	45 (2.4)	63 (3.4)	108 (2.9)
- Lost to follow-up	16 (0.9)	12 (0.7)	28 (0.8)
- Protocol specific withdrawal criteria	2 (0.1)	1 (0.1)	3 (0.1)
- Other reasons			
– Local evaluation performed but no central evaluation	6 (0.3)	7 (0.4)	13 (0.4)
– CUS/venography non evaluable/non diagnostic	155 (8.4)	172 (9.4)	327 (8.9)
– Only 1 leg evaluated	2 (0.1)	1 (0.1)	3 (0.1)
– Symptomatic evaluation therefore no screening	8 (0.4)	11 (0.6)	19 (0.5)
– Not reporting*	12 (0.6)	9 (0.5)	21 (0.6)
Last known day with no symptoms < 21	4 (0.2)	0	4 (0.1)
Total	330 (17.9)	360 (19.6)	690 (18.7)

% = n/N, where N is the number of patients in the ITT population

* *These 21 patients did not have a Day 21 visit and consequently no CRFs were completed at Day 21.*

Source: Table T5

The sponsor's primary and major secondary efficacy analyses are shown in the following table.

ITT Population: Summary of Venous Thromboembolism Incidences (Day 21+3)*

	Number of Patients (%)				p-value
Total Randomized	Placebo		Dalteparin		
	N=1833	%	N=1848	%	
Primary endpoint*	73/1473	4.96%	42/1518	2.77%	0.0015
Symptomatic VTE (DVT and/or PE)	17/1740	0.98%	10/1759	0.57%	
Symptomatic PE	6/1740	0.34%	5/1759	0.28%	
Proximal DVT (symptomatic and/or asymptomatic)	60/1474	4.07%	29/1518	1.91%	
All DVT (proximal DVT and/or distal symptomatic DVT)	64/1464	4.37%	32/1508	2.12%	
Symptomatic VTE (DVT and/or PE) and/or sudden death	20/1743	1.15%	15/1764	0.85%	
Total VTE	70/1470	4.76%	37/1513	2.45%	
Sudden death	3/1807	0.17%	5/1829	0.27%	

* symptomatic VTE, fatal PE, sudden death by day 21, and/or asymptomatic proximal DVT by day 21+3

reviewer's table based on tables in sponsor's study report

Though the primary efficacy endpoint failed to achieve its protocol-specified level of statistical significance ($p<0.001$), the analysis provided strong evidence that dalteparin provided effective thromboprophylaxis in this study as compared to placebo. See FDA Statistical Review (T. Permutt, 11/12/03). Where event rates were large enough to allow meaningful analysis, the secondary analyses were consistent with the primary analysis. The sponsor did not show the analysis of asymptomatic DVT alone at 21+3 days; however, it appears that these asymptomatic events accounted for the majority of the VTE events that occurred in the study.

Demographics and baseline characteristics of ITT and evaluable populations were similar. About 81% of patients were evaluable for the primary efficacy endpoint. Proportions of evaluable patients were similar in the two treatment groups. Efficacy results for the per protocol population were generally similar to the ITT results except that event rates were slightly smaller in both treatment groups.

Mean treatment duration was comparable in the two treatment groups (12.6 days in ITT population; 13.4 days in per-protocol population). About 40% of patients in the placebo group and 40% of patients in the dalteparin group experienced at least one adverse event during the study. The most frequent adverse events during the treatment period in this study are summarized in the following table:

Most Frequent Adverse Events (Day 1 to Day 90)*

	Number of Patients (%)	
Adverse Event	Placebo	Dalteparin
Chronic obstructive airways disease exacerbated	39 (2.1%)	29 (1.6%)
Pneumonia NOS	22 (1.2%)	28 (1.5%)
Diarrhea NOS	26 (1.4%)	23 (1.2%)
Headache NOS	24 (1.3%)	20 (1.1%)
Vomiting NOS	12 (0.7%)	20 (1.1%)

*does not include VTEs

reviewer's table based on sponsor's Table 24

Most adverse events were not considered related to study drug. Thrombocytopenia/thrombocytopenia aggravated was the most common event judged possibly or probably related to study drug (6 cases in each treatment group).

In the study from Day 1 to Day 90 about 5.5% of placebo patients and 5.7% of dalteparin patients died. Most common causes for death were cardiac disorders (2.5% and 2.5%), infections and infestations 1.0% placebo, 1.3% dalteparin). There were 16 sudden deaths (7 dalteparin and 9 placebo). Five of the dalteparin deaths and 3 of the placebo deaths occurred by Day 21. About 4.9% of patients in each treatment group experienced serious adverse events. The most frequent serious adverse events were pneumonia (1.0% in dalteparin group and 0.8% in placebo group) and chronic obstructive airways disease exacerbated (dalteparin, 1.5%; placebo, 1.9%).

Incidence of major bleeding events by during treatment (by Day 14) was 0% in the placebo group and 0.43% in the dalteparin group and at Day 21 was 0.16 in the placebo group and 0.49% in the dalteparin group. By Day 21 there were 2 fatal major bleeds in the dalteparin group and 1 in the placebo group. Incidence of minor bleeding events by during treatment (by Day 14) was 0.27% in the placebo group and 0.87% in the dalteparin group and at Day 21 was 0.55 in the placebo group and 1.03% in the dalteparin group. There was one drug-related allergic reaction in each treatment group. Eight placebo patients and 10 dalteparin patients experienced thrombocytopenia by Day 21 (most cases male and older patients). Adverse events led to comparable numbers of withdrawals in both treatment groups (placebo, 4.3%; dalteparin, 4.5%).

Conclusions and Recommendations:
The sponsor has submitted one adequate and well-controlled clinical trial (PREVENT) in patients demonstrating effectiveness of dalteparin 5000 IU administered subcutaneously once daily for 14 days in reducing the incidence of thromboembolic events in a population of medical patients at risk for VTE because of restricted mobility due to acute medical illness. Safety of dalteparin use in these patients is supported by PREVENT. Generally, the adverse event profile is similar to that in the current labeling for Fragmin. I recommend that this application be approved.

With regard to the labeling I have the following comments:

- The Fragmin PREVENT study enrolled patients having recent (≤3 days) immobilization [defined as being mainly confined to bed during waking hours] and being hospitalized due to acute medical illness (including NYHA Class III or IV heart failure, acute respiratory failure not requiring ventilatory support, acute infection without septic shock, acute rheumatic disorder, acute lumbar pain or sciatica or vertebral compression (caused by osteoporosis or tumor), acute arthritis of the legs, acute episode of rheumatoid arthritis in the legs) and having one or more predefined risk factors for VTE and with planned hospitalization for at least 4 days.

