CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-287/S-031

Name: Fragmin® (Dalteparin Sodium) Injection

Sponsor: Pharmacia & Upjohn

Approval Date: June 30, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-031

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-031

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-031

Pharmacia & Upjohn
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 January 14, 2003, received January 15, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin (dalteparin sodium injection) 10,000 IU.

We acknowledge receipt of your submission dated June 4, 2003.

This "Changes Being Effected" supplemental new drug application provides 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.

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 submitted labeling (package insert submitted June 4, 2003, immediate container and carton labels submitted January 14, 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 15 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-031." Approval of this submission by FDA is not required before the labeling is used.

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

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
6/30/03 05:42:00 PM
for Dr. Robert Justice

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-031

LABELING

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

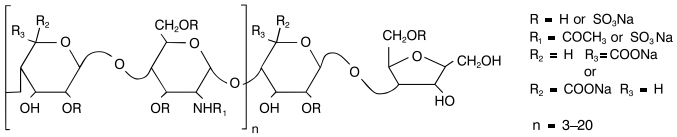
FRAGMIN Injection (dalteparin sodium injection) is a sterile, low molecular weight heparin. It is available in single-dose, prefilled syringes preassembled with a needle guard device, and multiple-dose vials. With reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard,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

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

Structural Formula



Fragmin

brand of dalteparin sodium injection

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

Fragmin

brand of dalteparin sodium injection

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.

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 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 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 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, 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**).

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 6 summarizes major bleeding events that occurred with FRAGMIN, heparin, and placebo in clinical trials of unstable angina and non-Q-wave myocardial infarction.

Table 6
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 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 7 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 7
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 8 summarizes bleeding events that occurred in clinical trials which studied FRAGMIN 2500 and 5000 IU administered once daily to abdominal surgery patients.

Table 8
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%)	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%)

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 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 tid.

Ongoing Safety Surveillance:

Since first international market introduction in 1985, there have been six reports of epidural or spinal hematoma formation with concurrent use of dalteparin sodium and spinal/epidural anesthesia or spinal puncture. Five of the six 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 of these cases. The sixth patient experienced temporary paraplegia but made a full recovery. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

OVERDOSAGE

Symptoms/Treatment:

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

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

Fragmin

brand of dalteparin sodium 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 9 lists the volume of FRAGMIN to be administered for a range of patient weights.

Table 9
Volume of FRAGMIN to be Administered by Patient Weight

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)[1]	0.55	0.65	0.75	0.90	1.00	1.00

[1] Calculated volume based on the 9.5 mL multiple-dose vial (10,000 anti-Factor Xa IU/mL)

Hip Replacement Surgery:

Table 10 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 10
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.

Fragmin

brand of dalteparin sodium injection

Administration:

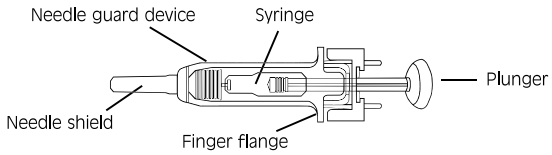
FRAGMIN is administered by subcutaneous injection. It must not be administered by intramuscular injection.

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 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. Prepare the syringe by pushing 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

Fragmin

brand of dalteparin sodium injection

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

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)

MASTER

Fragmin® 10,000 IU (anti-Xa) per 1 mL
℞ only
dalteparin sodium injection
See package insert.
Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].
Manufactured for: Pharmacia & Upjohn Co., Kalamazoo, MI 49001, USA
818 208 101
KV0234-01
5T0809

Fragmin® 10,000 IU (anti-Xa) per 1 mL
℞ only
dalteparin sodium injection
See package insert.
Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].
Manufactured for: Pharmacia & Upjohn Co., Kalamazoo, MI 49001, USA
818 208 101
KV0234-01
5T0809

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dalteparin sodium injection
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KV0234-01
5T0809

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KV0234-01
5T0809

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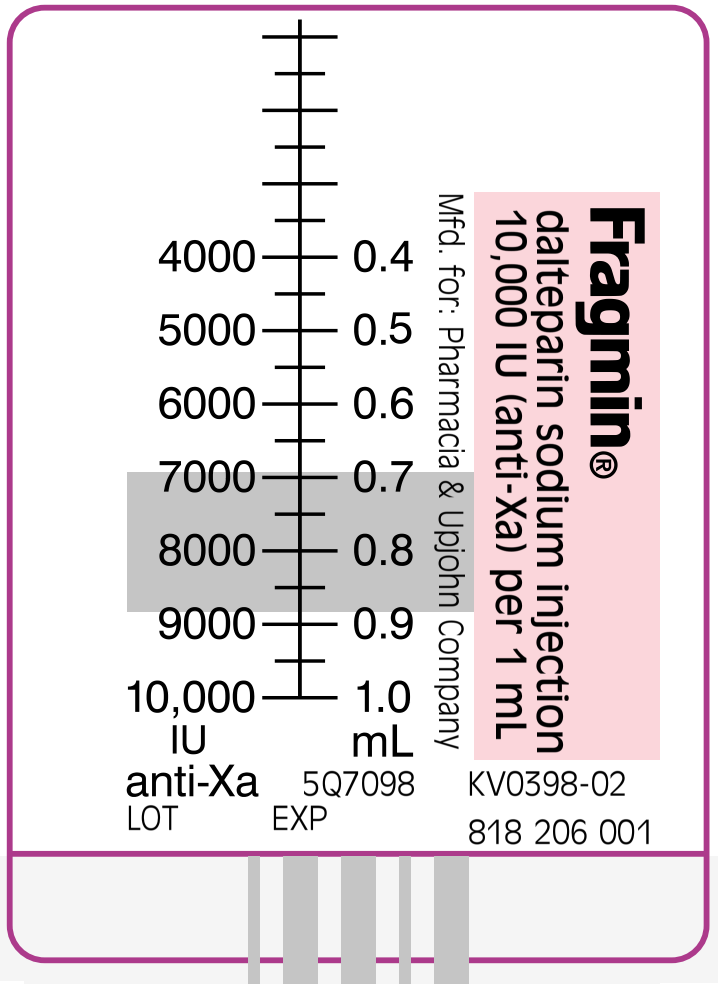
℞ only
dalteparin sodium injection
See package insert.
Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].
Manufactured for: Pharmacia & Upjohn Co., Kalamazoo, MI 49001, USA
818 208 101
KV0234-01
5T0809


