CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-287/S-034

Name: Fragmin® (Dalteparin Sodium) Injection

Sponsor: Pharmacia & Upjohn

Approval Date: April 21, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-034

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-034

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-034

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 supplemental new drug application dated September 8, 2003, received September 9, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin® (dalteparin sodium, injection).

We acknowledge receipt of your submission dated March 26, 2004.

Your submission of March 26, 2004, constituted a complete response to our March 9, 2004 action letter.

This "Changes Being Effected" supplemental new drug application provides for revisions to the DOSAGE AND ADMINISTRATION section of the package insert to add instructions to expel the air bubble prior to using the 10,000 IU single-dose graduated prefilled syringe.

We completed our review of this supplemental new drug application, as amended. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on March 26, 2004.

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 the requirements for an approved NDA set forth under 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 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/

Joyce Korvick
4/21/04 01:19:24 PM
for Dr. Robert Justice

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-034

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-034

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

Dear Mr. Brier:

Please refer to your supplemental new drug application dated September 8, 2003, received September 10, 2003, submitted under section 505 of the Federal Food, Drug, and Cosmetic Act for Fragmin® (dalteparin sodium injection).

This "Changes Being Effected" supplemental new drug application provides for revising the instructions to expel the air bubble prior to using the graduated syringe.

We completed our review of this application, and it is approvable. Before this application may be approved, however, you must submit final printed labeling revised as follows:

1. In the **DOSAGE AND ADMINISTRATION** section of the package insert (PI), in the **Administration** subsection, ***Instructions for using the prefilled single-dose syringes preassembled with passive needle guard devices*** sub-subsection, in the fifth sentence that begins "Depress the plunger . . ." delete the phrase "To ensure delivery of the full dose, do not expel the air bubble from the prefilled syringe before injection." so that the sentence reads "Depress the plunger of the syringe while holding the finger flange until the entire dose has been given."

2. In the **DOSAGE AND ADMINISTRATION** section, in the **Administration** subsection, ***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 down to the desired dose or volume, discarding the extra solution in an appropriate manner." delete 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 depress the plunger to the desired dose or volume, discarding the extra solution in an appropriate manner."

3. All previous revisions, as reflected in the most recently approved package insert, specifically S-032, must be included. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes.

Please submit the final printed labeling (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 but no more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

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
3/9/04 09:52:35 AM
for Dr. Robert Justice

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-034

LABELING

So 34

RECTO

Fragmin
dalteparin sodium injection

5R7216
464

Fragmin

dalteparin sodium injection PHARMACIA

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

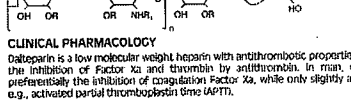
FRAGMIN Injection (dalteparin sodium injection) is a sterile, low molecular weight heparin. It is available in single-dose, prefilled syringes preassembled with a needle guard device, and multiple-dose vials. With reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard, 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:

< 2000 daltons	3.0-15%
2000 to 8000 daltons	65.0-79.0%
> 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 vitro, 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 (5 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 66 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).

Fragmin

brand of dalteparin sodium injection

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	43/741 (5.8%)[1]	86/757 (11.4%)
Secondary Endpoints - 6 day timepoint Death, MI, i.v. heparin, i.v. nitroglycerin, Revascularization	99/739 (13.0%)[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 1498 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, 274 received FRAGMIN and 279 received warfarin sodium. The mean age of the study population was 65 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 = 0.165

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. bid, 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 16/69; 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 65 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=0.469). 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 90 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 20 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

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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%)
		174 (1.7%)

Will use e-copy

3 major abdominal
GMIN 2500 IU once
rolled and treated;
combined groups
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 Non-Fatal	1/674 (0.1%) 2	1/669 (0.1%) 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: 1868 received FRAGMIN and 1933 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 qd s.c.	Placebo qd s.c.
All Treated Medical Patients During Acute Illness	1848	1933
Treatment Failure in evaluable patients (Day 21)[1] DVT, PE, or sudden death	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	29/1513 (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.
[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/mm³ and < 50,000/mm³ 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.

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Miscellaneous:

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

PRECAUTIONS

General:

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

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

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

Drug Interactions:

FRAGMIN should be used with care in patients receiving oral anticoagulants, 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 4.7 and 4.3%, respectively, of patients during treatment with FRAGMIN. Similar significant increases in transaminase levels have also been observed in patients treated with heparin and other low molecular weight heparins. Such elevations are fully reversible and are rarely associated with increases in bilirubin. Since transaminase determinations are important in the differential diagnosis of myocardial infarction, liver disease and pulmonary emboli, elevations that might be caused by drugs like FRAGMIN should be interpreted with caution.