  The Lovenox study for this same indication (MEDENOX) enrolled patients having autonomous walking distance <10 meters for ≤3 days prior to enrollment and presenting for hospitalization due to acute medical illness (including NYHA Class III or IV heart failure, acute respiratory failure, acute infectious disease, acute rheumatic disorder, active inflammatory bowel disease episode) and having one or more predefined risk factors for VTE and with planned hospitalization for at least 6 days (though they could be discharged home on day 5).

  Baseline characteristics and risk factors for the two study populations are summarized in the following table:

Baseline Characteristics of Patients in MEDENOX Trial and PREVENT Trial

	MEDENOX (enoxaparin)	PREVENT (dalteparin)
Mean age (yrs)	73	68.5
Gender (M/F)(%/%)	50/50	48/52
Reasons for Hospitalization (%):		
Heart failure NYHA Class III	24.9	51.8[1]
Heart failure NYHA Class IV	9.3	
Acute respiratory failure	53.5	30.5
Acute infectious disease	53.1	36.9
Acute rheumatic disorder	9.1	2.3
Acute lumbar pain or sciatica or Vertebral compression		5.4
Risk factors for VTE:		
Age >75 yrs	50	33.3[2]
History or current cancer	14	5.2
History of VTE	9	3.9
Obesity	20	30.4
Varicose veins	25	26.6
Chronic heart failure	32	50.8
Chronic respiratory failure	54	9.8

[1] NYHA Class III or IV
[2] ≥75 years

table based on sponsor's tables from Medical Officer's Reviews

Though the descriptions of inclusion and exclusion criteria are not identical for PREVENT and for MEDENOX, both studies allowed a broad range of patients in the

study. The study populations for the two trials appear generally comparable, though the MEDENOX study enrolled more chronic respiratory failure patients while the PREVENT study enrolled more chronic heart failure patients. The wording of the indication in the labeling for the two products (Lovenox and Fragmin) should be similar. The qualifier "severely" should be added before the words "restricted mobility" to more accurately describe these patients and to be consistent with the Lovenox labeling for the indication.

- The major effect of dalteparin in the study appeared to be in preventing asymptomatic DVT and the numbers of PE and sudden death were very small. Therefore, PE and sudden death should not be particularly highlighted in presenting the efficacy results. (e.g., [redacted].

- The numbers of patients should be updated in the new **Geriatric Use** section of the labeling.

- The sponsor should clarify what the percentages under **Drug/Laboratory Test Interactions:** ***Elevations of Serum Transaminases*** represent and update, if appropriate.

Additional recommendations from the Medical Officer's Review (Dr. R. He, 11/13/03) should be considered.

cc:
NDA 20-287
HFD-180/Division File
HFD-180/DMoore
HFD-180/RHe
HFD-180/KRobie-Suh
HFD-720/TPermutt
HFD-180/JChoudary
HFD-180/LZhou

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/s/

Kathy Robie-Suh
11/24/03 08:34:53 PM
MEDICAL OFFICER

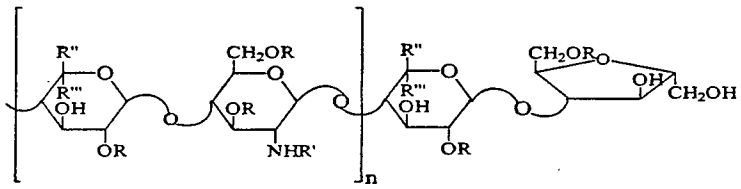
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-032

CHEMISTRY REVIEW

CHEMIST'S REVIEW # 1	1. Organization: HFD-180	2. NDA number: 20-287/SE1032	
3. Name and Address of Applicant (City & State): Pharmacia & Upjohn 7000 Portage Road Kalamazoo, MI 49001-0199		4. AF Number: 5. Supplement(s)	
6. Name of Drug: Fragmin®	7. Nonproprietary Name: Deltaparin Sodium injection	Numbers SC1-032	Dates 02/07/03
8. Supplement Provides for: Prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness.		9. Amendments & Other (Reports, etc.) Dates:	
10. Pharmacological Category: Anticoagulant	11. How Dispensed: RX X OTC	12. Related DMF(s):	
13. Dosage Form: Solution for Injection Subcutaneous	14. Potency: 2500 IU, 5000 IU, 10,000 IU, 25,000 IU, 7500 IU		
15. Chemical Name and Structure: Sulfated polysaccharide chains at the non-reducing end and 6-O-sulfo-2, 5-anhydro-Dmannitol at reducing end.		16. Records and Reports:	
		Current Yes X No	
		Reviewed Yes X No	



R= H or SO_3Na
R'= $COCH_3$ or SO_3Na
R"= H R"= COONa
OR
R"= COONa R'"= H
n= 3,20

17. Comments: The supplement may be approved from the Chemistry, Manufacturing and Controls point of view.
CC: NDA 20-287
HFD-180/Div File/NDA 20-287032
HFD-181/CSO/D. Moore
HFD-180/B.Justice
HFD-180/A.Al-Hakim
R/D init: L. Zhou
10-28-03 /Wordfiles\S\20287032

18. Conclusions and Recommendations:
Recommend that the regulatory Health Project Manager issue Approval letter for this supplement.

19. Reviewer

Name: Ali Al-Hakim, Ph.D.	Date Completed: October 28, 2003

Review Notes

This is an efficacy supplement provided for the use of Fragmin (Delta Sodium Injection) for Prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness.

The supportive information for the CMC related information in this supplement included the followings:

- **The Chemistry, Manufacturing and Controls** information for Fragmin will not change and will remain as per the approved NDA 20-287.
- **Pediatric Waiver Request.** The sponsor reported that data generated in pediatric population indicated that the new indication is a very rare in pediatric population and annual incidents of VTE in pediatric patients, in Canada and the Netherlands, is between 0.00007% and 0.000014%. Therefore, there is no need for conducting clinical trials. In accordance with 21 CFR 5.314.55 (c) (2), the sponsor requested a full waiver authorization from providing "Pediatric Use" information.
- **Environmental Assessment-Claim for Categorical Exclusion.** The applicant reported under the provisions of 21 CFR 25.3(b), action on an NDA are categorically excluded and, therefore, do not require the preparation of an Environmental Assessment (EA) or Environmental Impact statement (EIS) if the action increases the use of entry into the aquatic environment will be below 1 part per billion.
- **Claim for Exclusivity under 21 CFR 314.108(b)(5).** Pharmacia & Upjohn Company is claiming three years of exclusivity under the above CFR rule for supplemental NDAs.