Fragmin®
dalteparin sodium injection
10,000 IU (anti-Xa) per 1 mL
Mfd. for: Pharmacia & Upjohn Company
4000 0.4
5000 0.5
6000 0.6
7000 0.7
8000 0.8
9000 0.9
10,000 1.0
IU mL
anti-Xa
LOT 5Q7098 EXP
KV0398-02
818 206 001

10,000 IU (anti-Xa) per 1 mL
dalteparin sodium injection
Fragmin®
NDC 0013-5190-01

8P3730

8888

Usual dosage: See package insert for complete product information.

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

Each 1 mL syringe contains:
Dalteparin sodium 10,000 IU (anti-Xa) (equivalent to 64 mg)
Water for Injection to 1 mL
Sodium chloride is added to achieve isotonicity

MADE IN GERMANY

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

by: Vetter Pharma-Fertigung
Ravensburg, Germany

818 207 101

12

PHARMACIA

Fragmin®
dalteparin sodium injection
10,000 IU (anti Xa) per 1 mL

8P3730
KV0851-01

LOT
EXP

10 x 1 mL single dose graduated syringes, preassembled with needle guards
NDC 0013-5190-01

Fragmin®

dalteparin sodium injection

10,000 IU (anti-Xa) per 1 mL

Single dose graduated syringes

For subcutaneous injection

℞ only

PHARMACIA

40

123
1234567890

NDC 0013-5190-01 1

TSE-K666
SC044
ZWART
GR3288
GR343
R0032

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-031

LABELING REVIEWS

REGULATORY PROJECT MANAGEMENT LABELING REVIEW

Division of Gastrointestinal and Coagulation Drug Products (DGICDP)

Application Number: NDA 20-287/SLR-031

Name of Drug: Fragmin® (dalteparin sodium) Injection

Sponsor: Pharmacia & Upjohn Company

Materials Reviewed: Package Insert and immediate container and blister labeling for the 10,000 IU/1.0 mL graduated syringe.

Submission Date: January 14, 2003

Receipt Date: January 15, 2003

Background and Summary

Background:

Labeling Supplement-031 was submitted on January 14, 2003 (received January 15, 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. Pharmacia and Upjohn plan to implement the use of the needle safety guard for Fragmin 10,000 IU (1.0 mL) graduated prefilled syringes no sooner than March 3, 2003.

The needle safety guards are manufactured by Safety Syringes, Inc. (SSI) and were cleared under 510(K) Reference K011369. The sponsor claims to be in compliance with the recommendation stated in the Occupational Safety and Health Administrations's (OSHA) Needlestick Safety and Prevention Act dated November 6, 2000, and the Department of Labor, Occupational Safety and Health Administration (OSHA) regulations (29 CFR Part 1910 [Docket No. H370A] RIN 1218-AB85 Final Rule entitled, "Occupational Exposure to Bloodborne Pathogens; Needlestick and Other Sharps Injuries" dated January 18, 2001).

The most recently approved package insert (PI) for Fragmin is SLR-011 submitted August 25, 1998, received August 26, 1998, and approved February 27, 2003. SLR-011 provided for revisions to the **PRECAUTIONS** section, **Geriatric Use** subsection of the package insert (PI) in response to the Final rule entitled "Specific Requirements on Content and format of labeling for human Prescription Drugs: Addition of 'Geriatric Use' Subsection in the Labeling," published in the August 27, 1997 Federal Register (62 FR 45313-45326).

The most recently approved carton and immediate container labeling for the 10,000 IU/1.0 mL Fragmin graduated single dose syringe is contained in Supplement SCP-022, submitted on September 15, 2000, and approved on draft on April 4, 2002. Supplement-022 provided for the 7500 IU/0.75 mL single dose syringe presentation and the 10,000 IU/1.0 mL single dose syringe presentation.

