CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-287/S-017

Name: Fragmin (Dalteparin Sodium) Injection

Sponsor: Pharmacia & Upjohn Company

Approval Date: August 5, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-017

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-017

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-287/S-017

Pharmacia & Upjohn
Attention: Ms. Leslie Franks
Unit 0635-298-113
7000 Portage Road
Kalamazoo, Michigan 49001

Dear Ms. Franks:

Please refer to your supplemental new drug application dated February 7, 2000, received February 8, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin® (dalteparin sodium injection).

We acknowledge receipt of your submissions dated March 3, April 5, August 21 and 29, 2000. Your submission of August 21, 2000 constituted a complete response to our June 7, 2000 action letter.

This supplemental new drug application provides for the transfer of manufacturing, packaging, and quality control release testing for the 10,000 IU/mL, 9.5 mL multi-dose vial, from Stockholm, Sweden to the Pharmacia & Upjohn Company facility in Puurs, Belgium.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final printed labeling submitted August 21, 2000 (immediate container label and carton) and August 29, 2000 (package insert). Accordingly, the supplemental application is approved effective on the date of this letter.

Although not an approvability issue, we request that the package insert labeling be revised at the next printing. Specifically, in the CLINICAL TRIALS section, the "Prophylaxis of Deep Vein Thrombosis in Patients Following Hip Replacement Surgery" subsection, in the third paragraph (describing the third study), the word "both" should be changed to bold type-face in the following sentence to read: "Then, **both** of these groups began a dosing regimen of FRAGMIN 5000 IU once daily s.c. on postoperative day 1."

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

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

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

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

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 Karen Oliver, Regulatory Project Manager, at (301) 827-7457.

Sincerely,

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

/s/

Lilia Talarico
11/14/00 05:58:29 PM

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-017

APPROVABLE LETTER

NDA 20-287/S-017

Pharmacia & Upjohn Company
Attention: Ms. Leslie Franks
Unit 0635-298-113
7000 Portage Road
Kalamazoo, Michigan

Dear Ms. Franks:

Please refer to your supplemental new drug application dated February 7, 2000, received February 8, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin® (dalteparin sodium injection).

We acknowledge receipt of your submissions dated March 3 and April 5, 2000.

This supplement proposes the following change: the transfer of manufacturing, packaging and quality control release testing for the 10,000 IU/mL, 9.5 mL multi-dose vial, from Stockholm, Sweden, to the Pharmacia & Upjohn Company facility in Puurs, Belgium.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. Commit to provide data to demonstrate stability for 30 months storage to support the shelf-life of the product. Submit the stability data in the NDA annual report.

2. Provide data from media fills conducted in 1997 and 1998. No recent media fill records were submitted with the application.

3. Provide the environmental monitoring data for the most recent media fills. The application included environmental monitoring data only in support of the media fills performed in 1997 and 1998 (application Tables EC04 through EC42).

4. Provide English translation of the data in Tables EC04 through EC42 as required under 21 CFR 314.50(g)(2).

5. Submit a copy of each original literature publication for which an English translation is submitted.

In addition, it will be necessary for you to submit final printed labeling (FPL) revised as follows:

6. Regarding the package insert, reinstate the page numbers.

7. Regarding the immediate container label, provide for the "lot" and "exp" numbers.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 copies of the final printed labeling ten of which are individually mounted 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 the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. 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.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with the change prior to approval of this supplemental application.

If you have any questions, call Karen Oliver, Regulatory Health Project Manager, at (301) 827-7457.

Sincerely,

Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug Products, (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 20-287/S-017
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/L.Zhou
HFD-180/A.Al-Hakim
DISTRICT OFFICE

R/D init: A.Al-Hakim 06/02/00
R/D init: L.Zhou 06/02/00
Drafted by: KO/May 30, 2000
final: KO/06/07/00/c:\data\mydocments\NDA20287-S-017-05-30-00-AE.DOC

APPROVABLE (AE)

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-017

APPROVED LABELING

Fragmin®

dalteparin sodium injection

Pharmacia &Upjohn

For *Subcutaneous* Use Only

SPINAL/EPIDURAL HEMATOMAS

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

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

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

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

DESCRIPTION

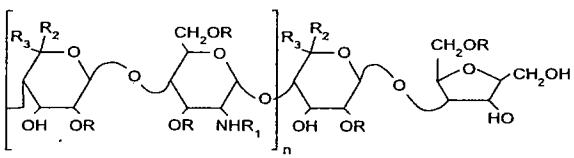
FRAGMIN Injection (dalteparin sodium injection) is a sterile, low molecular weight heparin. It is available in single-dose, prefilled syringes and a multiple-dose vial. With reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard, each syringe contains 2500 (16 mg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

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

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

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

Structural Formula



R = H or SO_3Na
$R_1 = COCH_3$ or SO_3Na
$R_2 = H$ $R_3 = COONa$
or
$R_2 = COONa$ $R_3 = H$

n = 3–20

ENLARGED TO 125% BY FDA STAFF

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	7/178 (3.9%)[1]	7/174 (4.0%)
Total Thromboembolic Events	3/178 (1.7%)	4/174 (2.3%)
Proximal DVT	3/178 (1.7%)	3/174 (1.7%)
Distal DVT	1/178 (0.6%)	0
PE		

[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	99/656 (15.1%)[2]	60/645 (9.3%)
Total Thromboembolic Events	18/657 (2.7%)	14/646 (2.2%)
Proximal DVT	80/657 (12.2%)	41/646 (6.3%)
Distal DVT		
PE	1/674 (0.1%)	1/669 (0.1%)
Fatal	2	4
Non-fatal		

[1] Major abdominal surgery with malignancy

[2] p-value = 0.001

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.

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, bulleous 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.

Fragmin

brand of dalteparin sodium injection

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

Administration:

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

Subcutaneous injection technique: Patients should be sitting or lying down and FRAGMIN administered by deep 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.