Conclusion
The supplement is recommended for approval from the Chemistry, Manufacturing and Controls point of view.

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/s/

Ali Al-Hakim
10/28/03 01:49:02 PM
CHEMIST

Liang Zhou
10/28/03 02:00:09 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-032

ENVIRONMENTAL ASSESSMENT

1. ENVIRONMENTAL ASSESSMENT – CLAIM FOR A CATEGORICAL EXCLUSION

Under the provisions of 21 CFR 25.31(b), action on an NDA are categorically excluded and, therefore, ordinarily do not require the preparation of an Environmental Assessment (EA) or an Environmental Impact Statement (EIS) if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion. The total planned production in the U.S. of dalteparin sodium (NDA 20-287 Fragmin) is estimated to be at levels where the aquatic concentration is under a concentration of 1 part per billion. Pharmacia & Upjohn Company, a subsidiary of Pharmacia Corporation, is not aware of the existence of any extraordinary circumstances that would require the preparation of an Environmental Assessment. In addition, Pharmacia & Upjohn does not have any information to indicate that dalteparin sodium may be toxic to organisms in the environment at the expected levels of exposure. Pharmacia & Upjohn claims a categorical exclusion to the EA requirements in accordance with 21 CFR 25.31(b).

1.1. Date

January 17, 2003

1.2. Name of Applicant

Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001-0199

Contact: Daniel E. Sullivan, Ph.D.
Tel. (269) 833-0394

1.3. List of Preparer

Daniel E. Sullivan, Ph.D.
Director of Environmental Affairs

Ph.D. Environmental Engineer with twenty- three years in chemical fate and effect evaluations, WWTP operations, and regulatory compliance.

1.4. Certification

The undersigned certifies that the information presented is true, accurate, and complete to the best knowledge of Pharmacia.

Daniel Sullivan 17 JANUARY 2003

Daniel E. Sullivan, Ph.D. Date

NDA 20-287
Fragmin® (dalteparin sodium, injection)
Pharmacia and Upjohn Company

Environmental Assessment

A categorical exclusion is claimed for this NDA in accordance with 21 CFR part 25.31 (b). as amended in the 29-Jul-1997 Federal Register. This was found to be satisfactory (see Chemistry Review dated October 28, 2003.

Diane Moore
11/26/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-032

STATISTICAL REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	20-287/SE1-032
Name of drug:	Fragmin (dalteparin sodium injection)
Indication:	prevention of venous thrombo-embolism in medical patients
Applicant:	Pharmacia & Upjohn
Dates:	letter 7 February 2003; user fee goal (10 months) 7 December 2003
Review priority:	standard
Biometrics division:	Division of Biometrics II
Statistical reviewer:	Thomas Permutt
Concurring reviewers:	none
Medical division:	Division of Gastro-intestinal and Coagulation Drug Products
Clinical reviewer:	Ruyi He, M.D.
Project manager:	Diane Moore

Keywords: NDA review, clinical studies, one-study application

1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

Dalteparin was effective in reducing the incidence of venous thrombo-embolic events in immobilized medical patients. Safety is discussed in Dr. He's review.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

The supplement is based on a single study in 3706 patients hospitalized for acute medical conditions.

1.3 STATISTICAL ISSUES AND FINDINGS

There are no statistical issues that importantly affect the interpretation of the results.

2 INTRODUCTION

2.1 OVERVIEW

Fragmin (dalteparin) is a low-molecular-weight heparin, made by depolymerizing biologically-derived heparin. It is approved as an anticoagulant under NDA 20-287, approved 22 December 1994.

The present supplement relates to prophylactic use in medical patients to prevent venous thrombo-embolic events. Bedridden patients are at risk for developing blood clots, especially in the legs. These are sometimes asymptomatic, but sometimes troubling in themselves. The most serious risk, however, is the possibility of migration of a clot to the lung (pulmonary embolism), which can be fatal. Anticoagulants are used prophylactically in bedridden patients, and dalteparin is approved for patients immobilized by surgery, but not before now in medical patients.

2.2 DATA SOURCES

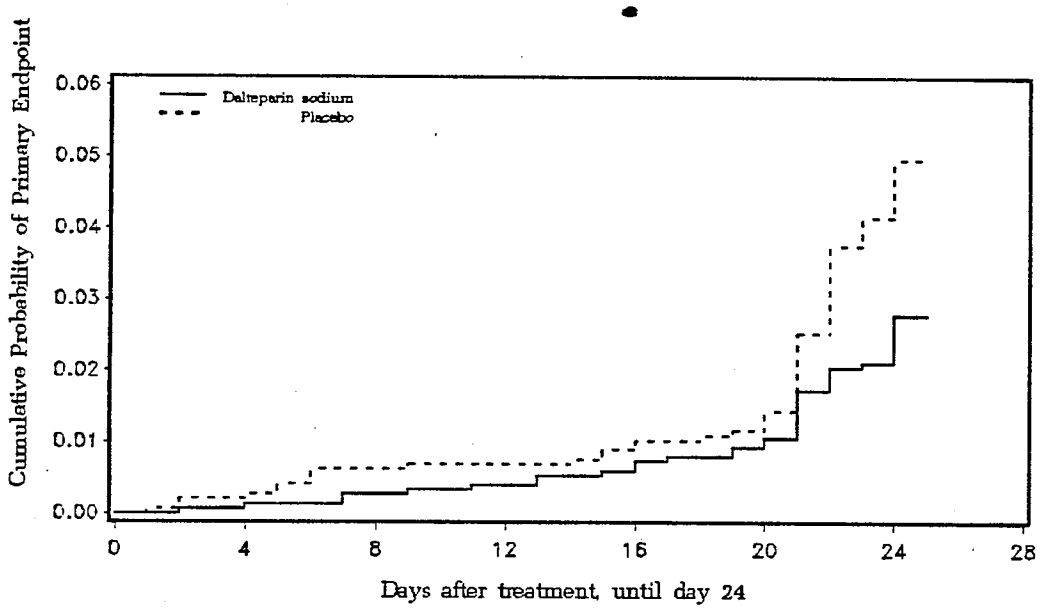
The supplement reports a single trial called PREVENT. It was a randomized, double-blind, placebo-controlled, parallel-group, multicenter trial in 3706 patients at 219 sites in 26 countries, mostly in Europe. Patients were required to be over 40, with an acute medical condition estimated to require at least four days' stay in hospital, and having been mainly confined to bed during waking hours in the past three days.