Similar supplements were submitted for the use of the UltraSafe Passive™ needle safety guards in conjunction with other strengths of approved Fragmin pre-filled syringes:

- Supplement SLR-027 was submitted on January 29, 2002, as a "Changes Being Effected-30" labeling supplement to add the use of the UltraSafe Passive™ needle safety guards in conjunction with the approved 2500 IU (0.2 mL) and 5000 IU (0.2 mL) single-dose pre-filled syringes.

  On February 4, 2002, a consult was sent to the Center for Devices and Radiological Health (CDRH), Office of Device Evaluation (ODE) Division of Dental, Infection Control, and General Hospital Devices (DDICGHD) to review the labeling for the UltraSafe Passive™ Needle Safety Guard used with FRAGMIN 2500 IU and 5000 IU single dose pre-filled syringes (S-027). Review of the consult was completed May 31, 2002, and received by DGICDP on June 3, 2002. CDRH recommended that the carton/device label for the 2500 IU and 5000 IU single-dose pre-filled syringes be revised to include the specific name of the safety feature, UltraSafe Passive Needle Guard, as indicated in the "**HOW SUPPLIED**" section of the PI and to more prominently display the name to allow the clinician to visually note the presence of a safety feature. CDRH also suggested that the carton label (for the 2500 IU and 5000 IU single-dose pre-filled syringes) be revised to contain the needle size (gauge and length).

  The DGICDP Medical Officer, Dr. Ruyi He, concurred with this recommendation in a verbal comment on July 26, 2002. In response to the comments from CDRH, the Division sent the following comment to the sponsor in an approvable letter to S-027 on July 29, 2002:

  > "Include the specific name of the safety feature "UltraSafe Passive Needle Guard" on the 2500 IU and 5000 IU cartons and 2500 IU and 5000 IU syringes prominently displayed and revise the carton labels to contain the needle size (gauge and length)."

  On July 31, 2002, the sponsor responded to the comment in a General Correspondence in response to the S-027 Approvable Letter. The sponsor objects to the comment and requests the FDA reconsider the addition of the needle gauge and length to the carton label and not require the changes as specified in the July 29, 2002, approvable letter.

  A consult was sent to CDRH on August 27, 2002, for comment on the sponsor's request. The sponsor's rationale for this item reads as follows:

  > "Finally, regarding the addition of the needle gauge and length to the carton label. P&U does not understand the reason for this request because this information is already in the

PI. Further, the needle is identical in size and gauze to the needle that has been used with all prefilled syringes for FRAGMIN, since the prefilled syringes were approved and first distributed 9 years ago. The addition of the needle information on the carton, although possible, does not seem to add useful safety information to health professionals, because there are no choices for using a different gauge and length needle when selecting a prefilled syringe."

Note: This comment applies to the 7500 IU and 10,000 IU strengths of prefilled syringes because the same safety apparatus is also being proposed for the 7500 IU and 10,000 IU strengths of prefilled syringes.

CDRH responded to the August 27, 2002, consult on October 3, 2002. The sponsor's request to reconsider the Agency request to include the specific name of the safety feature "Ultra Safe Passive Needle Guard" on the 2500 IU and 5000 IU cartons and 2500 IU and 5000 IU syringes prominently displayed and revise the carton labels to contain the needle size (gauge and length) is acceptable. Supplement-027 was approved November 1, 2002.

- Supplement SLR-029 was submitted on May 17, 2002, received May 20, 2002, as a "Changes Being Effected" (CBE-0)" labeling supplement to add the use of the UltraSafe Passive™ needle safety guards in conjunction with the approved 7500 IU (0.3 mL) single-dose pre-filled syringe. The sponsor implemented the use of the needle safety guard for the FRAGMIN 7500 IU/0.3 mL single dose pre-filled syringe on June 21, 2002. SLR-029 was approved November 19, 2002.

Review

I. Package Insert

The PI proposed for S-031 dated January 14, 2003, identified as version control code "5R6289 KV0404-12 818 312 006B" was compared to approved labeling from S-011 dated January 16, 2003, (received January 17, 2003; approved on draft February 27, 2003) identified as "818 312 005." The submitted PI is identical to the approved PI except for the following:

A. In the section above the black box warning, the sponsor added the name "Pharmacia" after the trademark "FRAGMIN dalteparin sodium injection."

The addition is editorial and acceptable.

B. **PRECAUTIONS** section

Following the ninth subsection entitled, "**Pediatric Use**:" the sponsor has not included the **Geriatric Use** subsection in SLR-011 submitted August 25, 1998, received August 26, 1998, and approved February 27, 2003. The section reads as follows:

"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 should be included in the FPL for SLR-031.

C. **DOSAGE AND ADMINISTRATION** section

Administration, *Subcutaneous Injection technique* subsection:

1. The sponsor capitalized the letter "I" in the title "*Subcutaneous Injection technique*"

   The revision is editorial and acceptable.

2. In the first paragraph, following the first sentence that begins, "patients should be sitting . . ." the sponsor has added the following sentence:

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

   The addition improves the directions for administration. The addition is acceptable.

3. In the fifth paragraph, prior to the first sentence that begins, "Hold the syringe assembly . . ." the sponsor has added the subheading "**Fixed dose syringes:**"

   The addition is editorial and acceptable.

4. Following the fifth paragraph that begins, "Hold the syringe assembly . . ." The sponsor has proposed the addition of the following paragraph:

   "**Graduated syringes**: Hold the syringe assembly by the open sides of the device. Remove the needle shield. Prepare the syringe by pushing 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."