HOW SUPPLIED

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

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

Package of 10:

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

9.5 mL multiple-dose vial:

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

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

℞ only

U.S. Patent 4,303,651

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

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

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

KV0404-09
818 312 001

Revised August 2000

APPEARS THIS WAY
ON ORIGINAL

■ NDC 0013-2456-06 ■ **Fragmin®** ■ **dalteparin sodium injection** 10,000 IU (anti-Xa) per mL **For subcutaneous injection** 9.5 mL multiple-dose vial	Contains benzyl alcohol as a preservative Usual dosage: See package insert for complete product information. Store at controlled room temperature 20° to 25°C (68° to 77°F) [See USP]. Manufactured for: Pharmacia & Upjohn Company, Kalamazoo, MI 49001, USA 818 123 000A USA_X001
Lot: Exp.:	Lot: Exp.:
■ NDC 0013-2456-06 ■ **Fragmin®** ■ **dalteparin sodium injection** 10,000 IU (anti-Xa) per mL **For subcutaneous injection** 9.5 mL multiple-dose vial	Contains benzyl alcohol as a preservative Usual dosage: See package insert for complete product information. Store at controlled room temperature 20° to 25°C (68° to 77°F) [See USP]. Manufactured for: Pharmacia & Upjohn Company, Kalamazoo, MI 49001, USA 818 123 000A USA_X001

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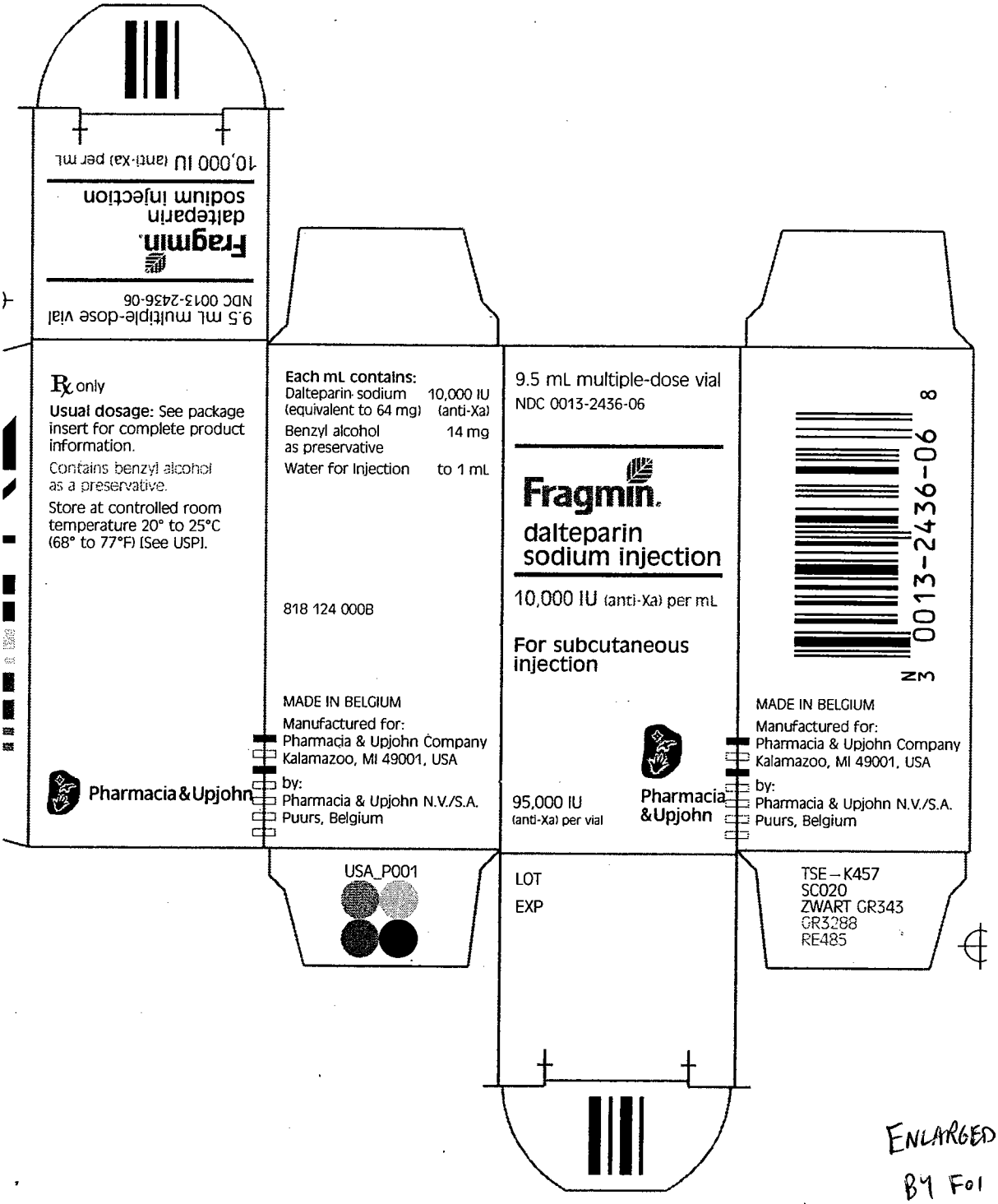

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-017

CSO LABELING REVIEW(S)

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-287/S-017

Name of Drug: Fragmin® (dalteparin sodium injection)

Sponsor: Pharmacia & Upjohn Company

Material Reviewed

Submission Date(s): March 3, 2000 (package insert)
April 5, 2000 (immediate container label and carton)

Receipt Date(s): March 6, 2000 (package insert)
April 6, 2000 (immediate container label and carton)

Background and Summary Description:

Supplement 017, submitted February 7, 2000, received February 8, 2000, provides for the following change: the transfer of manufacturing, packaging and quality control release testing for the 10,000 IU/mL, 9.5 mL multi-dose vial, from Stockholm, Sweden, to the Pharmacia & Upjohn Company facility in Puurs, Belgium.

Review

Package Insert

The annotated draft package insert (PI), submitted March 3, 2000, with a strike-out line through the identification code "132010599 Revised May 1999", was compared to the final printed labeling (FPL), identified as "132020599 Revised May 1999", approved May 25,1999, in Supplement 010. The package inserts were reviewed and were identical except for the following:

1. The page numbering in center of the bottom of the pages has been deleted.

   This is UNACCEPTABLE. The sponsor should be requested to reinstate the page numbering.

2. The bar coding has been deleted.

   This change is ACCEPTABLE.