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

Patients in the PREVENT trial were randomized in approximately equal numbers to subcutaneous injection of dalteparin sodium 5000 IU or placebo daily for 14 days. The

primary measure of efficacy was to be the rate of occurrence of a composite event: sudden death, symptomatic pulmonary embolism, symptomatic deep vein thrombosis, or asymptomatic, proximal deep vein thrombosis verified by venography or compression ultrasonography. The difference in rates of symptomatic events by day 21, or asymptomatic events confirmed by testing by then or within three days after, was to be tested by a Cochran-Mantel-Haenszel test stratified by geographic region. In view of the intent to rely on a single trial for this supplemental indication, a p-value of 0.001 was specified in the protocol. A single interim analysis was also specified. The charter of the data and safety monitoring board specified an O'Brien-Fleming significance level of 0.000003 (sic) for the interim analysis, with no adjustment of the final level.



The cumulative incidence of the composite endpoint is shown in the figure above (study report, p. 52). The jump in days 21–24 resulted from the detection of asymptomatic deep vein thromboses at this time through compression ultrasonography in patients who had not had a symptomatic event. This jump, of course, accounts for most of the difference between treatments. There is a difference in the same direction in symptomatic events up to day 21, but the numbers of such events are small: 15 in the dalteparin group and 20 in the placebo group. About 90 percent of patients were followed to day 90; from day 21 to day 90 there were five additional symptomatic venous thrombo-embolic events in the dalteparin group and four in the placebo group.

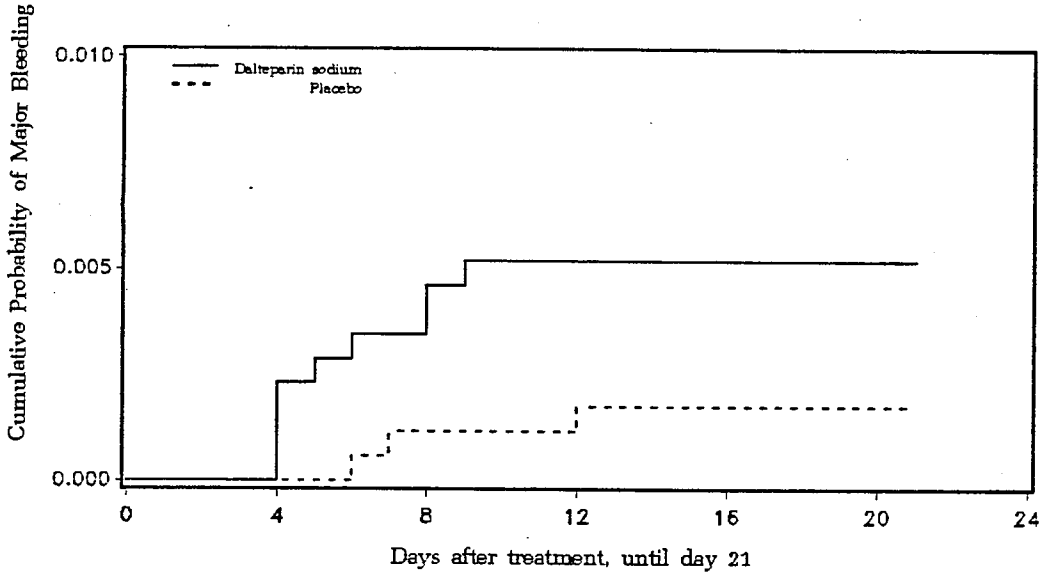
The Cochran-Mantel-Haenszel test of the rates for the composite outcome at day 21 gave a p-value of 0.0015, failing to meet the standard specified in the protocol.

Although the primary analysis is described as being on the basis of intent to treat, about 20 percent of the patients did not have the ultrasonographic evaluation, or had it but with inconclusive results. Thus, the number of patients with missing data dwarfs the number of events. Some sensitivity analyses were performed. If these patients were treated as not

having events, rather than as missing, the denominators were simply inflated, and the results were similar to those in the primary analysis. If they were treated as *having* events, the results were still statistically significant, but only because the number of missing observations in the placebo group exceeded that in the dalteparin group. Obviously the results could not withstand a worst-case analysis with placebo patients imputed as not having events and dalteparin patients imputed as having them.

3.2 EVALUATION OF SAFETY

The main risk of anticoagulation is bleeding. The cumulative incidence of major bleeding is shown in the figure below (p. 82). The numbers of events represented are 9 in the dalteparin group and 3 in the placebo group, so that the relative risk is subject to considerable uncertainty, but the excess in the dalteparin group is as expected. There was also an excess of minor bleeding events with dalteparin, but the incidence was still only 1 percent at day 21, compared to 0.6 percent with placebo.



One hundred seven patients died in the dalteparin group as did 103 patients in the placebo group. These rates are considered by the applicant to be lower than expected considering that the patients were seriously ill to begin with.

In other respects the adverse events seen do not require statistical comment. They are discussed in Dr. He's review.

4 FINDINGS IN SUBGROUPS AND SPECIAL POPULATIONS

4.1 SEX, RACE AND AGE

The treatment effect on the primary endpoint was similar for men and women and for patients under and over 65. It was statistically significant separately in men, in women, and in patients over 65, and nearly so in patients under 65, a smaller group. About 90 percent of the patients were white, so that the number of events in other racial groups was too small for meaningful analysis by race.

4.2 OTHER SUBGROUPS AND SPECIAL POPULATIONS

Similar relative risks for the primary endpoint were seen in eastern Europe, western Europe and the Americas although the absolute risks were lower in eastern Europe.

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

5.1.1 PRESPECIFICATION AND THE LEVEL OF SIGNIFICANCE

The protocol for this study said that the results would be tested for significance at the level 0.001. According to that criterion, this would simply be a failed study with respect to efficacy. I do not think it should be viewed that way.

Prespecification of statistical methods is important, in general, because of the problem of multiplicity. If we can make an error in several ways, each with probability, say, 0.05, the probability of making some one of the errors may be much larger than 0.05. Such considerations do not apply to different significance levels of the same test because the rejection regions are nested. That is, if the results are significant at level 0.0015, we do not have to consider an *additional* possibility that they might have been significant at level 0.001. Rather, the set of outcomes significant at level 0.001 is a *subset* of those significant at level 0.0015. Therefore, the interpretation of a significant result at level 0.0015 need not be different if a level of 0.001 was specified in the protocol than if it was not. The results are significant at level 0.0015, for whatever that is worth.