This is similar wording accepted for the 2500 and 5000 IU pre-filled single-dose (fixed) strengths approved in SLR-027 (see RPM review dated 10/29/02) in the previous paragraph. The Medical Officer, Ruyi He, M.D. agreed with this addition in a verbal comment to Diane Moore on April 11, 2003.

D. **HOW SUPPLIED** section

1 In the sixth sentence that begins, "1.0 mL single-dose . . " the sponsor has proposed to add the following phrase, "and preassembled with UltraSafe Passive™ Needle Guard* devices." so that the sentence reads, "1.0 mL single-dose graduated syringe, affixed with a 27-gauge x ½ inch needle and preassembled with UltraSafe Passive™ Needle Guard* devices."

This addition adds the name of the needle guard. The addition is acceptable. This is the same wording accepted for the 2500 and 5000 IU strengths approved in SLR-027 (see RPM review dated 10/29/02) and the 7500 IU strength approved in SLR-029 (see RPM review dated 11/19/02).

2. The sponsor revised the "Revised" date for the PI from "June 2002" to "August 2002." and revised the identification code from "818 312 005" to "5R6289 KV0404-12 818 312 006B."

The revisions are editorial and acceptable.

II. 10,000 IU/1.0 mL Carton Label

The carton labeling for the 10,000 IU syringe proposed for SLR-031 submitted January 14, 2003 (received January 15, 2003), identified as version"818 207 101B" was compared to the 10,000 IU carton from S-022 dated March 18, 2002, (approved April 4, 2002) identified as "818 207 000E." The submitted carton labeling is identical to the approved carton labeling except for the following:

A. Front Panel

1. The sponsor has added the words "preassembled with needle guards" to the top sentence of the front panel so that it reads, "10 x 0.3 mL single dose syringes, preassembled with needle guards. NDC 0013-5190-01."

This revision is acceptable per CDRH consult dated October 2, 2002 to SLR-027. This revision adds the name of the needle guard. The addition is acceptable.

Note: This is the same wording accepted for the 2500 and 5000 IU strengths approved in SLR-027 (see RPM review dated 10/29/02) and the 7500 IU strength approved in SLR-029 (see RPM review dated 11/19/02).

2. The company name (Pharmacia & Upjohn) and the associated logo above it has been replaced by the new company name *PHARMACIA* on the bottom of the front panel of the box.

   The revision of the company name is consistent with the change of sponsor ownership for the product. This is editorial and is acceptable.

B. Right Side Panel

The first two code numbers on the bottom section of the flap have been revised. The code "TSE-K636" was replaced by "TSE-K666." The code "SC041" was replaced by "SC044."

These are editorial changes and are acceptable.

C. Left Side Panel

The code at the bottom of the left side flap has been revised from "8P1880 KV0816-01" to "8P3730 KV0851-01."

These are editorial changes and are acceptable.

D. Back Side Panel

1. In the fourth section on the back panel that begins "MADE IN GERMANY," the sponsor has added the phrase, "A subsidiary of Pharmacia Corporation" after the phrase "Manufactured for:" so that the section reads "MADE IN GERMANY Manufactured for: Pharmacia & Upjohn Company A subsidiary of Pharmacia Corporation Kalamazoo, MI 49001, USA."

   This is an editorial revision and is acceptable. The revision of the company name is consistent with the change of sponsor ownership for the product.

2. The sponsor replaced the company name (Pharmacia & Upjohn) and the logo at the bottom of the back panel by the company name *PHARMACIA* on the bottom of the back panel.

   This is an editorial revision and is acceptable.

3. The sponsor replaced the identifier number "818 207 000E" with the identifier number "818 207 101B."

This is an editorial revision and is acceptable.

4. The bar code appears to have been revised on the back end flap. Codes by the colored boxes on the back side flap were revised from "192" to "12" and the code by the bar code on the end was revised from "8P1880" to "8P3730."

   These are editorial revisions and are acceptable.

III. Blister Label 10,000 IU/1 mL syringe

The blister labeling for the 10,000 IU/1.0 mL Fragmin syringe proposed for SLR-031, submitted January 14, 2003, received January 15, 2003 (identification code "818 208 101A KV0234-01 5T0809") was compared to the FPL blister labeling for the 10,000 IU/1.0 mL Fragmin pre-filled graduated syringe from SCP-022 submitted March 18, 2002, received March 19, 2002, approved April 4, 2002 (identification code "818 208 000F KV0691-01 5T0630"). The blister labeling for the 10,000 IU syringe are identical except for the following:

The sponsor revised the codes on the blister labeling from "818 2208 000F KV0691-01 5T0630" to "818 208 101A KV0234-01 5T0809."

This revision is editorial and acceptable. (Note: the sponsor claims that the blister label is longer. However, the proposed labeling appears to be the same size as the previously approved labeling).