3. After the HOW SUPPLIED section, the "manufactured by" section has been changed

from:

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

to:

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

This change was reviewed by the REVIEW CHEMIST, Dr. Ali Al-Hakim, and it is ACCEPTABLE.

4. The last page of the package insert (identified as page 12 in the approved labeling) was not presented. The identification numbers, "KV0404-08 1 2 3 4 5", listed vertically on that page have been deleted.

This deletion is ACCEPTABLE.

Immediate Container Label:

The computer generated, color mock-up, immediate container label for the 9.5 mL multiple-dose vial, submitted April 5, 2000, identified as "818 123 000A USA_X001" was compared to the approved labeling, identified as "152211197 435-974," submitted January 13, 1999 in annual report 004. The immediate container labels were reviewed and were identical except for the following:

4. The identification numbers were changed.

This change is ACCEPTABLE.

5. The bar coding was deleted.

This deletion is ACCEPTABLE.

6. In the title section, the format of the drug name was changed

from:

Fragmin
dalteparin sodium injection

to:

Fragmin
dalteparin sodium
injection

This change is ACCEPTABLE.

7. The words "exp" and "log", below the right column text, has been deleted.

This is UNACCEPTABLE. The sponsor should provide for the lot and expiration numbers on the label.

8. To the right of the vertical identification number, a rectangular box has been inserted, that contains no text.

This addition is ACCEPTABLE. This reviewer speculates that the "lot" and "exp" dating will be stamped, on line, in the space. However, the sponsor provided no explanation for the space on the label.

Carton

The computer generated, color mock-up, carton for the 9.5 mL multiple-dose vial, submitted April 5, 2000, identified as "818 124 000B", was compared to the multiple dose vial carton, identified as "132230798" submitted January 13, 1999, in annual report 004. The cartons were identical except for the following:

9. On the front panel, the tradename, "Fragmin", and the established name "dalteparin sodium injection", the lettering was changed to positive lettering (the word "Fragmin" printed with green ink, and the words "dalteparin sodium injection" printed in black ink) on a white background, as on the immediate container label. In addition, a single green line, has been placed above the word "Fragmin", and another single green line has been placed below the words "dalteparin sodium injection". Note: These additional green lines do not appear on the immediate container label. On the approved labeling,

the word "Fragmin" and the words "dalteparin sodium injection" are printed in white letters, inserted within a green rectangular box, with a green horizontal line above and below the box.

This change is ACCEPTABLE.

10. On the front panel, the "Pharmacia & Upjohn" name and logo has been relocated

    from:

    above, and to the right of the drug name "Fragmin"

    to:

    below, and to the right of the words "For subcutaneous injection".

This change is ACCEPTABLE. The reviewer notes that the placement of the logo is inconsistent with other Fragmin labeling (e.g., package insert, 2500 IU and 5000IU single dose syringes carton) where the logo is above and to the right of the name "Fragmin".

11. On the front panel, to the left of the phrase "95,000 IU (anti-Xa) per vial, the graphic of a vial was deleted.

This deletion is ACCEPTABLE.

12. On the tab attached to the front panel, the phrase "CODE 2436-06" was deleted and the words "LOT" and "EXP" were added.

These changes are ACCEPTABLE.

13. On the panel displayed to the immediate right of the front panel:

    a. The following phrase was changed

    from:

    MADE IN SWEDEN

    to:

    MADE IN BELGIUM.

This change was reviewed by the REVIEW CHEMIST, Dr. Ali Al-Hakim, and it is ACCEPTABLE.

b. The following phrase was changed

from:

by:

Pharmacia & Upjohn AB
Stockholm, Sweden

to:

by:

Pharmacia & Upjohn N.V./S.A.
Puurs, Belgium.

This change was reviewed by the REVIEW CHEMIST, Dr. Ali Al-Hakim, and it is ACCEPTABLE.

c. On the upper and lower flaps, the number "13" (upper flap) and the phrase "E son pac" (lower flap) have been deleted. The following was added to the lower flap:

TSE-K457	(black ink)		
SC020	(black ink)		
ZWART	(black ink)	GR343	(green ink)
GR3288	(blue ink)		
RE485	(red ink)		

These additions are ACCEPTABLE.

14. On the panel displayed to the immediate left of the front panel:

a. The numbers "420-263" (top flap) were deleted.

This deletion is ACCEPTABLE.

b. The following phrase was changed

from:

MADE IN SWEDEN

to:

MADE IN BELGIUM.

This change was reviewed by the REVIEW CHEMIST, Dr. Ali Al-Hakim, and it is ACCEPTABLE.

d. The following phrase was changed

from:

by:

Pharmacia & Upjohn AB
Stockholm, Sweden

to:

by:

Pharmacia & Upjohn N.V./S.A.
Puurs, Belgium.

This change was reviewed by the REVIEW CHEMIST, Dr. Ali Al-Hakim, and it is ACCEPTABLE.

e. On the bottom flap, the following phrase was added: USA-P001".

This addition is ACCEPTABLE.

15. On remaining panel:

a. The "Caution" statement was deleted and replaced with the phrase "Rx only".

This change is ACCEPTABLE.

b. On the flap, the following information was deleted and replaced

deleted:

NDC 0013-2436-06 (black ink)

EXP (black ink)
LOT (black ink)

replaced with:

9.5 mL multipl-dose vial (black ink)
NDC 0013-2436-06 (black ink)

---------- (green ink)
Fragmin (green ink)
dalteparin (black ink)
sodium injection (black ink)

10,000 IU (anti-Xa) per mL (red ink)

These changes are ACCEPTABLE.