What it is worth here, I think, is strong evidence that dalteparin has the purported effect of preventing venous thrombo-embolic events in this population. The primary significance test is supported by evidence of consistent effects by sex, age and region. The conclusion of efficacy is also supported by evidence of efficacy of dalteparin as an anticoagulant in other populations.

Such a conclusion, of course, has implications for the review of protocols specifying a small significance level. Whatever the protocol may say, we cannot truly expect (nor, I think, desire) the suppression of results that are otherwise meaningful but fail to achieve the

specified level. It follows, however, that such specifications will have little operational effect. Their inclusion in the protocol should be viewed as a sign of optimism rather than of rigor.

Similar considerations may apply to the prespecified interim analysis. Whatever the protocol and charter may have said, it is hard to imagine a data and safety monitoring board ignoring a significant result at, say, level 0.0001 because it was not significant at level 0.000003. Accordingly, the assertion that the final significance level needs no adjustment at all must be viewed a little skeptically. With any conceivable adjustment, however (doubling, for an extreme example), it would still be a small number.

5.1.2 MISSING DATA

The number of missing primary observations is much more than the number of primary events because the event to be prevented is serious but rare. This would cast serious doubt on the conclusions if the missingness of the data were thought to be related to treatment: for example, if it were thought that patients had dropped out of the dalteparin group *because* they had had an event that would have been detected later. There does not seem to be reason to think so, however. The proportion of missing data is not so large as to suggest bad practice; on the contrary, the protocol commendably called for following patients to the endpoint even if they discontinued treatment. It is simply hard to study rare events in an entirely satisfactory way.

5.2 CONCLUSIONS AND RECOMMENDATIONS

Dalteparin was effective in reducing the incidence of venous thrombo-embolic events in immobilized medical patients. Safety is discussed in Dr. He's review.

The supplement proposes adding a description of this study to the labeling under Clinical Trials. The wording of this section is acceptable from a statistical point of view, except that some spurious significant figures should be rounded off.

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/s/

Thomas Permutt

11/12/03 01:44:30 PM

BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-032

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 20-287 SUPPL # SE1-032
Trade Name Fragmin Generic Name dalteparin sodium
Applicant Name Pharmacia & Upjohn HFD- HFD-180
Approval Date December 10, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/__/ NO /_X_/

   b) Is it an effectiveness supplement? YES /_X__/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   d) Did the applicant request exclusivity?

      YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug

under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # NDA 20-287, original NDA for Fragmin

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 524-E-CVD-0042-033_(PREVENT)

Investigation #2, Study # _____

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the

approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1_, Study # 524-E-CVD-0042-033(PREVENT)

Investigation #2_, Study # _____

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out

under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #25,924 YES /_X__/ NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant

should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____
Signature of Preparer Date
Title: Regulatory Health Project Manager

Signature of Division Director Date

cc:

HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Diane V. Moore
12/10/03 06:01:10 PM

Joyce Korvick
12/10/03 06:33:07 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : NDA 20-287 Supplement Type (e.g. SE5): SE1 Supplement Number: S-032

Stamp Date: February 7, 2003 Action Date: December 10, 2003

HFD 180 Trade and generic names/dosage form: Fragmin (dalteparin sodium) injection

Applicant: Pharmacia & Upjohn Company Therapeutic Class: 8012010 (Low molecular weight heparins)

Indications previously approved: prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin therapy; prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction; prophylaxis of deep venous thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing hip replacement surgery and in patients undergoing abdominal surgery who are at risk for thromboembolic complications.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: _ prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

Is there a full waiver for this indication (check one)?

X Yes: Please proceed to Section A.

No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- X Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study

- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

APPEARS THIS WAY
ON ORIGINAL

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min ____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Diane V. Moore
12/10/03 07:18:50 PM

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA
Telephone: (616) 833-4000

February 7, 2003

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

RE: NDA 20-287
FRAGMIN®
(dalteparin sodium injection)

ELECTRONIC SUBMISSION

EFFICACY SUPPLEMENT
Prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness

Dear Sir or Madam:

Under the provisions of 21 CFR 314.71, Pharmacia & Upjohn (P&U) is submitting four CD-ROM's (approximately 2.2GB) in Common Technical Document (CTD) format an efficacy supplement to NDA 20-287 FRAGMIN (dalteparin sodium injection) to add a new indication for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness.

Clinical Information
The clinical information provided in this supplement includes data from one pivotal study identified by protocol number 524-E-CVD-0042-033 and entitled: Prophylaxis of venous thromboembolism in patients with acute medical conditions requiring prolonged immobilization: a comparison of dalteparin (Fragmin®) 5000 IU vs placebo in a double-blind, randomized, multicenter study (PREVENT). This study was done in accordance with the criteria for single study outlined in the May 1998 Guidance to Industry entitled: *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products.*

Pre-sNDA Meeting
In the pre-sNDA meeting with the Division of Gastrointestinal and Coagulation Drug Products on December 4, 2002, it was agreed that a complete Intent-To-Treat (ITT) analysis would be included. The ITT statistical analysis is included in Appendix 1.9 of the Prevent Study Report.

The supplement contains a complete discussion on the two potential review issues, "an apparent higher rate of death and major bleeding compared to placebo", discussed during the December meeting. These items are addressed in Module 2, Sections 2.5 Clinical Overview and Sections 2.7.4 Summary of Clinical Safety.

During the meeting, paper copies of certain Sections of this sNDA, a Common Technical Document (CTD) in electronic format, were requested. Specifically, 1 paper copy of clinical and pharmacology related sections and 3 paper copies of the summary volumes were requested. This request was further discussed between Ms. Diane Moore, Regulatory Project Manager of FDA and Greg Brier of P&U on January 29, 2003, and it was agreed that these Sections would be submitted as desk copies within a few weeks after the original submission. We also agreed that Modules 2, 4, and 5 cover the clinical and pharmacology related sections and that Module 2 represents the summary volumes. As requested, 5 paper copies of Module 2 will be provided.

Labeling
The labeling for the sNDA include both marked and clean versions of the proposed labeling. We are providing both PDF files and MS Word versions of the labeling. PDF files are for archive purposes and the MS Word files were requested as a review aide.

Pediatric Waiver
A request for a full waiver from conducting pediatric studies is provided in Module 1.

User Fee
The User Fee cover sheet and a copy of the User Fee Check and the transmittal letter are included in Module 1.

Application format
This efficacy supplement (sNDA) to NDA 20-287 is being submitted electronically on CD-ROM in Common Technical Document format. The CD-ROM's have been scanned with Trend Micro OfficeScan Corporate Edition for Windows NT version 5.02 and found to be virus free.