IV. 10,000 IU/1.0 mL Immediate Container Label

The proposed immediate container labeling for the 10,000 IU/1.0 mL Fragmin prefilled graduated syringe submitted January 14, 2003, received January 15, 2003, identification code "5Q7098 KV0398-02 818 206 001E" was compared to the immediate container labeling for the 10,000 IU/1.0 mL Fragmin prefilled graduated syringe in SCP-022 submitted March 29, 2002, received April 1, 2002, approved April 4, 2002 identification code "5QK6235 KV0398-01 818 206 000J." The submitted immediate container label is identical to the approved immediate container label except for the following:

A. The sponsor moved the text of the labeling that reads "Fragmin dalteparin sodium Injection 10,000 IU (anti-Xa) per 1 mL" one quarter of an inch to the right on the label and revised the graduations on the side of the syringe from "1000 IU (0.1 mL)" through "10,000 IU (1.0 mL) in 1000 IU (0.1 mL)" gradations to "4000 IU (0.4 mL)" through 10,000 IU (1.0 mL) in 1000 IU (0.1 mL)" gradations. There are line markings for the 3000 IU (0.3) gradation, but the numbers are not included on the syringe.

   The spring mechanism in the safety device obscures the top of the syringe where the 1000 – 3000 IU (0.1 – 0.3mL) markings would be. Moving the text to the right

places it in a better location to avoid being obscured by the spring mechanism in the syringe. There is medication in the tip of the syringe to account for that amount of product. (When the syringe is tipped downward, the bubble in the syringe occupies the space below the last marking (10,000 IU) showing the amount of product does not include the portion of the syringe beyond the 10,000 IU marking). The portion of the dose in the tip of the syringe is given first and would be incorporated in the total dose. The omission of the 1000, 2000 and 3000 numbers should not hinder the administration of the proper amount of the drug. The revision is acceptable.

B. The sponsor revised the identification code from "5Q6235 KV0398-01 818 206 000J" to "5Q7098 KV0398-02 818 206 001E."

This is editorial and acceptable.

CONCLUSIONS

1. **The following revisions are editorial and acceptable: I.A., I.C.1., I.C.3., I. D.2., II.A.2., II.B., II.C., II.D., III., and IV.B.**

2. **The following revisions are acceptable: I.C.2., I.D.1., II.A.1., IV. A.**

3. **Item I.C.4. is acceptable per the Medical Officer.**

4. **Item I.B. should be included in the FPL for SLR-031. The firm will be requested to submit a revised PI to include the 'Geriatric Use' subsection.**

Diane Moore, B.S.
Regulatory Health Project Manager

Ruyi He, M.D.
Medical Officer

Kathy Robie-Suh, M.D., Ph.D.
Medical Team Leader, Hematology

Julieann DuBeau, MSN, RN
Chief, Project Management Staff

Drafted: dm/April 3, 2002
Revised/Initialed: J.DuBeau, R.He, K.Robie-Suh 5.6.03
Finalized: May 7, 2003
Filename: N20287S31lblrev.doc

RPM LABELING REVIEW

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/s/

Diane V. Moore
5/6/03 05:15:49 PM
CSO

Ruyi He
5/6/03 06:04:45 PM
MEDICAL OFFICER

Kathy Robie-Suh
5/7/03 08:35:18 AM
MEDICAL OFFICER

Julieann DuBeau
5/8/03 09:25:55 AM
CSO

REGULATORY PROJECT MANAGEMENT LABELING REVIEW #2

Division of Gastrointestinal and Coagulation Drug Products (DGICDP)

Application Number: NDA 20-287/SLR-031

Name of Drug: Fragmin® (dalteparin sodium) Injection 10,000 IU/1.0 mL Graduated Syringe

Sponsor: Pharmacia & Upjohn Company

Materials Reviewed: Package Insert and immediate container and blister labeling for the 10,000 IU/1.0 mL graduated syringe.

Submission Date: June 4, 2003
Receipt Date: June 5, 2003

Background and Summary

Background:

Labeling Supplement-031 (SLR-031) was submitted on January 14, 2003 (received January 15, 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.

The needle safety guards are manufactured by Safety Syringes, Inc. (SSI) and were cleared under 510(K) Reference K011369. The sponsor claims to be in compliance with the recommendation stated in the Occupational Safety and Health Administrations's (OSHA) Needlestick Safety and Prevention Act dated November 6, 2000, and the Department of Labor, Occupational Safety and Health Administration (OSHA) regulations (29 CFR Part 1910 [Docket No. H370A] RIN 1218-AB85 Final Rule entitled, "Occupational Exposure to Bloodborne Pathogens; Needlestick and Other Sharps Injuries") dated January 18, 2001.

The most recently approved package insert (PI) for Fragmin is Labeling Supplement S-011 submitted August 25, 1998, received August 26, 1998, and approved February 27, 2003. S-011 provided for revisions to the **PRECAUTIONS** section, **Geriatric Use** subsection of the package insert (PI) in response to the Final rule entitled "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs: Addition of 'Geriatric Use' Subsection in the Labeling," published in the August 27, 1997 Federal Register (62 FR 45313-45326).

The most recently approved carton and immediate container labeling for the 10,000 IU/1.0 mL Fragmin graduated single dose syringe is Chemistry Supplement SCP-022 (S-022), submitted on September 15, 2000, and approved on draft April 4, 2002. Supplement-022 provides for the

7500 IU/0.75 mL single dose syringe presentation and the 10,000 IU/1.0 mL single dose syringe presentation.

The carton labeling for the 10,000 IU syringe proposed for S-031 submitted January 13, 2003 (received January 15, 2003), identified as version "818 207 101B" was compared to the 10,000 IU carton from S-022 submitted March 18, 2002 (approved April 4, 2002) identified as "818 207 000D." The revisions were found to be acceptable in the RPM Labeling Review for S-031 dated February 13, 2003.