Carcinogenicity, Mutagenesis, Impairment of Fertility:

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

Pregnancy: Pregnancy Category B.

Teratogenic Effects:

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

Nonteratogenic Effects:

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

Nursing Mothers:

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

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established.

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 hr 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 or transfusion of ≥ 2 units of blood, 2) intracranial, intraocular, spinal/epidural, or retroperitoneal bleeding, 3) required surgical intervention, or 4) led to death.

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)	Warfarin Sodium[1] oral (n=279)	FRAGMIN 5000 IU qd s.c. (n=69)	Heparin 5000 U tid s.c. (n=69)
Major Bleeding Events[2]	7/274 (2.6%)	1/279 (0.4%)	0	3/69 (4.3%)
Other Bleeding Events[3] 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.

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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				FRAGMIN vs Placebo		FRAGMIN vs FRAGMIN	
	Dosing Regimen				Dosing Regimen		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%)	31/508 (6.1%)	63/498 (12.7%)	14/192 (7.3%)	18/197 (9.1%)	88/1025 (8.7%)	125/1038 (12.1%)
Wound Hematoma	18/867 (2.1%)	19/867 (2.2%)	12/929 (1.3%)	6/898 (0.7%)	2/79 (2.5%)	2/77 (2.6%)	1/1030 (0.1%)	4/1039 (0.4%)
Reoperation Due to Bleeding	2/382 (0.5%)	5/292 (0.8%)	4/500 (0.8%)	2/398 (0.4%)	1/79 (1.3%)	1/78 (1.3%)	2/1030 (0.2%)	15/1039 (1.4%)
Injection Site Hematoma	1/466 (0.2%)	5/464 (1.1%)	36/506 (7.1%)	47/495 (9.5%)	8/172 (4.7%)	2/176 (1.1%)	55/1026 (5.4%)	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 qd s.c.	Placebo qd 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 35, 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 eruptions) and skin necrosis have occurred rarely. A few cases of anaphylactoid reactions have been reported.

Local Reactions:

Pain at the 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 bid.

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	0.80	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.

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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:

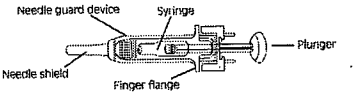
FRAGMIN is administered by subcutaneous injection. It must not be administered by intramuscular injection.

Subcutaneous injection technique: Patients should be sitting or lying down and FRAGMIN administered by deep s.c. injection. 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 needle guard devices:



Fixed dose syringes: To ensure delivery of the full dose, do not expel the air bubble from the prefilled syringe before injection. 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 push the plunger 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
195,000 anti-Factor Xa IU/vial — NDC 0013-5191-01

9.5 mL multiple-dose vial:
10,000 anti-Factor Xa IU/mL
195,000 anti-Factor Xa IU/vial — NDC 0013-2436-06

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

℞ 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)

818 312 1128

Revised March 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-034

LABELING REVIEWS

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

Application Number: NDA 20-287/SLR-034

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

Sponsor: Pharmacia & Upjohn Company (a subsidiary of Pfizer)

Materials Reviewed: Package Insert (PI)

Submission Date: September 8, 2003
Receipt Date: September 9, 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.

Labeling Supplement-031 (S-031) was submitted on January 14, 2003 (received January 15, 2003; approved on draft June 30, 2003) as a "Changes Being Effected" (CBE-O) supplement for the use of UltraSafe™ Passive needle safety guards in conjunction with the approved FRAGMIN® (dalteparin sodium injection) 10,000 IU/1.0 mL graduated pre-filled syringes. Among other sections revised in that labeling, the sub-subsection entitled "***Graduated syringes***" was added under the **Administration** subsection of the **DOSAGE AND ADMINISTRATION** section of the PI.

The most recently approved package insert (PI) for Fragmin is Efficacy Supplement-032 (S-032) (submitted February 7, 2003; received February 10, 2003; approved on draft December 10, 2003). S-032 is a prior approval efficacy supplement that added 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.

Supplement-034 is a Changes Being Effected (CBE) labeling supplement (submitted September 8, 2003; received September 9, 2003) that proposes to revise the instructions in the package insert (PI) that instruct the user to expel the air bubble prior to using the FRAGMIN graduated syringe.

Note: The revisions approved in S-032 (submitted February 7, 2003; received February 10, 2003; approved on draft December 10, 2003) were not included in the proposed labeling for S-034 (submitted September 8, 2003; received September 9, 2003) because S-034 was submitted three days before S-032 was approved.