If you have any questions regarding this submission, please contact me by telephone at 269.833.3670 or by fax at 269.833.8237. Send all correspondence to Mail-Code 0200-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Gregory A. Brier
Senior Regulatory Manager, BSChE, MBA
Global Regulatory Affairs

GAB:kmv

cc:

Ms. Diane Moore, Regulatory Project Manager (letter as desk copy)
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, Room 6B45
Rockville, MD 20857

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
JA 20-287	Efficacy Supplement Type SE-1	Supplement Number S-032	
Drug: FRAGMIN® (dalteparin sodium) Injection 2500, 5000, 7500 and 10,000 IU		Applicant: Pharmacia and Upjohn	
RPM: Diane Moore		HFD-180	Phone # (301) 827-7476
Application Type: (X) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority S	(X) Standard ( ) Priority
• Chem class (NDAs only)	N/A
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	December 10, 2003
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
❖ Exclusivity Summary (approvals only)	

❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	4/11/03
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	11/25/03
• Most recent applicant-proposed labeling	12/10/03
• Original applicant-proposed labeling	2/7/03
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DDMAC 11/20/03
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Lovenox, Arixtra, Iprivask
Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	N/A
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	N/A
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	February 15, 2001
• Pre-NDA meeting (indicate date)	December 4, 2002
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	X
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Clinical and Summary Information	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	MTL 11/24/03
❖ Clinical review(s) *(indicate date for each review)*	11/13/03
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	MO review 11/13/03 pg 39
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) *(indicate date for each review)*	11/12/03
❖ Biopharmaceutical review(s) *(indicate date for each review)*	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	10/28/03
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	10/28/03
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	10/28/03
Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	NA
❖ Facilities inspection (provide EER report)	Date completed: N/A ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (X) Not requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-032

Pharmacia & Upjohn Company
Attention: Gregory A. Brier
Senior Regulatory Manager
7000 Portage Road
Kalamazoo, MI 49001

Dear Mr. Brier:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Fragmin® (dalteparin sodium) Injection, 2500 IU, 5,000 IU, 10,000 IU, 25,000 IU and 75,000 IU

NDA Number: 20-287

Supplement number: S-032

Review Priority Classification: Standard (S)

Date of supplement: February 7, 2003

Date of receipt: February 10, 2003

This supplemental application proposes the following changes: The addition of a new indication for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 11, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be December 10, 2003.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Document Room 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Document Room 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any question, call me at (301) 827-7476.

Sincerely,

{See appended electronic signature page}

Diane Moore
Regulatory Project Manager
Division of Gastrointestinal and Coagulation
Drug Products (HFD-180)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Diane V. Moore
2/14/03 05:59:30 PM

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA 20-287/S-032 FRAGMIN® (dalteparin sodium) Injection, 5,000 IU; SE1

Applicant: Pharmacia & Upjohn

Date of Application: February 7, 2003
Date of Receipt: February 10, 2003
Date of Filing Meeting: March 24, 2003
Filing Date: April 11, 2003

Indication(s) requested: Prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness.

Type of Application: Full NDA _____ Supplement _SE1_____
(b)(1) ___X_____ (b)(2) _____
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S__X_____ P_____
Resubmission after a withdrawal or refuse to file _____
Chemical Classification: (1,2,3 etc.)__3____
Other (orphan, OTC, etc.)_____

Has orphan drug exclusivity been granted to another drug for the same indication? YES NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

N/A YES NO

If the application is affected by the application integrity policy (AIP), explain.

User Fee Status: Paid _____ Waived (e.g., small business, public health) _____
Exempt (orphan, government) ___NO_____
Form 3397 (User Fee Cover Sheet) submitted: YES_X_____ NO_____
User Fee ID#___4499_____
Clinical data? YES ___X____ NO _____ Referenced to NDA# _20-287_____
Date clock started after UN ____N/A_____

User Fee Goal date: __December 10, 2003_____

Action Goal Date (optional) _____

- Does the submission contain an accurate comprehensive index? YES NO
- Form 356h included with authorized signature? YES NO
  If foreign applicant, the U.S. Agent must countersign.

- Submission complete as required under 21 CFR 314.50? YES NO
  If no, explain:

- If electronic NDA, does it follow the Guidance? YES NO NA
  If an electronic NDA: all certifications must be in paper and require a signature.

- If Common Techinical Document, does it follow the guidance? YES NO NA

- Patent information included with authorized signature? YES NO

- Exclusivity requested? YES; If yes, ___3____years NO

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES NO
  If foreign applicant, the U.S. Agent must countersign.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, …."

- Financial Disclosure included with authorized signature? YES NO
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign.

- Has the applicant complied with the Pediatric Rule for all ages and indications? YES NO
  If no, for what ages and/or indications was a waiver and/or deferral requested: full waiver for all ages for prophylaxis of deep vein thrombosis which may lead to pulmonary embolism in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness.

- Field Copy Certification (that it is a true copy of the CMC technical section)? N/A YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? yes If not, have the Document Room make the corrections.

List referenced IND numbers:

End-of-Phase 2 Meeting? Date_Feb 15, 2000 NO
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date(s) Dec. 4, 2002 NO
If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC? (consult will be sent during review) YES NO

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support?
YES NO N/A

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support?
YES NO NA

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? YES NO NA

Advisory Committee Meeting needed? YES, date if known _____ NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
YES NO N/A

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? YES NO
  If no, did sponsor submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) package submitted? YES NO

- Parenteral Applications Consulted to Sterile Products (HFD-805)? YES NO N/A

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 24, 2003

BACKGROUND
(Provide a brief background of the drug, e.g., it was already approved and this NDA is for an extended-release formulation, whether another Division is involved, foreign marketing history, etc.)