The PI proposed for S-031 submitted January 14, 2003, (received January 15, 2003) identified as version control code "5R62889 KV0404-12 818 312 006B" was compared to approved labeling from S-011 dated January 16, 2003 (received January 17, 2003; approved on draft February 27, 2003) identified as "818 312 005." (See RPM Labeling Review dated February 13, 2003 for S-031). In that review, the 10,000 IU/1.0 mL carton labeling, the 10,000 IU/1 mL syringe blister labeling and the 10,000 IU/1.0 Immediate Container label were found to be acceptable. However, in the **PRECAUTIONS** section of the PI, the sponsor had not included the **Geriatric Use** subsection that was added in S-011. On May 8, 2003, Diane Moore, RPM, contacted Greg Brier, Senior Regulatory Manager at Pharmacia & Upjohn and requested revised labeling for Fragmin S-031 that includes the **Geriatric Use** subsection approved in S-011 on February 27, 2003. The final printed labeling for S-011 submitted April 22, 2003 (received April 23, 2003; identified as "5R6512 LV0404-12 818 312 007" for the syringes and "5R651358 818 312 107" for the multi-dose vial) was acknowledged and retained on May 12, 2003. Pharmacia & Upjohn submitted revised labeling to S-031 on June 4, 2003 (received June 5, 2003).

Review

The PI proposed for S-031 submitted June 4, 2003 (received June 5, 2003) identified as "5R6775 KV0404-13 818 312 008C" was compared to the final printed labeling (FA) submitted to S-011 on April 22, 2003 (received April 23, 2003; acknowledged and retained May 12, 2003) identified as "5R6512 LV0404-12 818 312 007" for the syringes and "5R651358 818 312 107" for the multi-dose vial. The proposed labeling for S-031 submitted June 4, 2003 (received June 5, 2003) identified as "5R6775 KV0404-13 818 312 008C" was identical to the final printed labeling submitted to S-011 on April 22, 2003 (received April 23, 2003; acknowledged and retained May 12, 2003) identified as "5R6512 LV0404-12 818 312 007" for the syringes and "5R651358 818 312 107" for the multi-dose vial except that the proposed revised labeling submitted to S-031 on June 4, 2003 (received June 5, 2003) identified as "5R6775 KV0404-13 818 312 008C" included the proposed revisions to the PI submitted to S-031 on January 14, 2003 (received January 15, 2003) identified as 5R6289 KV0404-12 818 312 006B" and the approved **Geriatric Use** paragraph added to the PI in S-011. (See RPM Labeling Review for S-031 dated February 13, 2003, for details).

The PI proposed for S-031 submitted June 4, 2003 (received June 5, 2003) identified as "5R6775 KV0404-13 818 312 008C" was also compared to the sponsor's proposed labeling submitted January 14, 2003 (received January 15, 2003, identified as "5R6289 KV0404-12 818 312 006B."

The proposed labeling for S-031 submitted June 4, 2003 (received June 5, 2003) identified as "5R6775 KV0404-13 818 312 008C" was identical to the proposed labeling submitted to S-031 on January 14, 2003 (received January 15, 2003) identified as "5R6289 KV0404-12 818 312 006B" except for the following:

I. **PRECAUTIONS** section

Following the ninth subsection entitled, "**Pediatric Use**" the sponsor added the same **Geriatric Use** subsection that was added in S-011. The paragraph reads as follows:

> "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**)."

In a telephone conversation on May 8, 2003, between Diane Moore, RPM in the Division of Gastrointestinal and Coagulation Drug Products (DGICDP) and Greg Brier, Regulatory Manager, at Pharmacia and Upjohn, DGICDP requested the sponsor to add the above paragraph. The addition of the paragraph updates the PI to include the most recently approved labeling. The addition is acceptable.

II. **DOSAGE and ADMINISTRATION** section, **Administration**, *Subcutaneous injection technique* subsection

The sponsor does not capitalize the letter "I" in the title "*Subcutaneous injection technique.*"

The revision is editorial and acceptable.

III. **HOW SUPPLIED** section

The sponsor revised the identification code from "5R6289 KV0404-12 818 312 008C" to "5R6775 KV0404-13 818 312 008C."

The revision is editorial and acceptable.