Review

The PI proposed for S-034 submitted September 8, 2003, received September 9, 2003, (identifying number 818 312-109) was compared to the FPL for S-032 (no identifying number) (submitted February 7, 2003; received February 10, 2003; approved on draft December 10, 2003). The proposed labeling for S-034 is identical to the approved labeling except for the following:

I. The revisions made in the following sections in S-032 were not incorporated in the proposed text in the PI for S-034:

CLINICAL TRIALS, INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS and **DOSAGE AND ADMINISTRATRATION** sections.

The revisions should be included in the labeling to S-034. (See approval letter to S-032 dated December 10, 2003, and RPM Labeling review to S-032 dated November 6, 2003).

II. **DOSAGE and ADMINISTRATION** section

A. **Administration** subsection

1. In the *Subcutaneous injection technique* sub-subsection, the first paragraph that begins "Patients should be sitting . . ." the sponsor proposes to delete the second sentence that reads "to ensure delivery of the full dose, do not expel the air bubble from the prefilled syringe before injection."

This section pertains to the 10,000 IU and 25,000 IU graduated syringes. The sponsor explains in the cover letter that the air bubble should be expelled prior to discarding the extra solution in the 10,000 IU single-dose graduated syringe. Expelling the air bubble makes it easier to accurately determine the amount of solution that should be left in the syringe to obtain the desired dose. The sentence that had been added to this section in S-031 (submitted on January 14, 2003; received January 15, 2003; approved on draft June 30, 2003) to retain the air bubble applies only to the fixed-dose syringes (2500, 5000, 7500 IU syringes). The details for administering the fixed dose syringes and the graduated syringes are given in separate sections below the *Subcuteneous injection technique* section. The deletion of the sentence in this section avoids drawing the conclusion that the air bubble should not be expelled for

subcutaneous injection. The deletion is acceptable per the Medical Officer, Dr. Ruyi He, in verbal communication to Diane Moore, RPM on February 3, 2004.

2. ***Instructions for using the prefilled single-dose syringes preassembled with passive needle guard devices*** sub-subsection

   a. In the ***Instructions for using the prefilled single-dose syringes preassembled with passive needle guard devices*** sub-sub-subsection the sponsor changed the font from bold underlined letters to bold italicized letters.

      The revision is editorial and acceptable.

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

      1) Before the first sentence, the sponsor inserted the sentence that reads "To ensure delivery of the full dose, do not expel the air bubble from the prefilled syringe before injection."

         This is the same sentence that was added in S-031 (submitted January 14, 2003; received January 15, 2003; approved on draft June 30, 2003) in the *Subcutaneous injection technique* section. It fits more appropriately here to instruct the user to not expel the air bubble from the fixed-dose syringe (as opposed to the graduated syringes). The addition of the sentence to this section is acceptable per the Medical Officer, Dr. Ruyi He, in a verbal communication to Diane Moore, RPM on February 3, 2004.

      2) In the fifth sentence that begins, "Depress the plunger . . ." the sponsor has inserted the same sentence as above ("To ensure delivery of the full dose, do not expel the air bubble from the prefilled syringe before injection.") in the middle of the phrase "**until the entire dose has been given**" so that the sentence reads as follows:

         "Depress the plunger of the syringe while holding the finger flange until the entire dose has To ensure delivery of the full dose, do not expel the air bubble from the prefilled syringe before injection. been given."

         This appears to be a typographical error as the new sentence does not belong in the middle of the original sentence. The revision is not acceptable.
         Note: The revision appeared in the WORD version submitted September 8, 2003 (received September 9, 2003) but not in the PDF version submitted September 8, 2003 (received September 9, 2003); both versions were submitted together as a package. Both are identified as

"818 312 109", however, the PDF version has an additional identification number of "5R6842 236."

c. *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 "push" 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."

1) **The replacement of the word "depress" with the word "push" is acceptable per the Medical Officer, Dr. Ruyi He, in verbal communication to Diane Moore, RPM on February 3, 2004.**

2) **The inclusion of the word "down" does not make sense since the instructions tell the reader to hold the syringe pointing up. The word "down" should be deleted from the sentence.**

Conclusions

1. **The revisions made in S-032 in the following item should be incorporated in the text of S-034: I.**

2. **The following items are acceptable: II.A.2.a. and II.A.2.c. 1).**

3. **The following items are acceptable per Dr. Ruyi He, Medical Officer: II.A.1. and II.A.2.b.1).**

4. **The following items are not acceptable: II.A.2.b.2). and II.A.2.c.2).**

5. **Because this supplement is a CBE supplement, the supplement should not be approved until the apparent typographical error in the DOSAGE AND ADMINISTRATION section, *Fixed dose syringes* sub-sub-subsection is corrected, the wording in the DOSAGE AND ADMINISTRATION section, *Graduated syringes* sub-sub-subsection is corrected and the revisions made in S-032 are incorporated into the labeling for S-034.**