Conclusions

1. All the identified changes are ACCEPTABLE except for numbers 1.and 7. identified above.

Karen Oliver, RN, MSN
Regulatory Health Project Manager

Liang Zhou, Ph.D.
Chemistry Team Leader

cc:
Original NDA 20-287/S-017
HFD-180/Div. Files
HFD-180/L.Zhou
HFD-180/A.Al-Hakim

draft: KO/May 8, 2000
final: KO/06/07/00/c:\mydocuments\NDA20287-S-017-05-08-00-labrev.doc

CSO REVIEW

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-287/S-017
NDA 20-287/S-018

Name of Drug: Fragmin® (dalteparin sodium injection)

Sponsor: Pharmacia & Upjohn Company

Material Reviewed

Submission Date(s): Supplement 017
August 21, 2000 (immediate container label and carton)
August 29, 2000 (package insert)

Supplement 018
August 28, 2000 (package insert only)

Receipt Date(s): Supplement 017
August 22, 2000 (immediate container label and carton)
August 30, 2000 (package insert)

Supplement 018
August 29, 2000 (package insert only)

Background and Summary Description:

Supplement 017

Supplement 017, submitted February 7, 2000, received February 8, 2000, provides for the following change: the transfer of manufacturing, packaging and quality control release testing for the 10,000 IU/mL, 9.5 mL multi-dose vial, from Stockholm, Sweden, to the Pharmacia & Upjohn Company facility in Puurs, Belgium.

On June 7, 2000, an approvable letter was issued. On August 21, 2000, the sponsor submitted a full response to the June 7, 2000 action letter including labeling (package insert, immediate container label, and carton). On August 29, 2000, the sponsor submitted revised package insert labeling.

Supplement 018

Supplement 018, submitted February 20, 2000, received March 1, 2000, provides for the addition of a postoperative dosing regimen for Fragmin; and (2) content changes to the package insert including the CLINICAL TRIALS section, "Hip Replacement Surgery" subsection; the ADVERSE REACTIONS section, "Hip Replacement Surgery" subsection; and the DOSAGE AND ADMINISTRATION section, "Hip Replacement Surgery" subsection. Supplement 18 was approved August 3, 2000. On August 28, 2000, the sponsor submitted final printed labeling (FPL) as requested in the August 3, 2000 approval letter.

Review

Package Insert (S-017 and S-018)

The identical package inserts for Supplements 017 and 018 (submitted hard copy and and pdf file on diskette in electronic format according to the guidance *Providing Regulatory Submissions in Electronic Format – NDAs (January 1999)*, were compared to the draft package insert submitted March 3, 2000 to S-017 (see Consumer Safety Officer Review dated June 7, 2000 and the changes requested in the June 7, 2000 approvable letter for S-017 and to the package insert text in the August 3, 2000 approval letter for S-018. The package inserts were reviewed and were identical except for the following:

1. Page numbering in center of the bottom of the pages has been added.

   This addition, requested in the June 7, 2000 approvable letter for S-017, is ACCEPTABLE.

2. In the CLINCICAL TRIALS section, the "Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction" subsection:

   a. In the first paragraph, the first sentence, a comma was added after the phrase "double-blind" and "randomized" to read: In a double-blind, randomized, placebo controlled clinical trial, patients who recently.....12 hours s.c."

      This change is ACCEPTABLE.

   b. In the first paragraph, the sixth sentence, the word "years" was added to the phrase "range 40 to 90" to read: "The mean age of the study population was 68 years (range 40 to 90) and the majority of patients were white (99.7%) and male (63.9%).

This change, provided for in the labeling text enclosed in the August 3, 2000 approval letter for S-018, is ACCEPTABLE. Identical changes, i,.e., the addition of the word "years" after the "range" (range --- to – years) was made in each of the subsections describing the age range of the study population.

c. In Table 1, the last column, the phrase "Q 12 hr" was changed to "q 12 hr".

This change is ACCEPTABLE.

3. In the CLINCIAL TRIALS section, the "Prophylaxis of Deep Vein Thrombosis in Patients Following Hip Replacement Surgery" subsection:

a. In the first paragraph (describing the first study), the first sentence, the hyphen between the words in-patient was removed to read: "In an open-label randomized study, FRAGMIN 5000 IU administered once daily s.c. was compared with warfarin sodium administered orally, in patients .....2500 IU dose s.c."

This change is ACCEPTABLE.

b. In the first paragraph (describing the first study), the second sentence, the lower case was used for the underlined words "Within" and "The" to read: Treatment with FRAGMIN was initiated with a 25000 IU dose s.c. within 2 hours before surgery the evening of the day of surgery.

This change is ACCEPTABLE.

c. In the third paragraph (describing the third study), the word "both" in the following sentence was changed from bold type-face, to regular type-face to read:

> Then, both of these groups began a dosing regimen of FRAGMIN 5000 IU once daily s.c. on postoperative day 1.

This change is UNACCEPTABLE. The word "both" should be bolded in the sentence as (provided for in the labeling text enclosed in the August 3, 2000 approval letter for S-018) to read:

> Then, **both** of these groups began a dosing regimen of FRAGMIN 5000 IU once daily s.c. on postoperative day 1.

4. In the CLINICAL TRIALS section, the "Prophylaxis of Deep Vein Thrombosis Following Abdominal Surgery in Patients at Risk for Thromboembolic Complications" subsection, in the first paragraph, the first sentence, a comma was added after the word "randomized" to read: "FRAGMIN administered once daily....at risk for thromboembolic complications in two double-blind, randomized, controlled clinical trials performed in patients undergoing major abdominal surgery."

This addition is ACCEPTABLE.

5. In the INDICATIONS AND USAGE section, the underlined words in the first sentence were changed

from:

> FRAGMIN Injection is indicated for the prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction <u>in patients</u>, when .....and non-Q Wave Myocardial Infarction.

to:

> FRAGMIN Injection is indicated for the prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction, when .....and non-Q-Wave Myocardial Infarction.

This deletion is ACCEPTABLE.

6. In the ADVERSE REACTIONS section, the "Hemorrhage" subsection, the "*Unstable Angina and Non-Q-Wave Myocardial Infarction*" subsection, in Table 6, the last column, the phrase "Q 12 hr" was changed to "q 12 hr".

This change is ACCEPTABLE.

7. In the DOSAGE AND ADMINISTRATION section, Table 10, dashes "----" were added to the blank cell.

This addition is ACCEPTABLE.

8. After the HOW SUPPLIED section, the "manufactured by" section has been changed

from:

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

to:

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

This change, provided for in S-017, is ACCEPTABLE.

Immediate Container Label (S-017 only):

The computer generated, color mock-up, immediate container label for the 9.5 mL multiple-dose vial, submitted August 21, 2000, identified as "818 124 000A USA_X001", was compared to the computer generated, color mock-up labeling, identified as "818 123 00A USA_X001", submitted April 5, 2000 (see CSO labeling review dated June 7, 2000). The immediate container labels were reviewed and were identical except for the following:

9. The words "exp" and "lot" have been added to the rectangular box (located in a vertical position on the right side of the label).