CONCLUSIONS

1. **The labeling for the 10,000 IU (1.0 mL) graduated prefilled syringe carton labeling identified as "818 207 101B", the 10,000 IU/1 mL syringe blister labeling identified as "818 208 101A KV0234-01 5T0809" and the 10,000 IU/1.0 mL immediate container label identified as "5Q7098 KV0398-02 818 206 001D" submitted January 14, 2003 (received January 15, 2003) were found to be acceptable in the RPM Labeling Review dated February 13, 2003.**

2. **The proposed revisions to the PI submitted January 14, 2003 (received January 15, 2003) identified as "5R6289 KV0404-12 818 312 006B" were found to be acceptable with the exception that the Geriatric Use subsection added to the PI in S-011 should be included in the PRECAUTIONS section of the labeling.**

3. **The proposed revisions to S-031 submitted January 14, 2003 (received January 15, 2003) are incorporated into the revisions proposed in the amendment submitted June 4, 2003 (received June 5, 2003).**

4. **The following revisions to the PI submitted June 4, 2003 (received June 5, 2003) are editorial and acceptable: II., III.**

5. **The following revision to the PI submitted June 4, 2003 (received June 5, 2003) is acceptable: I.**

6. **This labeling supplement should be approved referencing the PI submitted June 4, 2003 (received June 5, 2003) and the carton, blister and immediate container syringe labeling submitted January 14, 2003 (submitted January 15, 2003).**

Diane Moore, B.S.
Regulatory Health Project Manager

Julieann DuBeau, MSN, RN
Chief, Project Management Staff

Drafted: dm/June 25, 2003
Revised: J.DuBeau 6.26.03
Initialed: J.DuBeau 6.26.03
Finalized: June 26, 2003
Filename: N20287S31Lblrev2.doc

RPM LABELING REVIEW

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/s/

Diane V. Moore
6/26/03 04:50:24 PM
CSO

Julieann DuBeau
6/27/03 11:06:40 AM
CSO

Division of Gastrointestinal and Coagulation Drug Products

REGULATORY PROJECT MANAGEMENT LABELING REVIEW

Application Number: NDA 20-287/SCP-031 Final Printed Labeling (FPL)

Name of Drug: Fragmin® (dalteparin sodium) Injection, 10,000 IU/mL single dose graduated syringe

Sponsor: Pharmacia & Upjohn Company

Materials Reviewed: Package Insert (PI) and carton and immediate container labeling

Submission Date: July 18, 2003
Receipt Date: July 21, 2003

Background and Summary

Background:

This FPL is to NDA 20-287/S-031 (S-031), submitted January 14, 2003, received January 15, 2003, amended June 4, 2003; received June 5, 2003; approved on draft June 30, 2003). Supplement-031 provided for the use of Ultra Safe Passive™ needle safety guards in conjunction with the approved FRAGMIN® (dalteparin sodium injection) 10,000 IU/1.0 mL graduated pre-filled syringes.

Review

I. Package Insert

The Final Printed package insert (PI) proposed for Fragmin® (dalteparin sodium, injection), S-031 submitted July 18, 2003 (received July 21, 2003) identified as version control code "5R6775 KV0404-13 818 312 008" (Revised May 2003) was compared to the approved labeling from S-031 (submitted January 14, 2003, received January 15, 2003, amended June 4, 2003; received June 5, 2003; approved on draft June 30, 2003) identified as "5R6775 KV0404-13 818 312 008C" (Revised May 2003). The submitted package insert is identical to the approved package insert submitted June 4, 2003, except for the following:

The identifier numbers were revised from 5R6775 KV0404-13 818 312 008C (Rev. May, 2003) to "5R6775 KV0404-13 818 312 008" (Rev. May, 2003).

The revision is editorial and acceptable.

II. Immediate container labeling 10,000 IU 1.0 mL single-dose syringe

The FPL for the immediate container labeling for the 10,000 IU single-dose syringe for Fragmin® (dalteparin sodium, injection) S-031 submitted on July 18, 2003 (received July 21, 2003), coded "5Q7098 KV0398-02 818 206 001" was compared to the immediate container for the 10,000 IU single-dose syringe labeling from NDA 20-287/S-031 (submitted January 14, 2003; received January 15, 2003; approved on draft June 30, 2003), coded "5Q7098 KV0398-02 818 206 001E." The two labels are identical except for the following:

A. The identifier numbers were revised from 5Q7098 KV0398-02 818 206 001E." to "5Q7098 KV0398-02 818 206 001"

The revision is editorial and acceptable.

Note: On the pdf version of the immediate container labeling for the Fragmin® 10,000 IU 1.0 mL single-dose syringe, a gray shaded box can be seen on the numbers and line segments corresponding to "7000, 8000 and 9000 IU and 0.7, 0.8 and 0.9 mL" on the syringe barrel.

In a telephone conversation between Diane Moore, RPM, from DGCDP and Greg Brier, from Pfizer on October 31, 2003, Mr. Brier clarified that the gray box is an ———— used for online location verification of the label during the printing process. The gray box is not visible on the final product. The immediate container labeling is acceptable.

III. Blister labeling 10,000 IU syringe

The FPL blister labeling for the Fragmin® 10,000 IU single-dose syringe to S-031 submitted July 18, 2003 (received July 21, 2003), coded "818 208 101 KV0234-01 5T0809" was compared to the blister labeling for the Fragmin 10,000 IU single-dose syringe from NDA 20-287/S-031 submitted January 14, 2003 (received January 15, 2003; approved on draft June 30, 2003) coded "818 208 101A KV0234-01 5T0809." The two labels are identical except for the difference in the code number.

The revision is editorial and acceptable.