Diane Moore, B.S.
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Julieann DuBeau, MSN, RN
Chief, Project Management Staff

Drafted: dm/January 15, 2004
Revised: J.DuBeau 2.5.04/K.Robie-Suh 2.6.04
Initialed: J.DuBeau 2.5.04/R.He, K.Robie-Suh 2.6.04
Finalized: February 9, 2004
Filename: N20287S34LblrevSV.doc

RPM LABELING REVIEW

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
2/6/04 03:29:59 PM
CSO

Ruyi He
2/6/04 05:01:50 PM
MEDICAL OFFICER

Kathy Robie-Suh
2/9/04 09:24:10 AM
MEDICAL OFFICER

Julieann DuBeau
2/9/04 12:06:59 PM
CSO

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

Application Number: NDA 20-287/SLR-034

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

Sponsor: Pharmacia & Upjohn Company (a subsidiary of Pfizer)

Materials Reviewed: Package Insert (PI)

Submission Date: March 26, 2004
Receipt Date: March 29, 2004

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.

The most recently approved package insert (PI) for Fragmin is Efficacy Supplement-032 (S-032) (submitted February 7, 2003; received February 10, 2003; approved on draft December 10, 2003, no identifier code). S-032 is a prior approval efficacy supplement that added 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 sponsor submitted final printed labeling (FPL) for S-032 on January 9, 2004, (received January 10, 2004, identifier code "5R7065 376 818 312 111"). That PI included revisions proposed in S-034 and was found to be unacceptable (see RPM review to S-032 FPL by Diane Moore dated March 19, 2004.)

Supplement-034 is a Changes Being Effected (CBE) labeling supplement (submitted September 8, 2003; received September 9, 2003, identifier number "818 312 109") that proposes to revise the instructions in the PI that instruct the user to expel the air bubble prior to using the FRAGMIN graduated syringe. The revisions approved in S-032 (submitted February 7, 2003; received February 10, 2003; amended December 10, 2003, approved on draft December 10, 2003) were not included in the proposed labeling for S-034 (submitted September 8, 2003; received September 9, 2003) because S-034 was submitted three days before S-032 was approved. On March 9, 2004, DGCDP sent Pharmacia & Upjohn an approvable letter requesting the sponsor to 1) Correct the apparent typographical error in the **DOSAGE AND**

ADMINISTRATION section, **Administration** subsection, regarding deleting the phrase "To ensure delivery of the full dose, do not expel the air bubble from the prefilled syringe before injection" from the middle of the sentence "Depress the plunger of the syringe while holding the finger flange until the entire dose has been given." 2) delete the word "down" after the word "plunger" in the third sentence of the **DOSAGE AND ADMINISTRATION** section, **Administration** subsection, *Graduated syringes* sub-sub-subsection so that the sentence 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." and 3) include all previous revisions, as reflected in the most recently approved package insert, specifically S-032 (submitted February 7, 2003; received February 10, 2003; amended December 10, 2003, approved on draft December 10, 2003).

The sponsor submitted revised FPL for S-034 on March 26, 2004 (received March 29, 2004).

Review

The PI proposed for S-034 submitted March 26, 2004, received March 29, 2004, (identifying number 818 312-112B) was compared to the approved labeling for S-032 (no identifying number) (submitted February 7, 2003; received February 10, 2003; amended December 10, 2003, approved on draft December 10, 2003) and the approvable letter to S-034 dated December 10, 2003, with the list of deficiencies to S-034. The sponsor incorporated the revisions made in S-032 into the proposed PI text for S-034 (see RPM Labeling Review to S-034 dated February 9, 2004, by Diane Moore). The proposed labeling for S-034 is identical to the approved labeling in S-032 except for the following:

I. **DOSAGE and ADMINISTRATION** section

A. **Administration** subsection

1. In the *Subcutaneous injection technique* sub-subsection, the first paragraph that begins "Patients should be sitting . . ." the sponsor deleted the second sentence that reads "to ensure delivery of the full dose, do not expel the air bubble from the prefilled syringe before injection."

   The deletion is acceptable (see RPM Labeling Review to S-034 dated February 9, 2004, by Diane Moore).

2. ***Instructions for using the prefilled single-dose syringes preassembled with passive needle guard devices*** sub-subsection

   a. In the ***Instructions for using the prefilled single-dose syringes preassembled with passive needle guard devices*** sub-sub-subsection the sponsor changed the font from bold underlined letters to bold italicized letters.

      The revision is editorial and acceptable.