This additional information, requested in the June 7, 2000 approvable letter for S-017, is ACCEPTABLE.

Carton

The computer generated, color mock-up, carton for the 9.5 mL multiple-dose vial, submitted April 5, 2000, identified as "818 124 000B", was compared to the multiple dose vial carton, identified as ""818 124 000B", submitted April 5, 2000 (see CSO labeling review dated June 7, 2000). The cartons were reviewed and they are identical.

Conclusions

All the identified changes are ACCEPTABLE except for 3.c. identified above. An approval letter should be issued for S-017 and an acknowledge and retain letter for S-018. In each of these letters, the sponsor should be requested to initiate the change in the package insert, identified in 3.c. above, at the next printing.

Karen Oliver, RN, MSN
Regulatory Health Project Manager

Lilia Talarico, M.D.
Division Director

cc:
Original NDA 20-287/S-017
Original NDA 20-287/S-018
HFD-180/Div. Files
HFD-180/L.Zhou
HFD-180/A.Al-Hakim
R/D init: A. Al-Hakim 11/8/00
R/D init: L.Talarico 11/8/00

draft: KO/November 2, 2000
final: KO/11/09/00/c:\mydocuments\NDA20287-S-017-S-018-11-02-00-labrev.doc

CSO REVIEW

/s/

Karen Oliver
11/14/00 12:57:17 PM
CSO

Lilia Talarico
11/14/00 05:49:45 PM
MEDICAL OFFICER

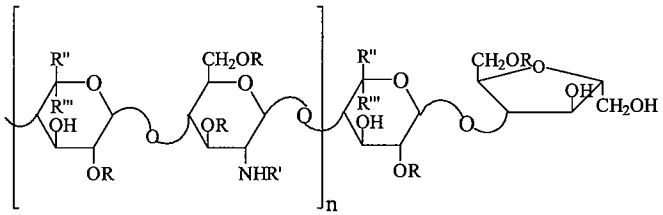
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-017

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW # 1	1. Organization: HFD-180	2. NDA number: 20-287/S-017	
3. Name and Address of Applicant (City & State): Pharmacia & Upjohn 7000 Portage Road Kalamazoo, MI 49001-0199		4. AF Number:	
		5. Supplement(s)	
6. Name of Drug: Fragmin®	7. Nonproprietary Name: Deltaparin Sodium injection	Numbers	Dates
		SCM/017	02/07/00
8. Supplement Provides for: Submitting documentation for transfer of manufacturing, packaging and quality control release testing for the 10,000IU/ml 9.5ml multi-dose vial drug product, from Stockholm, Sweden to Purrs, Belgium.		9. Amendments & Other (Reports, etc.) Dates: Amendment 03/03/00 Amendment 04/05/00	
10. Pharmacological Category: Anticoagulant	11.How Dispensed: RX X OTC __	12. Related DMF(s):	
13.Dosage Form: Solution for Injection	14. Potency: 10000 IU/9.5 ml		
15. Chemical Name and Structure: Sulfated polysaccharide chains at the non-reducing end and 6-O-sulfo-2, 5-anhydro-Dmannitol at reducing end.		16. Records and Reports:	
		Current Yes X No __	
		Reviewed Yes X No __	



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

17. Comments: The application is satisfactory from Chemistry, manufacturing and Control point of view, however, the microbiology review dated May 25, 2000 concluded that the application is Approvable due to a number of deficiencies. The EER recommendation for the site is acceptable (see report dated June 02, 2000).
CC: NDA 20-287
HFD-180/Div File/NDA 20-287
HFD-181/CSO/K. Oliver
HFD-180/L.Talarico
HFD-180/A.Al-Hakim
R/D init: L.Zhou
AA/ **F/T 06/02/00** /WORD: N:\Wordfiles\chem\S\20287017.1AA

18. Conclusions and Recommendations: Recommend an Approvable letter be sent to the applicant based on the conclusion and the subsequent deficiencies raised by the microbiology reviewer (Review dated May 25, 2000).