IV. 10,000 IU Carton labeling

The FPL for the Fragmin® 10,000 IU single-dose syringe proposed in S-031 (submitted July 18, 2003; received July 21, 2003), identified as version "8P3730 KV0851-01 818 207 101" was compared to the Fragmin® 10,000 IU single-dose syringe carton labeling proposed for the carton in S-031 submitted January 14, 2000; received January 15, 2003; approved on draft June 30, 2003) identified as 8P3730 KV0851-01 818 207 101B." The two labels are identical except for the difference in code numbers.

The revision is editorial and acceptable.

CONCLUSIONS

1. **The FPL for NDA 20-287/S-031 (submitted July 18, 2003, received July 21, 2003 is acceptable.**

4. **An "acknowledgement and retain" letter should be sent to the sponsor for the final printed labeling for NDA 20-287/S-031.**

Diane Moore, B.S.
Regulatory Health Project Manager

Drafted: dm/October 27, 2003
Finalized: November 3, 2003
Filename: N20287FAS31rev.doc

RPM LABELING REVIEW

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/s/

Diane V. Moore
11/3/03 04:28:35 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-031

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-031

CBE-0 SUPPLEMENT

Pharmacia & UpJohn
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) 10,000 IU
NDA Number:	20-287
Supplement number:	S-031
Date of supplement:	January 14, 2003
Date of receipt:	January 15, 2003

This supplemental application, submitted as "Supplement - Changes Being Effected" proposes the following change: The use of the UltraSafe Passive™ needle safety guards in conjunction with the approved FRAGMIN® (dalteparin sodium injection) 10,000 IU (1.0 mL) graduated prefilled syringes.

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 March 14, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 15, 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: Division 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 questions, call me, at (301) 827-7476.

Sincerely,

{See appended electronic signature page}

Diane Moore
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation
Drug Products (HFD-180)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Diane V. Moore
1/17/03 06:45:37 PM

Pharmacia & Upjohn

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

June 4, 2003

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Document Control Room 3rd Floor
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852

Re: NDA 20-287/S-031
FRAGMIN®
dalteparin sodium injection

ELECTRONIC SUBMISSION

AMENDMENT 1
Updated FPL For CBE-0
Use Of The Ultrasafe Passive™ Needle Safety Guard In Conjunction With The 10,000 IU/1.0 mL Graduated Syringes

Dear Sir/Madam:

Pharmacia & Upjohn Company is submitting, as requested, Amendment 1 consisting of updated Final Printed Labeling (FPL) to NDA-20-287, FRAGMIN® (dalteparin sodium injection), 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.

The FPL incorporates the most currently approved labeling based upon the Supplement S-011 for the addition of a Geriatric Use Statement along with the changes covered by the CBE-0 Supplement S-031 submitted on January 14, 2003.

The CD-ROM contains the following files and directory structure:

Main Directory – N20287

- cover.pdf Cover Letter
- 356h.pdf 356h Form
- ndatoc.pdf Table of Contents

Subdirectory – Labeling:

- Final Printed Labeling (pi.pdf)
- Final Printed Labeling for Editing in MSWord (pi.doc)
- Labeling Table of Contents (labeltoc.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 correspondence, please contact me by telephone at 269.833.3670 or fax at 269.833.8237. Please address any correspondence to Mail-Code 0200-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

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

GAB:mlw

Pharmacia & Upjohn

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

July 18, 2003

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Document Control Room 3rd Floor
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852

Re: NDA 20-287/S-031
FRAGMIN®
dalteparin sodium injection

ELECTRONIC SUBMISSION
FPL for Approved Supplement
NDA 20-287/S-031

Dear Sir/Madam:

Pharmacia & Upjohn Company is submitting final printed labeling for NDA-20-287, FRAGMIN® (dalteparin sodium injection), approved supplement 031. This Changes Being Effected (CBE-0) supplement provided for the use of UltraSafe Passive™ needle safety guards in conjunction with the approved FRAGMIN® (dalteparin sodium injection) 10,000 IU (1.0 mL) single dose pre-filled syringes.

The final printed labeling is identical to the labeling approved by the Agency on June 30, 2003. The package insert is identified by copy code 818 312 008, the carton by code 818 207 101, the blister label by code 818 208 101, and the immediate container label by code 818 206 001

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 Approval Letter for S-031 (other.pdf)

Subdirectory – Labeling:

- Package Insert copy code 818 312 008 (pi.pdf)
- Carton 818 207 101 (carton.pdf)
- Blister Label code 818 208 101 (blister.pdf)
- Immediate Container Label code 818 206 001 (container.pdf)
- Labeling Table of Contents (labeltoc.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 correspondence, please contact me by telephone at (269) 833-3670 or fax at (269) 833-8237. Please address any correspondence to Mail-Code 0200-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

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

GAB:mlw

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-287/S-031

Pharmacia and Upjohn Company
Attention: Gregory A. Brier, BSChE, MBA
Senior Regulatory Manager
Global Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001-0199

Dear Mr. Brier:

We acknowledge receipt of your July 18, 2003, submission containing final printed labeling in response to our June 30, 2003, letter approving your supplemental new drug application for Fragmin® (dalteparin sodium, injection).

We have reviewed the labeling that you submitted in accordance with our June 30, 2003, letter and we find it acceptable.

If you have any questions, call Diane Moore, Regulatory Health 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/

Diane V. Moore
11/6/03 02:52:11 PM
For Robert L. Justice, M.D., M.S.