ATTENDEES:

ASSIGNED REVIEWERS:

Discipline	Reviewer
Medical:	Dr. Ruyi He
Secondary Medical:	Dr. Kathy Robie-Suh
Statistical:	Tom Permutt
Pharmacology:	N/A
Statistical Pharmacology:	N/A
Chemist:	Ali Al-Hakim
Environmental Assessment (if needed):	
Biopharmaceutical:	N/A
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	Dr. Khin U (if needed)
Project Manager:	Diane Moore
Other Consults:	

Per reviewers, all parts in English, or English translation? YES___X__ NO___

CLINICAL – File ___X_____ Refuse to file _____

- Clinical site inspection needed: YES_____ NO_____ to be determined

MICROBIOLOGY CLINICAL – File__N/A_____ Refuse to file_____

STATISTICAL – File __X_____ Refuse to file _____

BIOPHARMACEUTICS – File __X_____ Refuse to file _____

- Biopharm. inspection Needed: YES_____ NO ___X_____

PHARMACOLOGY – File __X_____ Refuse to file _____

CHEMISTRY –

- Establishment(s) ready for inspection? YES__X___NO_____ File__X___ Refuse to file _____

REGULATORY CONCLUSIONS/DEFICIENCIES:

__X_____The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ The application is unsuitable for filing. Explain why:

_Diane Moore, RPM_____
Regulatory Project Manager, HFD-180

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF MEETING

MEETING DATE: March 24, 2003

TIME: 3:45 - 4:15 PM

LOCATION: Room 6B-45 (Parklawn)

APPLICATION: NDA 20-287/S-032; Fragmin® (dalteparin sodium) Injection, 5000 IU

TYPE OF MEETING: Filing Meeting

MEETING CHAIR: Dr. Kathy Robie-Suh

MEETING RECORDER: Ms. Diane Moore

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Robert L. Justice, M.D., M.S., Division Director
Joyce Korvick, M.D., Deputy Division Director
Kathy Robi-Suh, M.D., Hematology Team Leader
Ruyi He, M.D., Medical Officer
Diane Moore, Regulatory Health Project Manager

Division of New Drug Chemistry II (DNDCII) @ DGICDP (HFD-180)

Ali Al-Hakim, Ph.D., Chemist

Division of Biometrics II (DBII; HFD-715)
Tom Permutt, Ph.D., Statistical Team Leader

Office Medical Policy, Division of Scientific Investigations (HFD-046)
Ele Ibarra-Pratt, Consumer Safety Officer

BACKGROUND:

- Fragmin was approved December 22, 1994, for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing hip fracture surgery who are at risk for thromboembolic complications. Fragmin is also indicated for prophylaxis of deep vein thrombosis (DVT), which may lead to PE in patients undergoing hip replacement surgery and in patients undergoing abdominal surgery who are at risk for thromboembolic complications. On May 25, 1999, Fragmin was approved for prophylaxis of ischemic complications in unstable angina and non-Q-Wave myocardial infarction, when concurrently administered with aspirin therapy. The sponsor is seeking the indication of prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness.

MEETING OBJECTIVE:

To discuss the fileability of SE1-032 and to identify potential review issues regarding the submission to be included in a regulatory letter to the sponsor.

DISCUSSION POINTS:

Fileability and Possible Review Issues

1. Regulatory Project Management (RPM):
   - The supplement is fileable from a regulatory standpoint.
   - The RPM will send a consult to the Division of Drug Marketing, Advertising and Communication (DDMAC) for a labeling evaluation.
   - The Efficacy Supplement is a standard review. Reviews are due November 5, 2003
   - PDUFA goal date is December 10, 2003

2. Clinical:
   - The supplement is fileable.
   - There is one pivotal study (Study 524-ECVD-0042-033) entitled "Prophylaxis of venous thromboembolism in patients with acute medical conditions requiring prolonged immobilization: a comparison of dalteparin (FRAGMIN) 5000 IU Versus placebo in a double-blind, randomized, multi-center study (PREVENT)." The PREVENT study was submitted to support the proposed indication prophylaxis of DVT, which may lead to PE in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness.
     - Lovenox is approved for the proposed indication. The studies for Lovenox and Fragmin differ in the endpoints. The primary efficacy endpoint in the Lovenox study was a composite of DVT, PE and death considered to be thromboembolic in origin. The Lovenox study used mandatory end-of-study (14 days) venograms for DVT endpoint data. In the Fragmin study, the primary efficacy endpoint was a composite of symptomatic DVT [confirmed by compression ultrasound or venography], fatal or nonfatal PE, asymptomatic proximal DVT (verified by compression ultrasound or venography) and/or sudden death assessed at 21 days. Three thousand seven hundred six patients were enrolled in the intent-to-treat (ITT) population. The efficacy evaluable population in the protocol was 2805 patients. Twenty-five percent of the patients were excluded in the PREVENT study mainly because of missing or inadequate endpoint assessments. The protocol sample size calculations was based on the estimation that about 10.8% of patients would be non-evaluable for efficacy.
     - The majority of the patients in the study were from Europe (only 39 patients were from the United States (U.S.) and Canada). Two thirds of the patients were greater than 65 years of age. How adequately this patient population reflects the population in U.S. practice is a concern regarding this application.
     - The Medical Officer will determine a site for a clinical investigations inspection, if needed.

3. Statistics:
   - The supplement is fileable. The primary endpoint is 2.7% for the Fragmin group versus the primary endpoint of 5% for the placebo group. The "p" value for Fragmin is 0.0015. The predefined significant value is 0.001. Therefore, the study did not meet the predefined "p" value. The Fragmin group and the placebo group showed approximately the same result for mortality. The Fragmin group had a higher rate of sudden death than placebo (0.7% versus 0.15%). This may not be clinically significant. The safety profiles for the Fragmin group and the placebo group were similar except for major bleeding. Fragmin had a higher bleeding rate of 0.5% compared to placebo at 0.16%.

4. Clinical Pharmacology and Biopharmaceutics:
   - The supplement is fileable.

5. Pharmacology and Toxicology
   - The supplement is fileable. This is an approved drug. There are no pharmacology issues.

6. Chemistry, Manufacturing and Quality Controls:
   - The supplement is fileable.
   - The study used the 5000 IU subcutaneous dose of Fragmin once daily for 14 days. This dose is an approved dose. There are no CMC issues regarding this supplemental NDA.
   - The sponsor requested a categorical exclusion for the environmental assessment (EA). An EA is being requested by the CMC reviewer.

CONCLUSIONS:

1. The efficacy supplement is fileable.

2. A "review issues found" letter should be sent to the sponsor delineating that the following items are of potential concern regarding the application:
   - The study had a 25% exclusion rate in the ITT population, which seems high considering that the venography was required only for symptoms and the mandatory end-of-study evaluation for proximal DVT was by ultrasound (non-invasive).
   - The single study that was submitted in support of the application failed to achieve the predefined protocol "p" value.
   - There is concern regarding how adequately the study patient population reflects the target population in U.S. practice.

ACTION ITEMS:

A filing issues letter will be sent to the sponsor delineating that the following are potential review issues:
- The study had a 25% exclusion rate in the ITT population, which seems high considering that the venography was required only for symptoms and the mandatory end-of-study evaluation for proximal DVT was by ultrasound (non-invasive).
- The single study that was submitted in support of the application failed to achieve the predefined protocol "p" value.
- There is concern regarding how adequately the study patient population reflects the target population in U.S. practice.