19.Reviewer

Name: Ali Al-Hakim, Ph.D.	Signature	Date Completed: 06/02/00

REVIEW NOTES

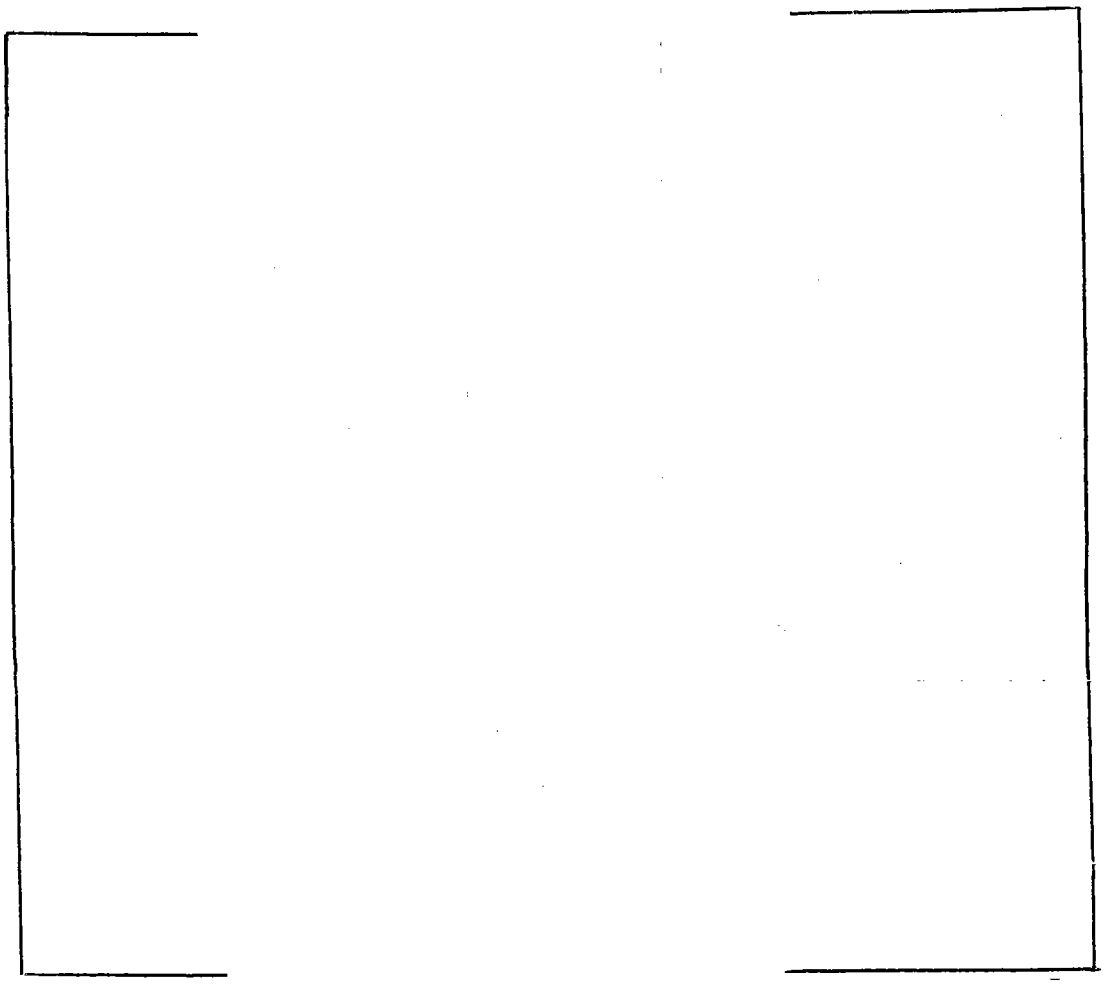
The firm indicated that the purpose of this supplemental application is to submit documentation for transfer of manufacturing, packaging and quality control release testing for the 10,000IU/ml 9.5ml multi-dose vial, from Stockholm, Sweden to Purrs, Belgium. The applicant reported that there are no changes in the packaging material of finished product specifications, no further production activities for the multi-dose vial in Sweden and no changes are proposed for the drug substance.
The amendment contains the following supporting information:

- Page 1. This page contains information about the multidose vial and its concentration (10000 IU anti-factor Xa/ml). The name of the new manufacturing site for the drug product Is:
  Pharmacia & Upjohn
  Rijksweg 12
  B-2870 Puurs
  Belgium

- Page 2. The applicant indicated that manufacturing process in Puurs is the same as one used in Stockholm except for the following proposed changes

The supplement contains the following supporting attachments:

- Attachment 2 (pages 6-8, volume 1). This attachment contains the GMP-certificate of analysis for the new drug product manufacturer. Information about the drug product manufacturer and supplier of packaging components is provided in this attachment.
- Attachment 3 (pages 9-27, volume 1). This attachment contains the description of the manufacturing and packaging processes and in-process controls. The flow chart of the manufacturing process is provided below.



precision. The method is described on pages 20-23. Method validation for the above test is provided on page 24-25. The microbiology reviewer will review this method (See Approvable Microbiology Review dated 05/25/00).

Comment: The NDA holder reported on page 26 that _____ Fragmin drug product marketed in the US.

- Attachment 4 (pages 28-80, volume 1) contains tests and methods used in evaluating the drug product. These tests and method are the same as those provided in the original application. No changes or modification have been introduced.
  Evaluation
  The information is satisfactory.

- Attachment 5 (81-128, volume 1) contains the methods validation for the analytical test methods. These are identical methods to the ones described in the original application.
  Evaluation
  The information is satisfactory.

- Attachment 6 (pages 129-130, volume 1) contains description of the drug product sampling plan and the tests for sample groups. Samples for sterility test and volume in container are also included.
  Evaluation

The information is satisfactory.

- Attachment 7 (pages 131-138, volume 1) contains release data on the primary stability lots produced in Puurs, Belgium for comparison with batch data on three batches from the present production site in Stockholm, Sweden. This attachment contained the comparison data between the two sites. Copies of the results (tests and specifications) are provided below.

  Evaluation

  The comparison data between the original manufacturing site in Stockholm, Sweden and the new site in Puurs, Belgium is satisfactory. The new site produced drug product batches within the approved NDA specifications. Details of the tests and specifications for each lot are presented in attachment 8. Satisfactory information is provided.

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CHEMISTRY REVIEW #1

A stability commitment to conduct stability studies on the first three commercial batches, in accordance with the stability program, is provided in this attachment.
Page 143 contains information (lot #, manufacturing place and date, lot size) for the three batches manufactured in Puurs. Stability program for 6 lots (schedule and test/assay) is provided on pages 145-150. Stability results for the first 6 months is also provided (pages 151-190). The results obtained so far show no out of specifications or unexpected changes for the Fragmin drug product solution.

Evaluation:

The applicant presented satisfactory information regarding the comparison of the analytical data between the new site and the original site. Stability data form the drug product manufactured at the new site indicated the drug product is identical to the product produced in the original site and the new site is producing drug product as per the approved NDA specifications.

- The amendment contains information regarding the Environment Assessment. Claim for Categorical Exclusion for Environment Assessment Preparation (page 4, volume 1). The applicant is requesting a categorical exclusion as per 21CFR 25.5 (c) (1) because the site transfer is a supplement to the NDA and does not increase the use of active moiety.

- Attachment 9 (pages 241-270, volume 1) contains the proposed Mater batch records for commercial production of the drug product.

- Attachment 10 (pages 271-354, volume 1) contains the batch records for the primary stability lots of the drug product.

- Attachments 11 through 13 (pages 355-387, volume 1) contain the test results for the primary stability lots and drug substance lots. Test results for the inactive ingredients and container/closure system used to manufacture these lots are also provided in this attachment.

- Attachment 14 (pages 1-13, volume 2) contains information about the buildings and facilities, location of equipment, cleanliness areas and floor plan.

- Attachment 15 (pages 14-15, volume 2) contains details about the overall manufacturing operations and flow of components and products.

- Attachment 16 (pages 16-107, volume 2) contains description of the drug product solution ———

  ———

  Note

  This attachment contains the validation of microbiological retention test using ———
  ——— This microbiological test will be reviewed and evaluated by microbiology reviewer.