{See appended electronic signature page}

Signature, recorder

{See appended electronic signature page}

Signature, Chair

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/s/

Diane V. Moore
4/11/03 04:05:35 PM
CSO

Julieann DuBeau
4/11/03 04:13:59 PM
CSO
Concur with NDA Regulatory Filing Review.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING ISSUES IDENTIFIED

NDA 20-287/S-032

Pharmacia & Upjohn
Attention: Gregory A. Brier
7000 Portage Road
Kalamazoo, MI 49001

Dear Mr. Brier:

Please refer to your February 7, 2003, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin® (dalteparin sodium injection) 5000 IU.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on April 11, 2003, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. The pivotal study 524-ECVD-0042-033 entitled "PREVENT" submitted in support of the proposed indication had a 25% exclusion rate from the intent-to-treat (ITT) population. This seems high considering that a sonogram or venography was required only for symptomatic VTE, or asymptomatic proximal DVT.

2. The PREVENT study that was submitted in support of this application failed to achieve the significance level predefined in the protocol.

3. The patient population studied in the protocol may not reflect the patient population seen in routine U.S. practice.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

Provide venous thromboembolic events (VTE) data by study site.

Please respond only to the above request for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Diane Moore, Regulatory Project Manager, at (301) 827-7476.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, MSN, RN
Chief, Project Management Staff
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Julieann DuBeau

4/11/03 05:01:53 PM

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA
Telephone: (616) 833-4000

May 2, 2003

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

RE: NDA 20-287/S-032
FRAGMIN®
(dalteparin sodium injection)

ELECTRONIC SUBMISSION

AMENDMENT 1 - EFFICACY SUPPLEMENT S-032
Venous Thromboembolic Events (VTE) Data
By Study Site

Dear Sir or Madam:

Pharmacia & Upjohn (Pharmacia) is submitting on CD-ROM Amendment 1 of the efficacy supplement S-032 to NDA 20-287 FRAGMIN (dalteparin sodium injection). This amendment consists of venous thromboembolic events (VTE) data (PREVENT Study 524-E-CVD-0042-033) grouped by study site as requested in FDA's letter dated April 11, 2003.

We acknowledge the 3 potential review issues listed in the same FDA letter from the filing review meeting. We understand the filing review is only preliminary evaluation of the application and review issues may be added, deleted, expanded upon, or modified as FDA progresses during the substantive review of S-032.

Pharmacia wishes to be of assistance to FDA during the review and is willing to provide further clarification or information to answer any questions FDA may have regarding S-032 as the substantive review progresses.

The CD-ROM contains the following files and directory structure:

Main Directory – N20287

- Cover Letter (cover.pdf)
- 356h Form (356h.pdf)
- Table of Contents (ndatoc.pdf)
- FDA Filing Letter dated April 11, 2003 (other.pdf)

Subdirectory – Clinstat

- Table of Contents (clintoc.pdf)
- PREVENT Study VTE Data Grouped by Study Site (other.pdf)

Each CD-ROM has been scanned with Trend Micro OfficeScan Corporate Edition for Windows NT version 5.02 and found to be virus free.

If you have any questions regarding this Amendment or S-032, please contact me by telephone at 269.833.3670 or by fax at 269.833.8237. Send all correspondence to Mail-Code 0200-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Gregory A. Brier
Senior Regulatory Manager, BSChE, MBA
Global Regulatory Affairs

GAB:kmv

Pharmacia&Upjohn

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA
Telephone: (269) 833-4000

June 6, 2003

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

RE: NDA 20-287/S-032
FRAGMIN®
(dalteparin sodium injection)

ELECTRONIC SUBMISSION

AMENDMENT 2 - EFFICACY SUPPLEMENT S-032
120 Day Safety Update Report

Dear Sir or Madam:

Pharmacia & Upjohn is submitting on CD-ROM, Amendment 2 of the efficacy supplement S-032 to NDA 20-287 FRAGMIN (dalteparin sodium injection). This amendment consists of 120 day safety update report in accordance with 21 CFR §314.50(d)(5)(vi)(b).

The CD-ROM has been scanned with Trend Micro OfficeScan Corporate Edition for Windows NT version 5.02 and found to be virus free.

If there are questions regarding this Amendment or S-032, please contact me by telephone at 269.833.3670 or by fax at 269.833.8237. Send all correspondence to Mail-Code 0200-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Gregory A. Brier
Senior Regulatory Manager, BSChE, MBA
Global Regulatory Affairs

GAB:SEH
Attachments

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: November 25, 2003

To: Alexandrea Pearce, Regulatory Affairs	**From:** Diane Moore, Regulatory Project Manager
Company: Pfizer	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (269) 833-8237	**Fax number:** (301) 443-9285
Phone number: (212) 733-6079	**Phone number:** (301) 827-7476

Subject: Proposed labeling for Supplement–032 for the indication Prophylaxis of deep vein thrombosis which may lead to pulmonary embolism in medical patients who are at risk for thromboembolic complications due to restricted mobility during acute illness.

Total no. of pages including cover: 18

Comments: Please see attached proposed revised labeling for NDA 20-287/S-032. In addition, please clarify the following questions regarding this supplement:

1. What is the reason 19 patients in the Fragmin group and 26 patients in the placebo group were non-evaluable for "sudden death."?
2. What is the number and proportion of patients in each treatment group having asymptomatic distal deep vein thrombosis (DVT) by Day 21 (+3)?

Document to be mailed: ☐ YES ☑ NO

16 Pages Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

11/25/2003 FDA FAX

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/s/

Diane V. Moore :
11/25/03 07:03:47 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-032

Pharmacia & Upjohn Company
Attention: Robert Clark
Vice President, Regulatory Affairs
235 E. 42nd Street
New York, NY 10017

Dear Mr. Clark:

Please refer to your February 7, 2003, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin® (dalteparin sodium, injection).

We also refer to your submission dated January 9, 2004, containing final printed labeling (FPL) for this supplemental application which was approved on December 10, 2003.

This supplemental application provides for a new indication for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in medical patients who are at risk for Thromboembolic complications due to restricted mobility during acute illness.

We note that this submission has been superseded by supplement S-034 (which was approved on April 21, 2004). Therefore, this submission will not be reviewed, but it will be retained in our files.

If you have any questions, call Diane Moore, Regulatory Health Project Manager, at (301) 827-7476.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Acting Director
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Kathy Robie-Suh
1/3/05 04:16:06 PM
for Dr. Joyce Korvick