- Attachment 17 (page108, volume 2) contains details regarding the specification of holding periods.

  Evaluation

  The applicant has provided satisfactory information regarding stability data and supporting information for the stability program.
  Information regarding the holding time for the bulk solution, ———
  ——— is described on pages 108 (see Approvable Microbiology Review dated 05/25/00).
  The applicant reported that the holding time has not been changed from the original NDA specifications.

- Attachment 18 (pages 109-167, volume 2) contains information about sterilization and depyrogenation of containers, closures, equipment and component. The amendment also contains procedures and specifications for media fills, actions concerning product when media fills fail, microbiological monitoring of the environment, sterility testing methods and release criteria, bacterial endotoxins test and evidence of formal written procedures.

  Evaluation

  Sterilization /depyrogenation of containers, closures, equipment and components and subsequent validation studies are described in this attachment. The firm provided full details and methods regarding the sterilization studies and the corresponding validation studies. This section will be reviewed and evaluated by microbiology reviewer. See review dated 05/25/00.

- Attachment 19 (pages 168-172, volume 2) contains information about the container/closure system. No changes were proposed for this section.

- Attachment 20 (pages 173-176, volume 2) contains the draft labeling section for the new manufacturing site.

  The labeling section contains the following revised information:

  - For the carton printed label,
    The name of the new production site in Puurs, Belgium.
    The trademark "Fragmin" and established name "deltaparin sodium injection' will be printed in positive lettering on a white background (previously, it was printed on the a green background).

  - For the label insert,
    The insert label has been modified; the old manufacturing address (Stockholm, Sweden) has been replaced by the new production address (Puurs, Belgium).

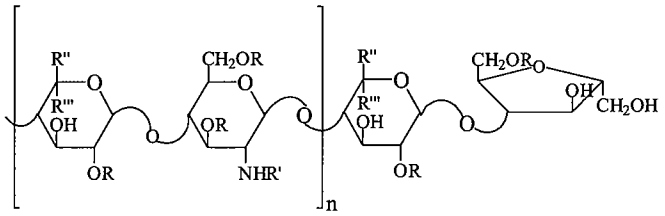
  Evaluation

  Satisfactory information is provided regarding the labeling section.

  EER dated June 02, 2000 indicated the site is acceptable. See attached EER.

APPEARS THIS WAY
ON ORIGINAL

CHEMIST'S REVIEW # 2	1. Organization: HFD-180	2. NDA number: 20-287/S-017	
3. Name and Address of Applicant (City & State): Pharmacia & Upjohn 7000 Portage Road Kalamazoo, MI 49001-0199		4. AF Number:	
		5. Supplement(s)	
6. Name of Drug: Fragmin®	7. Nonproprietary Name: Deltaparin Sodium injection	Numbers	Dates
		SCM/017 AZ	08/21/00
8. Supplement Provides for: Submitting documentation for transfer of manufacturing, packaging and quality control release testing for the 10,000IU/ml 9.5ml multi-dose vial drug product, from Stockholm, Sweden to Purrs, Belgium.		9. Amendments & Other (Reports, etc.) Dates: Amendment 03/03/00 Amendment 04/05/00	
10. Pharmacological Category: Anticoagulant	11.How Dispensed: RX X OTC __	12. Related DMF(s):	
13.Dosage Form: Solution for Injection	14. Potency: 10000 IU/9.5 ml		
15. Chemical Name and Structure: Sulfated polysaccharide chains at the non-reducing end and 6-O-sulfo-2, 5-anhydro-Dmannitol at reducing end.		16. Records and Reports: Chemistry review No. 1 dated 06/02/00 the original supplemental application dated 02/07/00.	
		Current Yes X No __	
		Reviewed Yes X No __	



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

17. Comments:
The original submission for this supplement was approvable based on the microbiology reviewer conclusion (there were no outstanding CMC issues in the original submission). The applicant submitted response to the microbiology information request. The microbiology reviewer found the response adequate and concluded that the supplement should be approved See microbiology review dated Oct. 24, 2000. I concur with the microbiology reviewer conclusion regarding approving this supplement.
CC: NDA 20-287
HFD-180/Div File/NDA 20-287
HFD-181/CSO/K. Oliver
HFD-180/L.Talarico
HFD-180/A.Al-Hakim
R/D init: L.Zhou
AA/ **10/31/00** /WORD: N:\Wordfiles\chem\S\20287017.2AA

18. Conclusions and Recommendations: Recommend that the project manager issue an Approval letter.

19.Reviewer

Name: Ali Al-Hakim, Ph.D.	Signature	Date Completed: 10/31/00

/s/

Ali Al-Hakim
11/1/00 09:24:02 AM
CHEMIST

Liang Zhou
11/1/00 02:04:00 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-017

MICROBIOLOGY REVIEW(S)

REVIEW FOR HFD-180
OFFICE OF NEW DRUG CHEMISTRY OR OFFICE OF GENERIC DRUGS
MICROBIOLOGY STAFF/HFD-805
MICROBIOLOGY REVIEW # 1 OF SUPPLEMENT

May 24, 2000

A. 1. NDA/ANDA/IND/: NDA 20-287/S-017

2. TYPE OF SUPPLEMENT: SCM

3. SUPPLEMENT PROVIDES FOR: Transfer of 10,000 IU/mL vial manufacturing, packaging and QC release testing from P & U Company Stockholm, Sweden to Puurs, Belgium.

4. APPLICANT/SPONSOR: Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, MI 49001-0199

5. **MANUFACTURING SITE:** Puurs, Belgium

6. **DRUG PRODUCT NAME:**
Proprietary: Fragmin®
Nonproprietary: Dalteparin sodium injection
Drug Priority Classification: 1

7. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Parenteral Solution 10,000 IU/mL, 9.5mL multi-dose vial.

8. METHOD (S) OF STERILIZATION: ———————

9. PHARMACOLOGICAL CATEGORY: Anti-factor X_a

B. 1. DOCUMENT/LETTER DATE: February 7, 2000
2. **RECEIPT DATE:** February 8, 2000
3. **CONSULT DATE:** February 24, 2000
4. **DATE OF AMENDMENT:** NA

5. **ASSIGNED FOR REVIEW**: April 12, 2000

6. **SUPPORTING/RELATED DOCUMENTS**: None

C. **REMARKS**: The consult requests review of a supplement application for the transfer of manufacturing, packaging and quality control release testing for the Fragmin® 10,000 IU/mL, 9.5mL multi-dose vial, from Stockholm, Sweden to the Pharmacia & Upjohn Company facility in Puurs, Belgium. The supplement was submitted in two volumes, Volume 1 contains information on drug product and Volume 2 contains information for ——— manufacturing process.

D. **CONCLUSIONS**: The Microbiology section of this supplement is approvable upon resolution of some concerns. Specific comments are provided in the review notes and list of deficiencies.

Vinnie Pawar, Ph.D.

cc:

Original NDA 20-287/**SCM-017**
HFD 180/Div. File
HFD 160/Consult
HFD 180/K. Oliver; A. Al-Hakim
HFD 160/Microbiologist/V.Pawar [HFD-805]

Drafted by: V. Pawar, 05/24/2000
R/D initialed by: P. Cooney

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MICROBIOLOGY REVIEW #1

REVIEW FOR HFD-180
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF/HFD-805
MICROBIOLOGY REVIEW # 2 OF SUPPLEMENT

September 28, 2000

A. 1. **NDA/ANDA/IND/**: NDA 20-287/S-017 AZ

2. **TYPE OF SUPPLEMENT**: SCM

3. **SUPPLEMENT PROVIDES FOR**: Transfer of 10,000 IU/mL vial manufacturing, packaging and QC release testing from P & U Company Stockholm, Sweden to Puurs, Belgium.

4. **APPLICANT/SPONSOR**: Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, MI 49001-0199

5. **MANUFACTURING SITE**: Puurs, Belgium

6. **DRUG PRODUCT NAME**:
Proprietary: Fragmin®
Nonproprietary: Dalteparin sodium injection
Drug Priority Classification: 1

7. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY**: Parenteral Solution 10,000 IU/mL, 9.5mL multi-dose vial.

8. **METHOD (S) OF STERILIZATION**: ———————

9. **PHARMACOLOGICAL CATEGORY**: Anti-factor X_a

B. 1. **DOCUMENT/LETTER DATE**: August 21, 2000
2. **RECEIPT DATE**: August 22, 2000
3. **CONSULT DATE**: August 28, 2000
4. **DATE OF AMENDMENT**: August 21, 2000
5. **ASSIGNED FOR REVIEW**: September 06, 2000
6. **SUPPORTING/RELATED DOCUMENTS**: None

C. **REMARKS**: The consult requests review of an amendment to the supplemental

application NDA 20-287/SCM-017. The supplemental application was submitted on February 7, 2000, for the transfer of manufacturing, packaging and quality control release testing for Fragmin® [10,000 IU/mL, 9.5mL multi-dose vial], from Stockholm, Sweden to the Pharmacia & Upjohn Company facility in Puurs, Belgium. The review of supplement resulted in a list of deficiencies, which were submitted to the sponsor. The sponsor addressed these deficiencies in an amendment dated August 21, 2000. The amendment contains information on most recent media fills, environmental monitoring and a translation of Tables EC04 through EC42.

D. CONCLUSIONS: The Microbiology section of this amended supplement is recommended for approval based on the information provided.

Vinnie Pawar, Ph.D.

cc:

Original NDA 20-287/**SCM-017 AZ**
HFD 180/Div. File
HFD 160/Consult
HFD 180/K. Oliver; A. Al-Hakim
HFD 160/Microbiologist/V.Pawar [HFD-805]

Drafted by: V. Pawar, 09/28/2000
R/D initialed by: P. Cooney

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MICROBIOLOGY REVIEW #2

The translation of the above tables was provided.

Satisfactory

Comments: None

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-287/S-017

CORRESPONDENCE

NDA 20-287/S-017

Pharmacia & Upjohn Company
Attention: Ms. Leslie Franks
Unit 0635-298-113
7000 Portage Road
Kalamazoo, Michigan 49001

Dear Ms. Franks:

We acknowledge receipt of 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)

NDA Number: 20-287

Supplement Number: S-017

Therapeutic Classification: Standard (S)

Date of Supplement: February 7, 2000

Date of Receipt: February 8, 2000

This supplement proposes the following change: the transfer of manufacturing, packaging and quality control release testing for the 10,000 IU/mL, 9.5 mL multi-dose vial, from Stockholm, Sweden to the Pharmacia & Upjohn Company facility in Puurs, Belgium.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 8, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be June 8, 2000 and the secondary user fee goal date will be August 8, 2000.

All communications concerning this supplemental application should be addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: DOCUMENT CONTROL ROOM, 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact me at (301) 827-7457.

Sincerely,

Karen Oliver, RN, MSN
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 20-287/S-017
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/L.Zhou
HFD-180/A.Al-Hakim
DISTRICT OFFICE
Drafted by: KO/February 15, 2000
final: KO/02/15/00/c:\data\mydocuments\NDA20287-S-017-02-15-00-acksupp.doc

SUPPLEMENT ACKNOWLEDGEMENT (AC)

NDA 20-287/S-017

Pharmacia & Upjohn Company
Attention: Ms. Leslie Franks
Unit 0635-298-113
7000 Portage Road
Kalamazoo, Michigan 49001

Dear Ms. Franks:

We acknowledge receipt on August 22, 2000, of your August 21, 2000 resubmission to your supplemental new drug application for Fragmin® (dalteparin sodium injection).

This resubmission contains additional microbiology information, revised package insert labeling, and color mock-ups for the immediate container and carton labels for the 9.5 mL multiple-dose vial [10,000 IU (anti-Xa) per mL], in response to our June 7, 2000 action letter.

With this amendment, we have received a complete response to our action letter.

If you have any questions, contact me at (301) 827-7457.

Sincerely,

Karen Oliver, RN, MSN
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 20-287/S-017
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/L.Zhou
HFD-180/A.Al-Hakim
DISTRICT OFFICE
Drafted by: KO/August 28, 2000
final: KO/08/28/00/c:\data\mydocuments\NDA20287-S-017-08-28-00-ackfullresponse.doc

SUPPLEMENT ACKNOWLEDGEMENT (AC)